

THE ESSENTIAL PRACTICAL GUIDE FOR WORKING
WITH RENAL PATIENTS

OXFORD HANDBOOK OF NEPHROLOGY AND HYPERTENSION

Simon Steddon | Neil Ashman | Alistair Chesser
John Cunningham

Provides concise, practical advice about day-to-day management

Covers both evidence- and reality-based medicine, and practical procedures

Includes the most up-to-date guidelines, policy and practice

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2
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Oxford Handbook of Nephrology and Hypertension

Second edition

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Preface to the second edition

Much has changed in our specialty since the appearance of the first edition of this Handbook. Chronic Kidney Disease, a fledgling classification at the time, is now well established internationally and, more recently, acute renal failure has emerged from a comparable makeover as Acute Kidney Injury. Although not without detractors, these re-imaginings have helped to raise general awareness of kidney disease and provided a welcome platform from which nephrologists have re-engaged with colleagues in both primary and secondary care. International efforts to produce consensus guidelines (albeit from disappointingly thin evidence) must also be applauded. However, whilst we may inexplicably struggle to complete sufficient RCTs of good quality, we remain admirable innovators of clinical services. It is a great privilege to be part of a global renal community best characterized by its restlessness to do things better.

You'll find a little more depth to the information in this edition, although this remains balanced with the more pragmatic advice that was so well received last time out. With unlimited knowledge just a few keyboard strokes away, it seemed even more important to bring essential information to the fore and present it in as palatable and practical a way as possible. We hope the additional detail will also prove useful during preparation for postgraduate examinations and assessments.

This Handbook now sits in a larger family, having been joined by the excellent *Oxford Specialist Handbooks of Renal Transplantation* and *Paediatric Nephrology*. Along with the well-established *Oxford Handbook of Dialysis* and the newer *Oxford Desktop Reference of Nephrology*, we believe these represent a formidable resource across our entire specialty.

The first edition was the idea of a few enthusiastic London trainees, cultivated through animated caffeine-fuelled discussions as their lab experiments simmered nearby. Whilst still enthusiastic (on the whole), said trainees are now undeniably greyer, balder, rounder and grumpier (we'll let those of you who know us decide which adjective fits each of us best) and it has inevitably proved challenging to complete this new version around the demands of busy professional and personal lives. We are therefore extremely grateful to all our contributors as well as to OUP for (almost) being as patient as our families. But, ultimately, it is the support and good humour of the latter that has really allowed us to complete the text you are about to read.

It had always been our intention to create a Handbook that makes the practice of renal medicine a little easier and a lot more enjoyable. And on that thought, we offer this new edition to you as meagre thanks for the wonderful fortune that brought our good friend and colleague Shaun Summers, all too briefly, into our lives.

SS & NA, London, 2013

Preface to the first edition

The ability to recognize and understand renal disease and hypertension is an important part of practice in almost any area of medicine. Acute renal failure, often preventable, occurs in up to 7% of all hospital admissions and remains responsible for much morbidity and mortality. The recent reclassification of chronic kidney disease (CKD) has exposed the scale of a serious public health issue, relevant to all medical practitioners both in primary and secondary care. Furthermore, irrespective of specialist interest, regular clinical contact with patients who are dialysis-dependent or who have undergone renal transplantation is now the norm, not the exception. Hypertension needs no introduction as the most common indication for prescription drug therapy and the most important cause of premature death in the developed world.

Many doctors are nervous of renal disease—there persists a belief that renal patients suffer exclusively from complex, esoteric conditions that can only be managed in a specialist environment and by specialists who are often more difficult and demanding than their patients. Our intention has been to write a concise but robust handbook that is first and foremost practical: what needs to be done in a busy casualty department or GP surgery several miles from the nearest renal unit. We hope it will be a useful resource not only to doctors, nurses, and other members of the multiprofessional team already engaged in the care of renal patients but also to a broader audience. For those interested in how renal disease evolves, we've provided a good grounding in the fundamentals of nephrology—hopefully dismantling some myths along the way, and giving readers the confidence to manage the day-to-day associated with kidney disease.

In line with existing Oxford Handbooks we have attempted to strike a balance between practical information, helpful to those working 'at the coal face', and the more detailed knowledge that enables effective ongoing care. The authors are all consultants working in busy renal units where theory and practice are balanced to provide effective and efficient care. The book is as up-to-date as possible and a conscious mix of evidence and reality-based medicine.

The book is laid out in twelve chapters, allowing easy access to information on a particular clinical theme. Clinical importance is measured in space, so diabetic nephropathy is given more attention than, for example, Fanconi's syndrome. The section on renal replacement therapies gives an overview of the essential elements of both dialysis and transplantation. Those looking for more detailed notes on all aspects of dialysis therapy are referred to our sister volume *The Oxford Handbook of Dialysis*, or, for general nephrology and transplant topics, our parent text *The Oxford Textbook of Nephrology*. For completeness, we have included practical procedures but would ask that these pages are used for guidance only—all must be taught by experienced operators and cannot be learnt solely from a book.

We make no apology for emphasizing the importance of clinical assessment. Yes, tubular physiology is here (we are nephrologists after all), but this book is aimed principally at clinicians in training and we still believe that without a detailed history and thorough physical examination it is impossible to order and interpret appropriate laboratory tests or imaging, let alone provide good quality care. This seems more important than ever at a time when many lament a diminished sense of enjoyment in the practice of medicine.

We are grateful to all of our colleagues who helped bring this project to fruition as well as to our families for tolerating so many lost evenings and weekends with such good grace. We hope that we have produced a book with personality, and one that brings its subject matter alive. We would like readers to enjoy the highways and byways of renal medicine and that we have avoided, in the words of Mark Twain, a book that 'everyone wants to have read, but no-one wants to read'.

SS, NA, AC, JC
London, July 2006

Contents

Contributors *x*

Symbols and Abbreviations *xi*

1	Clinical assessment of the renal patient	1
2	Acute kidney injury (AKI)	87
3	Chronic kidney disease (CKD)	191
4	Dialysis	273
5	Transplantation	335
6	Hypertension	449
7	Diseases of the kidney	529
8	The kidney in systemic disease	603
9	Essential urology	705
10	Fluids and electrolytes	777
11	Pregnancy and the kidney	839
12	Drugs and the kidney	869
13	Renal physiology	913
14	Appendices	935

Index *957*

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Symbols and Abbreviations

α	alpha
β	beta
♂	male
♀	female
1°	primary
2°	secondary
↑	increased
↓	decreased
▶	important
▶▶	don't dawdle
⚠	warning
⚡	controversial topic
∴	therefore
→	leading to
↔	normal
°	degree
~	approximately
≈	equal to
®	registered trademark
>	greater than
<	less than
≥	equal to or greater than
≤	equal to or less than
=	equal to
&	and
£	pound sterling
\$	US dollar
+ve	positive
-ve	negative
AAA	abdominal aortic aneurysm
Ab	antibody
ABD	adynamic bone disease
ABPM	ambulatory blood pressure monitoring
ACE-I	angiotensin-converting enzyme inhibitor
ACR	albumin/creatinine ratio

ACS	abdominal compartment syndrome; acute coronary syndrome
ACT	activated clotting time
ACTH	adrenocorticotrophin hormone
AD	autosomal dominant
ADH	antidiuretic hormone
ADMA	asymmetric dimethyl arginine
ADPKD	autosomal dominant polycystic kidney disease
AF	atrial fibrillation
AFB	acid-fast bacilli
AG	anion gap
AGE	advanced glycation end-product
A2	angiotensin II
AIDS	acquired immunodeficiency syndrome
AIN	acute interstitial nephritis
AKD	acute kidney disease
AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
Al	aluminium
Alb	albumin
ALP	alkaline phosphatase
ALT	alanine transaminase
a.m.	<i>ante meridian</i>
AMR	antibody-mediated rejection
AN	analgesic nephropathy
ANA	anti-nuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibodies
ANP	atrial natriuretic peptide
APC	antigen-presenting cell
APD	automated peritoneal dialysis
APS	antiphospholipid syndrome
APTT	activated partial thromboplastin time
AR	autosomal recessive
ARAS	atherosclerotic renal artery stenosis
ARB	aldosterone receptor blocker
ARDS	acute respiratory distress syndrome
ARPKD	autosomal recessive polycystic kidney disease
ARR	aldosterone–renin ratio
ARVD	atherosclerotic renovascular disease
ASAP	as soon as possible

ASCT	autologous stem cell transplantation
ASOT	anti-streptolysin O titre
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
ATI	acute tubular injury
ATN	acute tubular necrosis
ATP	adenosine triphosphate
AV	atrioventricular; arteriovenous
AVF	arteriovenous fistula
AVM	arteriovenous malformation
AVP	arginine vasopressin
AXR	abdominal X-ray
AZA	azathioprine
BAL	bronchoalveolar lavage
BAT	baroreceptor activation therapy
BBV	blood-borne viruses
BC	blood culture
BCG	basal cell carcinoma; bacille Calmette–Guérin
BCR	B cell receptor
bd	twice daily
BE	base excess
BEN	Balkan endemic nephropathy
BHS	British Hypertension Society
BM	basement membrane
B ₂ M	beta 2 microglobulin
BMD	bone mineral density
BMI	body mass index
BMT	bone marrow transplantation
BNP	brain natriuretic peptide
BOO	bladder outlet obstruction
BP	blood pressure
BPH	benign prostatic hyperplasia
BVAS	Birmingham vasculitis activity score
BVM	blood volume monitoring
Ca ²⁺	calcium ion
CaCl ₂	calcium chloride
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
CAKUT	congenital abnormalities of the kidney and urinary tract
CAN	chronic allograft nephropathy

CAPD	continuous ambulatory peritoneal dialysis
CAPS	catastrophic antiphospholipid syndrome
CaR	calcium-sensing receptor
CaxP	calcium phosphate product
CBPM	clinic BP monitoring
Cbsa	cationic bovine serum albumin
CCB	calcium channel blocker
CCF	congestive cardiac failure
CCPB	calcium-containing phosphate binder
CCPD	continuous cycling peritoneal dialysis
CD	collecting duct
CDC	complement-dependent cytotoxicity; Centers for Disease Control
CEPD	continuous equilibrium peritoneal dialysis
CERA	continuous EPO receptor activator
cfu	colony-forming unit
CG	Cockcroft–Gault
CHCC	Chapel Hill Consensus Conference
CHD	coronary heart disease
C ₂ H ₅ OH	ethanol
CHr	reticulocyte haemoglobin content
CIC	ciclosporin
CIS	carcinoma <i>in situ</i>
CIT	cold ischaemic time
CK	creatine kinase
CKD	chronic kidney disease
Cl ⁻	chloride ion
CLL	chronic lymphocytic leukaemia
cm	centimetre
CMI	cell-mediated immune
CMV	cytomegalovirus
CN	cranial nerve
CNI	calcineurin inhibitor
CNS	central nervous system
cTnl	cardiac troponin I
cTnT	cardiac troponin T
CO	cardiac output
CO ₂	carbon dioxide
COC	combined oral contraceptive
COP	colloid osmotic pressure

COX	cyclo-oxygenase
CPAP	continuous positive airway pressure
CPET	cardiopulmonary exercise testing
CPM	central pontine myelinosis
CPS	calcium polystyrene sulphate
Cr	creatinine
CRB	catheter-related bacteraemia
CrCl	creatinine clearance
CRF	chronic renal failure
CRH	corticotrophin-releasing hormone
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CRS	cardiorenal syndrome
C+S	culture and sensitivity
CT	computed tomography
CTA	computed tomography angiography
CTS	carpal tunnel syndrome
CUA	calific uraemic arteriopathy
CV	cardiovascular
CVA	cerebrovascular accident
CVC	central venous catheter
CVD	cardiovascular disease
CVP	central venous pressure
CVVHD	continuous veno-venous haemodialysis
CVVHDF	continuous veno-venous haemodiafiltration
CVVHF	continuous veno-venous haemofiltration
CXR	chest X-ray
d	day
3D	three-dimensional
Da	dalton
DA	dopamine
DBD	donation after brain death
DBP	diastolic blood pressure
DCD	donation after cardiac death
DCT	distal convoluted tubule
DDAVP	desmopressin
DEXA	dual-energy X-ray absorptiometry
DFO	desferrioxamine
DGF	delayed graft function
DHT	dihydrotestosterone

DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
dL	decilitre
DM	diabetes mellitus
DMARD	disease-modifying anti-rheumatic drug
DN	diabetic nephropathy
DNA	deoxyribonucleic acid
DRA	dialysis-related amyloidosis
DRE	digital rectal examination
DSA	donor-specific antibody
dsDNA	double-stranded deoxyribonucleic acid
DSE	dobutamine stress echocardiography
DT	distal tubule
DTT	dithiothreitol
D&V	diarrhoea and vomiting
DVT	deep vein thrombosis
DW	dry weight
EABV	effective arterial blood volume
EBCT	electron beam CT
EBV	Epstein–Barr virus
ECD	extended criteria donors
ECF	extracellular fluid
ECG	electrocardiogram
ECHO	echocardiography
EEG	electroencephalogram
EF	ejection fraction
EG	ethylene glycol
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
EMA	European Medicines Agency
EMT	epithelial to mesenchymal transition
EMU	early morning urine
ENA	extractable nuclear antigen
ENaC	epithelial Na ⁺ channel
eNOS	endogenous nitric oxide synthase
ENT	ear, nose, and throat
EPO	erythropoietin
EPO-R	erythropoietin receptor

ERT	enzyme replacement therapy
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EST	exercise stress testing
ESWL	extracorporeal shock wave lithotripsy
FBC	full blood count
FDA	Food and Drug Administration
FFP	fresh frozen plasma
FFR	fractional flow reserve
FFS	five factor score
FH	family history
FISH	fluorescence <i>in situ</i> hybridization
FMD	fibromuscular dysplasia
FMF	familial Mediterranean fever
FOB	faecal occult blood
FPG	fasting plasma glucose
FSGS	focal and segmental glomerulosclerosis
FSH	follicle-stimulating hormone
g	gram
GA	general anaesthesia
GBM	glomerular basement membrane
GCS	Glasgow Coma Score
Gd	gadolinium
GDP	glucose degradation product
GFR	glomerular filtration rate
GH	growth hormone
GI	gastrointestinal
GN	glomerulonephritis
GnRH	gonadotropin-releasing hormone
GP	general practitioner
GPA	granulomatosis with polyangiitis
G6PD	glucose-6-phosphate deficiency
G6PDH	glucose-6-phosphate dehydrogenase
GRA	glucocorticoid-remediable aldosteronism
G&S	group and save
GST	glutathione S-transferase
GTN	glyceryl trinitrate
GUTB	genitourinary tuberculosis
h	hour
H ⁺	hydrogen ion

HAART	highly active antiretroviral therapy
Hb	haemoglobin
HBPM	home blood pressure measurement
HBV	hepatitis B virus
HC	hydroxycarbamide
HCDD	heavy chain deposition disease
HCO_3^-	bicarbonate ion
H_2CO_3	carbonic acid
HCP	haemopoietic cell phosphatase
Hct	haematocrit
HCV	hepatitis C virus
HD	haemodialysis
HDF	haemodiafiltration
HDL	high-density lipoprotein
H+E	haematoxylin and eosin
HELLP	haemolysis, elevated liver enzymes, and low platelet
HF	haemofiltration; heart failure
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HIVAN	HIV-associated nephropathy
HIVICK	HIV immune complex kidney disease
HIV-TMA	HIV-associated thrombotic microangiopathy
HLA	human leucocyte antigen
H_2O	water
HoLEP	holmium laser enucleation of the prostate
hpf	high-powered field
HR	heart rate
HRBC	hypochromic red blood cell
HRCT	high-resolution computed tomography
HRE	hypoxia response element
hrEPO	human recombinant erythropoietin
HRS	hepatorenal syndrome
HRT	hormone replacement therapy
HSP	Henoch–Schönlein purpura
HSV	<i>herpes simplex virus</i>
HTA	Human Tissue Authority
HTLV	human T lymphotropic virus
HUS	haemolytic uraemic syndrome
IAH	intra-abdominal hypertension
IAP	intra-abdominal pressure

IBD	inflammatory bowel disease
IBW	ideal body weight
IC	immune complex
iCa ²⁺	ionized calcium
ICA	intracranial aneurysms
ICAM-1	intercellular adhesion molecule-1
IDH	intradialytic hypotension
IDL	intermediate density lipoprotein
IDPN	intradialytic parenteral nutrition
IE	infective endocarditis
IF	interstitial fibrosis
IFN	interferon
Ig	immunoglobulin
IgAN	IgA nephropathy
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor-binding protein
IGRA	interferon gamma release assays
IHD	ischaemic heart disease; intermittent haemodialysis
IL	interleukin
IM	intramuscular
IMN	idiopathic membranous nephropathy
IMPDH	inosine monophosphate dehydrogenase
IMWG	International Myeloma Working Group
INHHD	in-hospital nocturnal haemodialysis
iNOS	inducible nitric oxide synthase
INR	international normalized ratio
IP	intraperitoneal
IPSS	international prostate symptom score
ITP	idiopathic thrombocytopenic purpura
ITU	intensive treatment unit
IU	international unit
IUGR	intrauterine growth restriction
IV	intravenous
IVC	inferior vena cava
IVDSA	intravenous digital subtraction angiography
IVDU	intravenous drug user
IVI	intravenous infusion
IVIg	intravenous immunoglobulin
IVU	intravenous urogram
JBS	Joint British Societies

JNC	Joint National Committee
JVP	jugular venous pressure
K ⁺	potassium ion
kcal	kilocalorie
KCl	potassium chloride
KCO	diffusion capacity for carbon monoxide
kDa	kilodalton
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
kPa	kilopascal
KUB	kidneys–ureter–bladder
L	litre
LA	local anaesthesia; lupus anticoagulant
LAKIN	London AKI Network
LDH	lactic acid dehydrogenase
LDL	low-density lipoprotein
L-FABP	liver-type fatty acid-binding protein
LFT	liver function test
LH	luteinizing hormone; loop of Henle
LIDD	light chain deposition disease
LMW	low molecular weight
LMWH	low molecular weight heparin
LN	lymph node
LP	lumbar puncture
LPS	lipopolysaccharide
LUTS	lower urinary tract symptoms
LV	left ventricular
LVF	left ventricular failure
LVH	left ventricular hypertrophy
m	metre
mAb	monoclonal antibody
MAC	membrane attack complex
MACE	major adverse cardiovascular events
MAHA	microangiopathic haemolytic anaemia
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MARS	molecular absorbent recirculating system
Mb	myoglobin
MBD	mineral and bone disorder
MCD	minimal change disease

MCGN	mesangiocapillary glomerulonephritis
MCN	minimal change nephropathy
M,C+S	microscopy, culture, and sensitivity
MCUG	micturating cystourethrography
MDRD	Modification of Diet in Renal Disease
MEN	multiple endocrine neoplasia
meq	milliequivalent
MFI	median fluorescence intensity
mg	milligram
Mg ²⁺	magnesium ion
MGUS	monoclonal gammopathy of uncertain significance
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MIDD	monoclonal immunoglobulin deposition disease
min	minute
mIU	milli international unit
mm	millimetre
MMF	mycophenolate mofetil
mmHg	millimetre of mercury
mmol	millimole
MMR	mumps, measles, and rubella
MN	membranous nephropathy
mOsmol	milliosmole
MPA	mycophenolic acid; microscopic polyangiitis
MPO	myeloperoxidase
MPS	myocardial perfusion scan; mycophenolate sodium
MR	magnetic resonance; modified release; mineralocorticoid receptor
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRSA	meticillin-resistant <i>Staphylococcus aureus</i>
MRSI	magnetic resonance spectroscopy imaging
MS	multiple sclerosis
MSCT	multislice computed tomography
MSU	midstream urine
mTOR	mammalian target of rapamycin
mU	milliunit
MVR	mitral valve replacement
MW	molecular weight

Na ⁺	sodium ion
NAC	N-acetylcysteine
NaCl	sodium chloride
NADR	noradrenaline
NAG	N-acetyl- β -D-glucosaminidase
NaHCO ₃	sodium bicarbonate
NB	take note (<i>nota bene</i>)
NBM	nil by mouth
NFAT	nuclear factor of activated T cells
ng	nanogram
NG	nasogastric
NGAL	neutrophil gelatinase-associated lipocalin
NH ₄ ⁺	ammonium ion
NHHD	nocturnal home haemodialysis
NHL	non-Hodgkin's lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIPD	night-time intermittent peritoneal dialysis
NK	natural killer
NKF-KDOQI	National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative
nm	nanometre
NMSC	non-melanoma skin cancer
NO	nitric oxide
NODAT	new-onset diabetes after transplantation
nPCR	normalized protein catabolic rate
NR	normal range
NSAID	non-steroidal anti-inflammatory drug
NSF	nephrogenic systemic fibrosis
NSTEMI	non-ST elevation myocardial infarction
N+V	nausea and vomiting
NYHA	New York Heart Association
O ₂	oxygen
od	once daily
OSA	obstructive sleep apnoea
OSP	oral sodium phosphate
p	probability
PAC	pulmonary artery catheter
PAK	pancreas after kidney

PAN	polyarteritis nodosa
PaOP	pulmonary artery occlusion pressure
PAS	periodic acid–Schiff
PC	pelvicalyceal
PCA	patient-controlled analgesia
PCP	pneumocystis pneumonia
PCR	protein/creatinine ratio; polymerase chain reaction
PCT	proximal convoluted tubule
PD	peritoneal dialysis
PDGF	platelet-derived growth factor
PEEP	positive end expiratory pressure
PEG	percutaneous endoscopic gastrostomy; polyethylene glycol
PET	peritoneal equilibration test; positron emission tomography
PEX	plasma exchange
PFT	pulmonary function test
pg	picogram
PIGN	post-infectious glomerulonephritis
PIH	pregnancy-induced hypertension
PIN	prostatic intraepithelial neoplasia
PIGF	placental growth factor
plt	platelet
pmol	picomole
pmp	per million of population
PNCL	percutaneous nephrolithotomy
PNH	paroxysmal nocturnal haemoglobinuria
PO	orally
PO ₄	phosphate ion
POF	premature ovarian failure
POTS	postural tachycardia syndrome
PP	pulse pressure
PPI	proton pump inhibitor
PR3	proteinase 3
PRA	panel reactive antibody
PRCA	pure red cell aplasia
PRES	posterior reversible encephalopathy syndrome
prn	as required
PSA	prostate-specific antigen
PT	prothrombin time
PTA	pancreas transplant alone
PTC	proximal tubular cell; peritubular capillary

PTFE	polytetrafluoroethylene
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTLD	post-transplant lymphoproliferative disorder
PTRA	percutaneous transluminal renal angioplasty
PUJ	pelvi-ureteric junction
PUV	posterior urethral valves
PV	per vagina
PVAN	polyomavirus-associated nephropathy
PVD	peripheral vascular disease
PVP	photoselective vaporization of the prostate
qds	four times daily
RA	rheumatoid arthritis
RAAS	renin–angiotensin–aldosterone system
RAS	renin–angiotensin system
RBC	red blood cell
RBF	renal blood flow
RBP	retinol-binding protein
RCC	renal cell carcinoma
RCT	randomized controlled trial
R&D	research and development
RF	radiofrequency
Rh	rhesus
RhF	rheumatoid factor
RI	resistive index
RJ	right internal jugular
RLV	renal-limited vasculitis
RN	reflux nephropathy
RNA	ribonucleic acid
RNP	ribonuclear protein
RO	reverse osmosis
RPF	retroperitoneal fibrosis
RPGN	rapidly progressive glomerulonephritis
RPLS	reversible posterior leucoencephalopathy syndrome
RR	respiratory rate
RRT	renal replacement therapy
RTA	renal tubular acidosis
RVD	renovascular disease
RVT	renal vein thrombosis
RWMA	regional wall motion abnormality

s	second
SA	sinoatrial
SAA	serum amyloid A
SAH	subarachnoid haemorrhage
S _a O ₂	oxygen saturation
SAP	serum amyloid P
SBP	systolic blood pressure; spontaneous bacterial peritonitis
SCC	squamous cell carcinoma
SCM	sternocleidomastoid
SCN	sickle cell nephropathy
SCr	serum creatinine
ScvO ₂	central venous oxygen saturation
SDHD	short daily haemodialysis
SE	side effect
SEP	synthetic erythropoiesis protein; sclerosing encapsulating peritonitis
SFLC	serum free light chain
SGA	subjective global assessment
SHPT	secondary hyperparathyroidism
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SLED	sustained low-efficiency dialysis
SNGFR	glomerular filtration rate of single nephron
SNP	single nucleotide polymorphism
SNS	sympathetic nervous system
SOB	shortness of breath
SPEP	serum protein electrophoresis
SPK	simultaneous kidney–pancreas
spp.	species
SPS	sodium polystyrene sulphonate
SSc	systemic sclerosis
SSRI	serotonin-specific reuptake inhibitor
STD	sexually transmitted disease
STEMI	ST elevation myocardial infarction
SVC	superior vena cava
SVR	systemic vascular resistance; sustained virologic response
T	temperature
t _{1/2}	half-life
TA	tubular atrophy

TAC	tacrolimus
TALH	thick ascending loop of Henle
TB	tuberculosis
TBW	total body water
TC	total cholesterol
TCC	transitional cell carcinoma
TCR	T cell receptor
T1DM	type 1 diabetes
T2DM	type 2 diabetes
tds	three times daily
TFT	thyroid function test
THMP	Tamm–Horsfall mucoprotein
TIA	transient ischaemic attack
TIBC	total iron-binding capacity
TIMP	tissue inhibitor of metalloproteinases
TIN	tubulointerstitial nephritis
TINU	tubulointerstitial nephritis and uveitis
TIPS	transjugular intrahepatic portosystemic shunt
TLS	tumour lysis syndrome
TMA	thrombotic microangiopathy
TMD	thin membrane disease
TMP	transmembrane pressure
TNF	tumour necrosis factor
TOD	target organ damage
TOE	transoesophageal echocardiography
TOR	target of rapamycin
TMPT	thiopurine methyltransferase
TPN	total parenteral nutrition
TRUS	transrectal ultrasound
TSAT	transferrin saturation
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiography
TTP	thrombotic thrombocytopenic purpura
TUIP	transurethral incision of the prostate
TUMT	transurethral microwave therapy
TUNA	transurethral needle ablation
TURBT	transurethral resection of bladder tumour
TURP	transurethral resection of the prostate
U	unit
UAG	urine anion gap

U&E	urea and electrolytes
UF	ultrafiltration
UFH	unfractionated heparin
UK	United Kingdom
UKM	urea kinetic modelling
UO	urine output
UPEP	urine protein electrophoresis
Ur	urea
URR	urea reduction ratio
USA	United States of America
USRDS	United States Renal Data System
USS	ultrasound scan
UTI	urinary tract infection
UV	ultraviolet
VC	vascular calcification
VDR	vitamin D receptor
VDRA	vitamin D receptor agonist
VE	vaginal examination
VEGF	vascular endothelial growth factor
VL	viral load
VPI	vasopeptidase inhibitor
vs	versus
VTE	venous thromboembolism
VUR	vesicoureteric reflux
vWF	von Willebrand factor
VZV	varicella zoster virus
WCC	white cell count
WHO	World Health Organization
WIT	warm ischaemia time
wk	week
WWII	World War II
yr	year

Clinical assessment of the renal patient

- Clinical history: introduction 2
- Clinical history: symptoms and social history 4
- Clinical history: drug, treatment, and family 6
- Clinical history: additional factors 8
- Physical examination 10
- Physical examination: the circulation 12
- Urine: appearance 14
- Urinalysis: chemical analysis 16
- Urinalysis: further tests 18
- Urinalysis: protein 20
- Urinalysis: red blood cells 22
- Urinalysis: cells, organisms, and casts 24
- Urinalysis: crystals 28
- Determining renal function 30
- Creatinine 32
- eGFR 34
- GFR measurement: other methods 36
- Renal function in the elderly 38
- Immunological and serological investigation 40
- Diagnostic imaging: X-ray 44
- Diagnostic imaging: ultrasound 46
- Diagnostic imaging: CT and MRI 50
- Diagnostic imaging: IVU 52
- Diagnostic imaging: nuclear medicine 54
- Diagnostic imaging: angiography and urology 56
- Clinical syndromes: proteinuria—introduction 58
- Clinical syndromes: proteinuria 60
- Clinical syndromes: haematuria—introduction and classification 62
- Clinical syndromes: haematuria assessment 64
- Clinical syndromes: microscopic haematuria 66
- Clinical syndromes: microscopic haematuria screening 68
- Clinical syndromes: CKD, AKI, and the nephritic syndrome 70
- Clinical syndromes: pulmonary renal syndromes 72
- Clinical syndromes: urine volume and urinary tract pain 74
- Clinical syndromes: tubular syndromes 76
- Clinical syndromes: bladder outflow obstruction 78
- Renal biopsy: introduction 80
- Renal biopsy: indications 82
- Renal biopsy: complications 84

Clinical history: introduction

In nephrology, as in all branches of medicine, a competent clinical assessment is crucial. This should incorporate symptoms and signs:

- Arising locally from the kidneys and urinary tract.
- Resulting from impaired salt and water handling.
- Caused by failing renal excretory and metabolic function.
- Relating to a systemic disease, causing or contributing to renal dysfunction.

Several additional factors need to be considered:

- Asymptomatic patients often require assessment, following the discovery of an abnormal BP, urinalysis, or eGFR.
- Symptoms, signs, and investigation findings are organized into clinically useful syndromes (see Box 1.1).
- Biochemistry, radiology, and/or histopathology are almost always required for accurate diagnosis (although a thorough clinical assessment will lessen over-reliance on expensive and potentially invasive tests).
- Diagnosis is often suggested by treatment, e.g. cessation of a nephrotoxic drug or restoration of adequate circulatory volume.

See Table 1.1 for renal disease associations.

Box 1.1 Renal clinical syndromes

- Asymptomatic urinary abnormalities:
 - Proteinuria (📖 p. 58).
 - Microscopic haematuria (📖 p. 66).
- Macroscopic haematuria (📖 p. 62).
- Nephritic syndrome (📖 p. 71):
 - Rapidly progressive glomerulonephritis (RPGN).
- Pulmonary renal syndromes (📖 p. 72).
- Nephrotic syndrome (📖 p. 554. PCR in mg/mmol.)
- Renal tubular syndromes (📖 p. 76).
- Hypertension (📖 Chapter 6).
- Acute kidney injury (AKI) (📖 Chapter 2).
- Chronic kidney disease (CKD) (📖 Chapter 3).

Past medical history

- Urinary tract problems as a child (e.g. infections, nocturnal enuresis).
- Previously documented renal or urinary tract disease of any kind. Ask specifically about infections, stone disease, and, in ♂, prostatic disease.
- Hypertension. When diagnosed? Who is responsible for follow-up? Current and historical treatment? Level of control? Self-monitoring with home BP monitor?
- Cardiovascular risk factors or disease (e.g. IHD, CVA, PVD, dyslipidaemia).
- Other relevant systemic disease (e.g. diabetes mellitus, connective tissue disorder, gout, inflammatory bowel disease, sarcoidosis).
- Insurance or employment medicals can provide invaluable historical benchmarks. Can they recall a past BP check or providing a urine specimen? Have they had blood tests in the past?

Table 1.1 Important renal disease associations

Medical condition	Renal association
General	
Hypertension	Hypertensive nephrosclerosis, 2° ↑ BP is associated with many renal disorders
Diabetes mellitus	Diabetic nephropathy
Cardiovascular disease	CKD, renovascular disease, atheroembolism
Liver disease	
Cirrhosis	Hepatorenal syndrome
Hepatitis B and C	Membranous GN, mesangiocapillary GN (MCGN)
Inflammatory	
SLE and other connective tissue disorders	Lupus nephritis, MCGN, and others
Sarcoidosis	Interstitial disease
Raynaud's	Scleroderma, SLE, cryoglobulinaemia
Pleuropericardial disease	Connective tissue disorders
Haemoptysis	Vasculitis, lupus nephritis, anti-GBM disease
Infection	
Gastroenteritis	Pre-renal AKI, haemolytic uraemic syndrome
TB	Urinary tract TB, amyloidosis
HIV	HIVAN, HIVICK and others
Recurrent UTIs	Vesicoureteric reflux and chronic pyelonephritis
Streptococcal infection	Post-infective GN
Endocarditis	Post-infective GN
Chronic infection	Amyloidosis
Dermatological	
Cutaneous vasculitis	Vasculitis, HSP, IgA nephropathy
Livedo reticularis	Antiphospholipid antibody syndrome Cryoglobulinaemia
Malignancy	
Solid organ tumours	Membranous GN, thrombotic microangiopathy
Lymphoma	Minimal change disease, FSGS, fibrillary GN
Myeloma	Light chain disease, amyloid, cast nephropathy
Other	
ENT problems	Granulomatosis with polyangiitis (Wegener's)
Hearing loss	Alport syndrome
Ophthalmic conditions	Retinopathy and anterior lenticonus in Alport's Cystine deposits in cystinosis Retinitis pigmentosa in Senior-Løken syndrome Retinal oxalate deposition in hyperoxaluria
Chronic pain	Analgesic nephropathy
Thrombotic tendency	Antiphospholipid antibody syndrome
Sickle cell disease	Sickle cell nephropathy, papillary necrosis

Clinical history: symptoms and social history

Local symptoms of urinary tract disease

- Pain:
 - Loin pain.
 - Ureteric colic.
 - Suprapubic pain.
- Haematuria.
- Change in urine appearance.
- Changes in urine volume:
 - Polyuria.
 - Oliguria and anuria.
- Lower urinary tract symptoms (LUTS):
 - Obstructive (voiding) symptoms:
 - Impaired size or force of the urinary stream.
 - Hesitancy or abdominal straining.
 - Intermittent or interrupted flow.
 - Post-micturition dribble.
 - A sensation of incomplete emptying.
 - Acute retention of urine.
 - Storage (filling) symptoms:
 - Nocturia.
 - Daytime frequency.
 - Urgency.
 - Urge incontinence.
 - Dysuria.

Social history

- Smoking: general CV risk in (and progression of) CKD, renovascular disease, urothelial malignancy (~4-fold risk), pulmonary haemorrhage in Goodpasture's disease.
- Physical activity.
- Occupational history: risk factors for urothelial malignancy (📖 p. 750). Hydrocarbon exposure has been implicated in glomerular disease, particularly anti-GBM disease.
- Hepatitis and HIV risk factors.
- A patient's understanding of their kidney disease should be evaluated, and they should be encouraged to be involved in decisions about their care.

Renal diseases are often chronic disorders, incurring appreciable social morbidity. Factors, such as social isolation, accommodation, and work situation, are hugely important. In ESRD, social circumstance will exert an important influence on choice of, and ability to cope with, a particular dialysis modality. Livelihood may also be affected—one of the goals of RRT, wherever possible, should be to keep an individual in employment. Quality of life must never be forgotten amidst all the blood tests.

Review of systems

May provide clues to an underlying systemic condition, such as connective tissue disorder or vasculitis.

- Skin rashes.
- Photosensitivity.
- Mouth ulcers.
- Painful, stiff, or swollen joints.
- Myalgia.
- Raynaud's phenomenon.
- Fevers.
- Night sweats.
- Thromboembolic episodes.
- Red or painful eyes.
- ENT:
 - Sinusitis.
 - Rhinitis.
 - Epistaxis.
 - Hearing loss.
- Sicca symptoms (dry eyes, dry mouth).
- Haemoptysis.
- Hair loss.
- Paraesthesiae.

Clinical history: drug, treatment, and family

Drug and treatment history

- The importance of the drug history cannot be overstated—it will often tell a story of its own. ► Ask candidly about compliance.
- Antihypertensive therapy—past and present. Any important tablet intolerances or side effects.
- Analgesics—ask specifically about common NSAIDs (by their over-the-counter names, if necessary). Then ask again.
- Any ‘one-off’ courses of therapy that may not be mentioned as part of regular treatment, e.g. recent antibiotics (interstitial nephritis).
- Oral contraceptive (↑ BP).
- Steroids, immunosuppressive agents—type and duration.
- Non-prescription, recreational (cocaine, IVDU), and herbal (📖 p. 901) medicines.
- Current or historical exposure to important nephrotoxic drugs (see Box 1.2).

Family history

- Essential hypertension: more common if one or both parents affected.
- Diabetes mellitus (types 1 and 2): more common if close relative affected.

See Table 1.2 for inherited kidney diseases.

Table 1.2 Inherited kidney diseases

Cystic kidney diseases	Adult and juvenile polycystic kidney disease	
Primary glomerular	Alport's syndrome and variants	
	IgA nephropathy (occasionally)	
	FSGS (rarely)	
	Others (rarely)	
Metabolic diseases with renal involvement	Non-glomerular	Cystinosis, primary hyperoxaluria, inherited urate nephropathy
	Glomerular	Fabry's disease
Non-metabolic disease	Non-glomerular	Nephronophthisis
	Glomerular	Congenital nephrotic syndrome, nail-patella syndrome
Benign and malignant tumours	Tuberous sclerosis (renal angiomyolipoma) von Hippel–Lindau (renal cell carcinoma)	
Tubular disorders	Cystinuria, various inherited tubular defects	
Disorders with a 'genetic influence'	Vesicoureteric reflux, haemolytic uraemic syndrome, diabetic nephropathy	

Box 1.2 Important nephrotoxins (📖 see Chapter 11)**'Pre-renal' renal insufficiency**

Diuretics

Any antihypertensive agent (esp. ACE-Is and ARBs that aggravate other pre-renal states)

Haemodynamically mediated

NSAIDs and COX-2 inhibitors

ACE-Is and ARBs

Ciclosporin

Tacrolimus

Vasoconstrictors

Glomerulopathy

NSAIDs

Penicillamine

Gold

Hydralazine

Interferon

Anti-thyroid drugs

Carbon tetrachloride and other organic solvents (e.g. glue sniffing)

Silica dust (? granulomatosis with polyangiitis or Wegener's)

Thrombotic microangiopathy

Chemotherapeutic agents:

Mitomycin

Cisplatin

Bleomycin

Immunosuppressive agents:

Ciclosporin

Tacrolimus

Clopidogrel

Quinine

Oral contraceptive

Tubular crystal formation

Aciclovir and other antivirals

Ethylene glycol (antifreeze)

Sulfonamide antibiotics

Methotrexate

Indinavir (antiretroviral)

Acute tubular necrosis

Aminoglycosides

Antifungals:

Amphotericin

Ifofamide

Foscarnet

Antivirals:

Adefovir

Cidofovir

Tenofovir

Cisplatin

Heavy metals (arsenic, mercury, and cadmium)

Herbal remedies

Interleukin-2

Intravenous immunoglobulin (previously with sucrose-containing formulations)

Paracetamol

Paraquat

Pentamidine

X-ray contrast agents

Interstitial nephritis (these and many, many others)

Antibiotics:

Penicillins

Cephalosporins

Quinolones

Rifampicin

Sulfonamides

Allopurinol

Cimetidine (rarely ranitidine)

NSAIDs and COX-2 inhibitors

Diuretics

5-aminosalicylates (sulfasalazine and mesalazine)

Proton pump inhibitors, e.g. omeprazole

Chronic interstitial disease

Lead

Lithium

Analgesics

Chinese herbs

Clinical history: additional factors

Sexual, gynaecological, and obstetric history

- Decreased libido and impotence are extremely common in both ♂ and ♀ with CKD.
- Irregular menses and subfertility are frequently encountered in ♀. Amenorrhoea is common in ESRD.
- Previous pregnancies and any complications (UTI, proteinuria, ↑ BP, pre-eclampsia). Miscarriages, terminations? Were infants healthy and born at term?
- In CKD, maternal and fetal outcomes are importantly related to GFR, degree of proteinuria, and BP (📖 p. 856).
- Cytotoxic drugs used in the treatment of glomerular disease can → premature menopause in ♀ or infertility in ♂. This may influence treatment in a ♀ of childbearing age. Pre-treatment sperm banking can be offered in ♂.
- Risk factors for sexually transmitted disease when appropriate (HIV, hepatitis B and C can all cause glomerular disease).

Dietary history

Changes in appetite and weight. Dietary habits (alcohol, vegan, ethnic diet, protein or creatine supplements). Dietary advice is an important part of the management of many renal disorders (↑ BP, AKI, CKD, the nephrotic syndrome, stone disease, dialysis).

Ethnicity and renal disease

- IgA nephropathy: Caucasians and certain Asian populations (China, Japan, and Singapore).
- Diabetic nephropathy: black, Mexican American, Pima Indian (a native American tribe in Southern Arizona, beloved of epidemiologists and geneticists). An increasing problem in the immigrant Asian population in the UK.
- SLE: Asian and black patients (and more aggressive disease).
- Hypertension and hypertensive renal failure: black patients.
- In the UK, the incidence of end-stage renal disease (ESRD) is ~3× higher in South Asian and black patients than in Caucasians.

Approach to the patient on renal replacement therapy

When managing a dialysis or transplant patient, there are a few direct questions that will help you to get to grips with (and reassure the patient that you are familiar with) their treatment. It will also facilitate discussion with the patient's renal unit.

The patient on haemodialysis

- Where does the haemodialysis treatment take place?
- How many times per week do they dialyse and how many hours is each treatment?
- What is the patient's current access for dialysis (e.g. an arteriovenous fistula, a PTFE graft, or a tunnelled dialysis catheter)?
- What is their usual fluid gain between treatments?
- Do they know their blood pressure at the end of a dialysis session?

The patient on peritoneal dialysis

- Are their exchanges performed manually during the day (CAPD) or automated overnight (APD)?
- How many exchanges do they perform?
- How many litres is each exchange?
- Do they have fluid in at the moment?
- Do they need assistance to perform an exchange?
- Do they measure their own blood pressure at home? What have the readings been recently?
- Is the exit site of their dialysis catheter clean and dry?
- Are the dialysis bags clear or cloudy on drainage?
- When was their last episode of peritonitis?

All dialysis patients

- How long have they been on dialysis?
- How much urine do they pass, if any?
- What is their dry (aka flesh, target, post-dialysis) weight?
- What is their daily fluid allowance?
- Do they adhere to a renal diet?
- Do they know the cause of their end-stage renal disease?
- Do they receive erythropoietin injections? Who performs these?
- Have they always been on the same modality of dialysis?
- Are they 'listed' for deceased donor transplantation?
- Have they previously received a transplant?
- How are they coping with dialysis?

The transplant patient

- When and where was the transplant performed?
- What immunosuppression is the patient taking?
- Who is responsible for their follow-up?
- Do they know their baseline SCr?
- Was the transplant from a living or deceased donor?
- Do they use sunblock and attend a skin clinic?
- Do they know if they had any rejection episodes?
- Do they know the cause of their end-stage renal disease?
- What mode of dialysis were they on prior to transplantation?

Physical examination

See Fig. 1.1 for examination by area and Fig. 1.2 for examination by system.

General inspection

Short stature
(CKD in childhood)
Weight
Pallor
Brown-yellow skin hue
'Sallow' complexion
Hearing aid/hearing impairment
(Alport's syndrome)
SVC obstruction
Evidence of past or present
haemodialysis access
(e.g. tunnelled lines,
scars from previous
dialysis lines, AV fistula)

Forearms

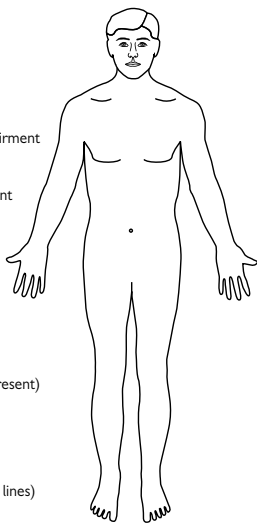
Myopathy
Bony tenderness
(hyperparathyroidism)
Dialysis access (past or present)

Nails

Brittle
Leuconychia
Splinters (SBE)
Transverse ridges (Beau's lines)

Face

Periorbital oedema



Mouth

Fetor
Oral hygiene (SBE)
Gum hypertrophy
(ciclosporin)
Oral candida
(immunosuppression)

Hands

Metabolic flap
(severe uraemia)
Shortening of distal
phalanges + pseudoclubbing
(severe hyperparathyroidism)

Raynaud's
Sclerodactyly
Calcinosis } Systemic
sclerosis

Skin

Dry
Scratch marks
Bruising
(uraemic bleeding tendency)
Vasculitic rash
Subcutaneous nodules
(soft tissue calcification)
Uraemic frost
(severe uraemia)
Transplant patient:
cutaneous malignancies

Fig. 1.1 Examination by area.

Neurological

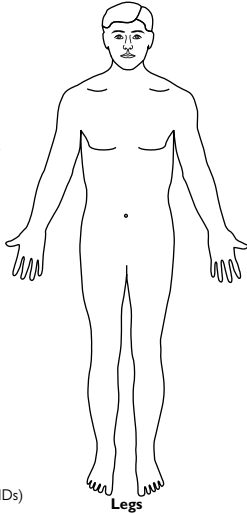
Conscious level
Mental state
Myoclonic jerks
Seizures
Tetany
(hypocalcaemia)
Peripheral neuropathy

Cardiorespiratory

Respiratory pattern
(? Acidosis)
Blood pressure
JVP
Oedema
Carotid bruits
Apex beat
Heart sounds
Pericardial rub
Lung fluids
Pulmonary oedema
Effusion

Musculoskeletal

Bony deformity
Joint inflammation
Osteoarthritis (? NSAIDs)

**Legs**

Peripheral pulses
Oedema
Femoral bruits
Restless legs

Ophthalmic

Dry, red, or painful eyes
(iritis, episcleritis)
Corneal calcification

Retina

Hypertension
Diabetes mellitus
Vasculitis
Cholesterol emboli

Abdomen

Scars
? Tenckhoff catheter
Ascites
Palpation:
Loin tenderness
Palpable kidney(s)
Palpable bladder
Transplant kidney
(right or left iliac fossa)
Abdominal bruit
Rectal (prostate) } Obstruction
Pelvic exam

Fig. 1.2 Examination by system.

Palpating the kidneys

- The kidneys are generally only palpable in very thin patients.
- The right kidney is more accessible than the left.
- Place the left hand posteriorly in the loin and the right hand on the abdomen lateral to the umbilicus.
- On deep inspiration, the lower pole may be palpable by pushing the right hand gently inwards and upwards.
- The normal kidney surface usually feels firm and smooth.
- 'Balloting' the kidney refers to palpation whilst pushing up firmly from behind. Using this technique, it may be possible to gently 'bounce' an enlarged kidney back and forth between the hands.

Physical examination: the circulation

► The ability to assess the volume status of a patient is critical to the practice of renal medicine. In the vast majority of cases, it can be achieved at the bedside without invasive monitoring.

Hypovolaemia

Salt and water (or blood) loss leads to ↓ effective circulating volume and eventual shock. Signs include:

- ↓ BP (and ↓ pulse pressure).
- Postural ↓ BP (fall in SBP >10mmHg); if it is not possible to stand the patient up, then BP measurements with the patient supine, and then with the head of the bed raised, can be helpful.
- Sinus tachycardia and postural ↑ HR (↑ in HR >10 beats/min).
- ↓ JVP. Neck veins flat, even if supine.
- Cool peripheries and peripheral vasoconstriction (△ septic patients may be vasodilated and warm).
- Poor urine output (UO).
- Decreasing weight.
- Positive response to a fluid challenge.
- Positive passive leg raising test.

(Much) less reliable signs include:

- ↓ capillary refill, poor skin turgor (forehead and anterior triangle of the neck), dry mouth and mucous membranes, sunken eyes.

Hypervolaemia

Increased ECF volume may be found with ↑ intravascular volume, ↑ interstitial space volume—or both. △ It is possible to be simultaneously salt- and water-overloaded and intravascularly depleted (e.g. CCF or a nephrotic patient receiving diuretics). See Box 1.3.

Box 1.3 Volume expansion and overload

Increased circulating volume	Increased interstitial fluid
↑ BP	Peripheral or generalized oedema
Elevation of the JVP	Pulmonary oedema (tachypnoea, tachycardia, a third heart sound ± basal crackles)
	Pleural effusion(s)
	Ascites
	Increasing weight

Both fluid depletion and fluid overload are harmful. Extremes can be relatively easy to recognize, but it is difficult to consistently diagnose euvolaemia, i.e. the point at which fluid administration is no longer necessary. Clinical assessment relies on frequent evaluation of the patient's response to fluid challenges. In case of progressive AKI, particularly in the context of multi-organ dysfunction, a referral to critical care for haemodynamic monitoring should be considered.

Invasive monitoring: a primer for the non-intensivist

In critically ill patients, the main priority is to reverse/prevent organ (including renal) dysfunction through restoration of tissue perfusion and O_2 delivery. This involves the optimization of fluid status and cardiac output (CO) (*reminder*: O_2 delivery = heart rate \times stroke volume \times O_2 saturation \times Hb \times 1.36).

The aim of haemodynamic resuscitation is to avoid both fluid depletion and overload (i.e. patient '*not too dry and not too wet*') and to optimize CO whilst avoiding excess catecholamine ('*enough but not more*'). To achieve these goals, clinical assessment may be unreliable, and non-invasive haemodynamic monitoring is often desirable—especially in patients with sepsis, hypoproteinaemia \pm cardiac failure.

Measurement of cardiac output

Historically, haemodynamic monitoring centred on measurement of CVP and pulmonary artery occlusion pressure (PaOP or 'wedge pressure'). However, many studies demonstrated that these do not accurately correlate with fluid status and cardiac performance, particularly in patients with cardiac failure. Instead, more dynamic parameters have increasingly supplanted them, e.g. variation in stroke volume, arterial pressure, or pulse pressure after a fluid challenge. Evidence remains light; other than for passive leg raising, there is little evidence underpinning the use of dynamic variables for prediction of volume responsiveness in non-ventilated patients.

Haemodynamic monitoring used in the critical care environment

- **Pulmonary artery catheter (PAC):** insertion of a balloon-tipped catheter into the pulmonary artery allows measurement of CVP, right atrial pressure, right ventricular pressure, pulmonary artery pressure, PaOP, CO, and mixed venous O_2 saturation. ⚠ Utility remains controversial. Associated with significant risks (Δ damage to chordae, arrhythmias, rupture of pulmonary artery). Use decreasing.
- **Echocardiography:** an excellent tool for assessment of haemodynamics but operator-dependent and not a continuous technique.
- **Oesophageal Doppler:** measures blood flow velocity in descending aorta (correlates with CO). Non-invasive but dependent on operator's skill and placement/positioning. Not tolerated in non-ventilated patients.
- **Lithium dilution technique:** measures CO via rate of change in lithium chloride concentration between venous and arterial system. Requires arterial line and CV line. Suitable for non-ventilated patients.
- **Pulse contour analysis:** continuous measurement of CO and stroke volume variation, using the arterial waveform. Underlying principle: the contour of the waveform is proportional to stroke volume and the mechanical properties of the artery. Stroke volume is calculated by the change from end-diastole to systole over time. Requires an arterial line. Can be used in non-ventilated patients.
- **Thoracic electrical bioimpedance:** CO measurement via electrodes on the patient's chest and neck. Non-invasive. Less accurate with pulmonary oedema, pleural effusions, and chest wall oedema. Specialist expertise required, so not in routine use.

Urine: appearance

► Examination of the urine should be considered a routine extension of the physical examination in all patients.

Appearance

- Depending on concentration, normal urine is clear or given a light yellow hue by urochrome and uroerythrin pigments.
- Cloudy urine may result from high concentrations of leucocytes, epithelial cells, or bacteria. Precipitation of phosphates can also produce turbidity in urine refrigerated for storage.
- Specific circumstances result in characteristic changes in the appearance of the urine that may assist diagnosis at an early stage (see Box 1.4).
- Blood causes a pink to black discoloration, depending on the number of RBCs and length of time present.
- Jaundice (conjugated hyperbilirubinaemia) may cause dark yellow or brown urine.
- Haemoglobinuria from intravascular haemolysis (📖 p. 155) and myoglobinuria from muscle breakdown (📖 p. 152) are both causes of dark urine that tests +ve for blood on dipstick examination. However:
 - If the sample is centrifuged, the supernatant will remain coloured and continue to test +ve.
 - No red cells are seen on microscopy.
 - Specific assays for haemoglobin and myoglobin are available.
- Normal urine tends to darken on standing (urobilinogen oxidizes to coloured urobilin) (see Box 1.4).
- Chyluria is a rare cause of turbid urine. It has a milky appearance (particularly after fatty meals) and settles into layers on standing. Results from a fistulous connection between the lymphatic and urinary systems (usually malignancy, though lymphatic obstruction by *Filaria bancrofti* is more important worldwide).
- Beetroot can produce red urine due to enhanced intestinal absorption of the pigment betalaine in genetically susceptible individuals. Rarely causes diagnostic confusion.

Odour

Offensive urine usually denotes infection (bacterial ammonium production). Sweet urine suggests ketones. Certain rare metabolic diseases confer characteristic smells—one can only hope to encounter maple-syrup urine disease before isovaleric acidaemia ('sweaty feet urine') (see Box 1.5).

Pneumaturia

- The presence of air bubbles in urine suggests a vesicocolic fistula.
- Causes:
 - Diverticular disease.
 - Colonic cancer.
 - Inflammatory bowel disease.

Box 1.4 Coloured urine

Causes of a coloured urine

- Beetroot ingestion (red).
- Blood (pink/red to brown/black).
- Chloroquine (brown).
- Chyluria (milky white).
- Haemoglobin (pink/red to brown/black).
- Hyperbilirubinaemia (yellow/brown).
- Methylene blue (er ... blue).
- Myoglobin (pink/red to brown/black).
- Nitrofurantoin (brown).
- Onchocerciasis (black).
- Phenytoin (red).
- Propofol (green).
- Rifampicin (orange).
- Senna (orange).

Urine that darkens on standing

- Alkaptonuria (homogentisic acid).
- Imipenem-cilastin treatment.
- Melanoma (melanogen).
- Methyl dopa.
- Metronidazole.
- Porphyruria (porphobilinogen).

Box 1.5 Proust's chamber pot

While Proust wrote lyrically about the unusual bouquet of his urine following asparagus ingestion, there are many who remain oblivious to a phenomenon instantly recognizable to others.

Two potential explanations for this olfactory diversity have been offered: (i) the production of the required fragrant metabolites is subject to variation through genetic polymorphism, i.e. some individuals excrete the perfumed compound(s), while others do not; (ii) everyone produces the metabolite(s), but only some have the necessary olfactory talent required to detect it/them.

The genetics are not straightforward, although an association between the ability to notice one's own 'asparagus urine' and a cluster of olfactory receptor genes on chromosome 1 has been described. Even the identity of the relevant substances remains uncertain, with a plethora of sulphur-containing compounds, such as methanethiol and dimethyl sulphide, proposed as the culprits.

Overall, it seems likely that there is genetic variation and that the two theories are not mutually exclusive, i.e. those who produce asparagus-perfumed urine may not always be able to detect it, while those who can might not necessarily produce it themselves.

Urinalysis: chemical analysis

Osmolality and specific gravity

Specific gravity

Refers to the weight of a solution, with respect to an equal weight of distilled water (normal range 1.003–1.035 in urine). Can be estimated with a dipstick, but, for accurate measurement, an osmometer (urinometer) is required.

Osmolality

Refers to the solute concentration of a solution. It cannot be measured with a dipstick. In the absence of significant glycosuria, the concentrations of Na^+ , Cl^- , and urea are the most important determinants in urine. The ability to vary urine osmolality (range 50–1350mOsmol/kg) plays a central role in the regulation of plasma osmolality (maintained across a narrow range: 280–305mOsmol/kg).

Generally speaking, specific gravity and osmolality correlate. An exception is when relatively large particles, such as glucose, proteins, and radio contrast media, are present in the urine. These produce an \uparrow in specific gravity, with little change in osmolality.

Uses

Investigation of polyuria and hypo-/hypernatraemic states (📖 p. 782). Recurrent stone formers can monitor their own urine specific gravity to maintain a dilute urine that discourages stone development.

Isosthenuria

CKD leads to a progressive \downarrow in the range of urinary osmolality that the kidneys can generate. In advanced renal insufficiency, the osmolality becomes relatively fixed at $\sim 300\text{mOsmol/kg}$ (~ 1.010 specific gravity)—close to that of glomerular filtrate. In this situation, the urine cannot be adequately concentrated or diluted in response to Na^+ and water depletion and overload, respectively. This is termed isosthenuria.

Urinary pH

Urinary pH ranges from 4.5 to 8.0 (usually 5.0–6.0), depending on systemic acid–base status. Most people (except vegans) pass acidic urine the majority of the time. Isolated urinary pH measurements provide very little useful information. Their main clinical use is the investigation of systemic metabolic acidosis. In this situation, a fall in urinary pH (to around 5) is expected, as acid is excreted. Failure of this response may indicate renal tubular acidosis (📖 p. 824). Most urine dipsticks have an indicator strip for estimation of pH, but, if a tubular disorder is suspected, a pH meter should be used.

In certain situations, the therapeutic manipulation of urinary pH might be useful (see Box 1.6).

Box 1.6 Therapeutic urinary alkalization

(🔍 see relevant chapters.)

- Urinary stone disease (cysteine and urate stones) (📖 p. 716).
- Poisoning (📖 p. 909):
 - Salicylates.
 - Barbiturates.
 - Methotrexate.
- Rhabdomyolysis (📖 p. 152).
- AKI 2° to cast nephropathy in myeloma (📖 p. 622).

Urinalysis: further tests

Further dipstick tests

Leucocyte esterase and nitrites

Increasingly used as indicators of infection. Detection of neutrophil esterase activity identifies white cells (pyuria), while the nitrite test exploits the ability of some urinary pathogens (though not all—notably certain Gram +ve organisms, including *Strep. faecalis*, *Staph. albus*, *Neisseria gonorrhoeae*, as well as many *Pseudomonas* spp. and mycobacteria) to reduce nitrate → nitrite. Positivity requires an adequate dietary nitrate intake as well as sufficient bladder dwell time (preferably >4h).

When combined, these methods possess good specificity (i.e. take seriously if +ve) though only modest sensitivity (i.e. treat a -ve result with caution if infection is likely clinically). ► While they can serve as a useful screening test in at-risk populations they are not a substitute for microscopy and culture.

Bilirubin and urobilinogen

- Conjugated (∴ water-soluble) bilirubin → biliary excretion → small bowel → converted to urobilinogen → distal reabsorption → partially excreted in the urine.
- This means: (i) unconjugated (water-insoluble) bilirubin does not pass into the urine (∴ dipstick +ve bilirubin indicates hepatic or cholestatic disease); (ii) the absence of dipstick urobilinogen in a jaundiced patient suggests biliary obstruction.

Glucose

Glycosuria results when tubular reabsorptive capacity for glucose is exceeded (plasma level >10mmol/L). A valuable screening tool, but less useful for diagnosis and monitoring of DM.

'Renal' glycosuria occurs when proximal tubular injury leads to a failure to reabsorb filtered glucose (📖 p. 76).

Causes of a +ve dipstick for ketones

- Dipsticks semi-quantitatively detect acetoacetate (but not β -hydroxybutyrate).
- A +ve test can be seen in:
 - Diabetic ketoacidosis (and occasionally severe intercurrent illness in T2DM).
 - Prolonged fasting and starvation diets (e.g. Atkins' diet).
 - Alcoholic ketoacidosis.
 - Severe volume depletion.
 - Isopropyl alcohol poisoning (hand-rubs, solvents, and de-icers).

Urinary test strips

A variety of test strips for urinalysis are available. Some have a specific purpose, e.g. Clinistix[®] (glucose), Hemastix[®] (blood), and Albustix[®] (albumin). Others cast a wider net, with various combinations of the following:

- Specific gravity.
- pH.
- Leucocytes.
- Nitrites.
- Glucose.
- Urobilinogen.
- Bilirubin.
- Ketones.
- Albumin or protein.*
- Blood.

*Dipsticks able to detect microalbuminuria are also available.

Urinalysis: protein

Introduction

- Urinary protein excretion should not exceed 150mg/day, of which less than 20mg is albumin.
- The remainder consists mainly of non-serum-derived tubular mucoprotein, such as Tamm–Horsfall/uromodulin.
- ↑ excretion of albumin is a sensitive marker of renal, particularly glomerular, disease (📖 p. 58).
- Protein excretion can be measured in untimed ('spot') or timed (usually 24h) samples.

Proteinuria (total protein) and albuminuria (albumin) are not strictly interchangeable terms. When screening for early renal disease, specific tests for albumin are preferable.

Dipsticks

Convenient, highly specific, but less sensitive. Contain pH-sensitive indicators that change colour when bound to negatively charged proteins. Predominantly detect albumin (some are albumin-specific, e.g. Albustix®) and may not identify large amounts of other proteins, e.g. Bence–Jones. Dipsticks have completely superseded sulphosalicylic acid turbidity testing.

A +ve result occurs with protein excretion ≥ 300 mg/L. Lower amounts of proteinuria, particularly in the context of diabetes, are termed micro-albuminuria (📖 p. 60) (defined as 30–300mg/day) and usually measured by ELISA or radioimmunoassay (although sensitive dipsticks are available).

Dipsticks are semi-quantitative. As a *rough* guide:

Trace	~0.15–0.3g/L
+	~0.3g/L
++	~1g/L
+++	~2.5–5g/L
++++	>10g/L

⚠ Changes in urinary concentration affect the result. If volumes are high and the urine dilute, large amounts of protein can go undetected (specific gravity may be a clue). Concentrated morning samples are \therefore preferable.

► If +ve dipstick test of $\geq 1+$, repeat after 1–2wk. If persistent, verify with a protein/creatinine ratio (uPCR) or albumin/creatinine ratio (uACR).

Timed collections

Historically, 24h urine collections were preferred to spot urine samples. However, they suffered from significant drawbacks, including inaccurate collection (see Box 1.7) and the time required for lab processing.


Box 1.7 uACR and uPCR (see also  p. 197)

- Untimed ('spot') urine samples are now used virtually universally for the detection and monitoring of proteinuria.
- Urinary excretion of creatinine generally remains constant (~10mmol/day).
- uACR and uPCR correct for variations in urinary concentration (caused by changes in hydration) and correlate well with measurements obtained from timed collections.
- A first morning urine specimen is preferable.
- ► The relationship between uACR and uPCR is non-linear (see Table 1.3).
- It can be helpful to multiply uPCR $\times 10$ to provide an estimate of 24h excretion, e.g. uPCR of 125mg/mmol approximates to 1.25g/24h.
- In the USA and in labs where urinary Cr is measured in mg/dL, rather than mmol/L, uACR is expressed as mg/g.
 - Normal: <30mg/g.
 - Microalbuminuria: 30–300mg/g.
 - Overt proteinuria: >300mg/g.
- uACR and uPCR will underestimate proteinuria when Cr excretion is high (black people, muscular build) and overestimate when Cr excretion is low (elderly, cachectic). However, they are useful for serial monitoring in individual patients.
- uACR is more sensitive than uPCR if screening for early disease in high-risk groups (especially diabetes), but total uPCR is an adequate alternative in most circumstances.
- Dipsticks that aim to estimate uPCR await further validation.

Table 1.3 Relationship between uACR and uPCR

uACR (mg/mmol)	uPCR (mg/mmol)	g/24h	Interpretation
3–30		<0.3	Microalbuminuria
30	~50	~0.5	Overt proteinuria
70	~100	~1	
300	~350	~3.5	Nephrotic range

Timed 24h collection: what to tell the patient

- Non-acidified, clearly labelled container.
- Pick a convenient day with minimum commitments.
- Discard first urine void on that day.
- Start collection—all subsequent urine into the container (including overnight).
- First void the following day into the collection.
- Since Cr excretion, or creatinine clearance (CrCl) ( p. 33), should be similar in two successive samples from the same patient, their measurement in 'back to back' 24h collections may enhance reliability (i.e. disregard the result if CrCl differs greatly between the two).

Urinalysis: red blood cells

Introduction

Haematuria is defined (arbitrarily) as the presence of two RBCs per high-powered field (hpf) in spun urine. The amount determines whether it is visible to the naked eye (macroscopic haematuria) or requires a dipstick or microscopy for detection (microscopic haematuria). Causes and investigation are considered later (📖 p. 62).

Dipstick

Hb induces a colour change (usually green) in a dye linked to organic peroxide. Dipsticks detect as little as two RBCs per field and are at least as sensitive as microscopic examination (though appreciable false -ve rate). However, if a dipstick is +ve, it is still desirable to perform confirmatory microscopy.

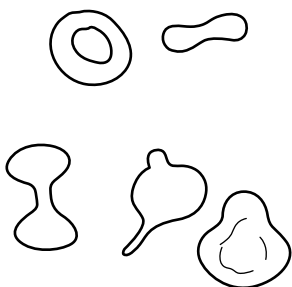
Dipsticks detect Hb and \therefore remain +ve, even after RBC lysis. They also detect haemoglobinuria from intravascular haemolysis as well as myoglobin from muscle breakdown (\rightarrow though red cells will be absent on microscopy in both situations).

Urine sediment

Regrettably, a dying art, but microscopic examination of the urine sediment remains a valuable investigation (see Box 1.8).

Urinary RBCs may have variable morphology (see Fig. 1.3). Those that have passed through the glomerular basement membrane and suffered osmotic stress in the tubules may have an abnormal appearance, best appreciated under phase contrast microscopy (see Box 1.8).

In expert hands, the presence of these 'dysmorphic' red cells can help distinguish glomerular from lower urinary tract bleeding. Δ However, the presence of dysmorphic cells does not rule out a lower tract lesion.



Non-glomerular bleeding:

Red blood cells have normal morphology

Glomerular bleeding:

Red blood cells that pass into the urine through an inflamed or damaged glomerulus may show budding, spiculation or other surface irregularities

Fig. 1.3 Morphology of red blood cells.

Box 1.8 Examination of the urine sediment


- Tell the patient to discard the first few mL of urine and then collect 20mL into a universal container.
- Process and analyse the sample within a few hours (red cell lysis!).
- Centrifuge a 10mL aliquot at 400g for 10min.
- Remove 9.5mL of supernatant with a pipette.
- Resuspend the pellet in the remaining 0.5mL of urine (gently!).
- Transfer a drop of resuspended urine to a slide.
- Cover the sample (unstained) with a coverslip.
- Examine (preferably) with a phase contrast microscope at 160 × and 400 × magnification.
- Cellular elements are quantitated as number per high-powered field.
- Look also for casts and other elements.
- Use polarized light to identify crystals.
- Clean the microscope, and discard all the urine!
- In an urgent situation, e.g. for rapid diagnosis of UTI, an unspun sample may be examined.
- It may be necessary to acidify the urine to prevent precipitation of (view-obscuring) phosphate crystals.



Urinalysis: cells, organisms, and casts

Leucocytes

Neutrophils: leucocytes are a prominent feature of urinary infection but may also be present in inflammatory renal conditions (GN, TIN). Sterile pyuria refers to the situation wherein leucocytes are seen consistently on microscopy, but subsequent culture is sterile.

Causes of sterile pyuria

- Partially treated UTI or fastidious organism (e.g. *Chlamydia*).
- Calculi.
- Prostatitis.
- Bladder tumour.
- Papillary necrosis.
- TIN.
- TB (send 3 × EMUs,  p. 696).
- Appendicitis.

Lymphocytes: may be a feature of chronic tubulointerstitial disease. *Eosinophils*: identified with Hansel's or Wright's stain. Associated with TIN ( p. 580) but also occasionally present in other conditions, including RPGN, prostatitis, and atheroemboli. *Renal tubular cells*: large, oval cells. Present in normal urine but ↑ in tubular damage (ATN or TIN). *Squamous epithelial cells*: large cells with small nuclei, often of urethral origin (or skin/vaginal contaminant). *Transitional epithelial (urothelial) cells*: suggest cystitis. *Malignant cells*: special stains, immunocytochemistry, and flow cytometry all assist detection ( p. 751).

Microorganisms

- *Bacteriuria*: normal urine is sterile. Simultaneous presence of leucocytes suggests true infection, rather than contamination. Gram staining enables initial identification and cell count while culture and sensitivity results are awaited.
- *Fungi*: *Candida* species are most frequently encountered. Typical appearance is that of a small pale green cell, often with visible budding. May result from genital contamination. Risk factors for colonization are: indwelling foreign body (ureteric stents, bladder catheter), DM, antibiotic therapy, and immunosuppression.
- *Trichomonas*: oval and flagellate (motile if alive). Usually a genital contaminant.
- *Schistosoma haematobium*: ova detection is an important technique in endemic areas.

Urine culture

M,C+S differentiates contamination from true infection and guides treatment. A pure growth of $>10^5$ colony-forming units (cfu)/mL is the conventional diagnostic criterion for urinary tract infection (📖 p. 707).

Casts

Casts are plugs of Tamm–Horsfall mucoprotein within the renal tubules, with a characteristic cylindrical shape. They are classified according to appearance and the cellular elements embedded in them. Though produced in normal kidneys, they can be valuable clues to the presence of renal disease (see Fig. 1.4).

Non-cellular casts

- *Hyaline casts*: mucoprotein alone and virtually transparent. A non-specific finding that occurs in concentrated urine.
- *Granular casts*: granular material (aggregates of protein or cellular remnants) is embedded in the cast. Often pathological but non-specific.
- *Broad or waxy casts*: hyaline material with a waxy appearance under the microscope. Form in dilated, poorly functioning tubules of advanced CKD.

Cellular casts

- *Red cell casts*: ► virtually diagnostic of GN.
- *White cell casts*: characteristic of acute pyelonephritis—may help to distinguish upper from lower tract infection. Also occur in TIN.
- *Epithelial cell casts*: sloughed epithelial cells embedded in mucoprotein. A non-specific feature of ATN. Also found in GN.
- *Fatty casts*: contain either lipid-filled tubular epithelial cells or free lipid globules. Distinguished from other casts by ‘Maltese cross’ appearance under polarized light. Occur in the lipid-laden urine of the nephrotic syndrome. Lipids may also appear as droplets or crystals. When clumped, these are referred to as *oval fat bodies*.
- *Other casts*: under the right conditions, any constituent of the urine (microorganisms, crystals, bilirubin, or myoglobin) may become entrapped in a mucoprotein cast.

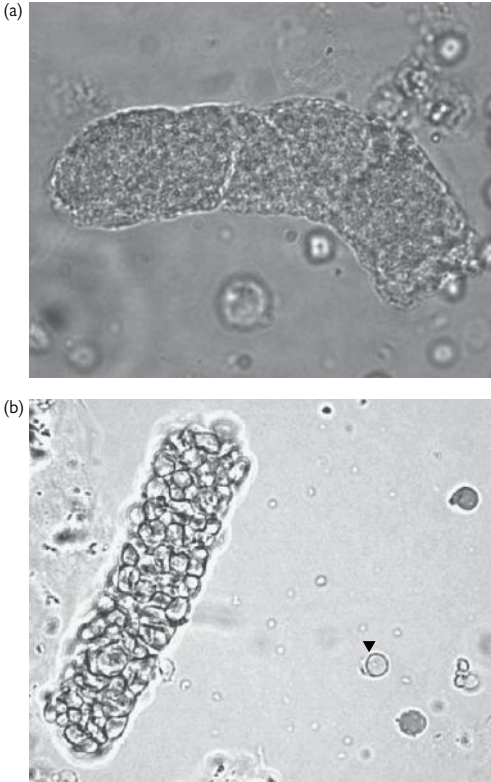


Fig. 1.4 a) Granular cast. b) Red cell cast. Reproduced from Barrett, J, Harris, K, Topham, P. *Oxford Desk Reference of Nephrology* (2008), with permission from Oxford University Press.

Urinalysis: crystals

Detected by examining the urine under polarized light (see Fig. 1.5).
⚠ Most crystals are clinically irrelevant.

Uric acid

Usually lozenges with a yellow-brown hue. Precipitate at acid pH. A few may be normal (e.g. high meat intake), but ↑ quantities may indicate hyperuricosuria. May be present in acute urate nephropathy (tumour lysis syndrome, 📖 p. 160).

Calcium oxalate

May be monohydrated (ovoid) or bihydrated (pyramidal—like the back of an envelope). Prefer an acidic pH but not always. A few may be normal (spinach and chocolate ingestion) but can denote hypercalciuria or hyperoxaluria (📖 p. 721). A diagnostic clue in ethylene glycol poisoning in both real life and exams (📖 p. 910).

Calcium phosphate

Heterogeneous in their appearance (→ needles, prisms, stars). Favoured by alkaline pH. Might be a risk factor for calcium stone formation.

Magnesium ammonium phosphate (triple phosphate)

Birefringent prisms ('coffin lids'). Prefer alkaline pH. If present, exclude a *Proteus* UTI.

Amorphous phosphates

Unattractive clumps in (alkaline) urine cooled for storage. No clinical significance.

Cystine

Hexagonal. Cystine is not a constituent of normal urine so always significant. Prefer acid urine. A marker of cystinuria (📖 p. 719).

Cholesterol

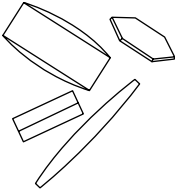
Thin plates with sharp edges. Occur with heavy proteinuria.

Drug-induced crystalluria

Many drugs can precipitate in the renal tubule. In severe cases this may cause AKI.

- Antibiotics: sulfadiazine, amoxicillin.
- Antiviral agents: aciclovir, valaciclovir, famciclovir, ganciclovir, valganciclovir, and indinavir.
- Methotrexate.
- Primidone (a barbiturate).
- Triamterene.
- Vitamin C (calcium oxalate deposition).

Uric acid



Calcium oxalate

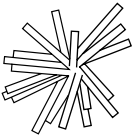
Bihydrated



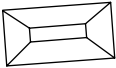
Monohydrated



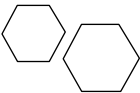
Calcium phosphate



Magnesium ammonium phosphate



Cystine

**Fig. 1.5** Urinary crystals.

Determining renal function

Introduction

Several aspects of renal function can be measured. The most important is glomerular filtration rate (GFR). Glomerular filtrate refers to the ultrafiltrate of plasma that crosses the glomerular barrier into the urinary space. GFR is measured per unit time (usually expressed mL/min) and represents the sum of filtration rates in all functioning nephrons (∴ a surrogate for the amount of functioning renal tissue).

GFR is relatively constant in an individual. ↓ GFR may result from a reduction in nephron number or a reduction in the GFR of single nephrons (↓ SNGFR). A reduction in number can be compensated for by an increase in SNGFR through elevated glomerular capillary pressure or glomerular hypertrophy (⚠ this means significant kidney damage may not initially be associated with ↓ GFR).

GFR is useful for:

- Providing a consistent measure of kidney function.
- Monitoring progression of CKD (and response to treatment).
- Forecasting the need for dialysis and transplantation.
- Determining appropriate drug dosing in renal impairment (📖 p. 874). It provides no information regarding the cause of renal insufficiency.

Measurement of GFR

- Measured indirectly by evaluating clearance from plasma of a (renally excreted) marker substance.
- Clearance: the volume of plasma from which this substance is removed per unit time.
- Suitable markers require certain characteristics shown in the following list and may be endogenous (e.g. Cr) or exogenous (e.g. inulin).
- Inulin, a fructose polysaccharide for which (along with flatulence) we have the Jerusalem artichoke to thank, remains the gold standard. Cost and technical considerations (it requires a continuous infusion) prohibit routine use.

Characteristics of an ideal clearance marker

- Safe to administer, economical, and easy to measure.
- Freely filtered at the glomerulus.
- Not protein-bound (able to distribute in the extracellular space).
- Present at a stable plasma concentration.
- No extra-renal elimination.
- Not reabsorbed, secreted, or metabolized by the kidney.

In clinical practice, GFR is estimated by one of the following means:

- Serum Cr (and, to a lesser extent, urea).
- Formulae based on the serum creatinine (estimated or eGFR).
- Creatinine clearance (CrCl) from a 24h urine collection.
- Isotopic clearance (e.g. EDTA-GFR or DTPA-GFR).

Aspects of renal function

- Glomerular filtration rate (GFR).
- Tubular function (including Na^+ and K^+ handling and urinary concentrating/diluting capacity).
- Acid–base balance.
- Endocrine function:
 - Renin–angiotensin system (RAS).
 - Erythropoietin production.
 - Vitamin D metabolism.

Not measured in clinical practice

- Autocrine (→ production of endothelins, prostaglandins, natriuretic peptides, nitric oxide).
- Protein and polypeptide metabolism (e.g. insulin catabolism).

Creatinine

Serum creatinine

- Convenient and inexpensive—the most commonly used indirect measure of GFR. It is estimated that it is measured over 300 million times annually in the USA.
- Generated from non-enzymatic metabolism of creatine in skeletal muscle. Production is proportional to muscle mass (20g muscle → ~1mg Cr). Little short-term variation in an individual.
- ~25% is derived from dietary meat intake (creatine mostly; creatinine if the meat is stewed).
- ↓ muscle mass (elderly, cachectic) → ↑ Cr production → overestimation of GFR.

$U_{Cr} \times V$ is relatively constant in the formula for CrCl (where V is volume).

So $CrCl = (\text{urineCr} \times V) / \text{plasmaCr}$

Becomes $CrCl = \text{constant} / \text{plasmaCr}$

Hence, serum Cr varies inversely with GFR: ↓ GFR → ↑ SCr (until a new steady state is reached).

- Cr meets many, but not all, of the criteria for a clearance marker. Shortcomings:
 - It is secreted by the proximal tubule (~10–20% when GFR is normal), so the amount excreted in the urine exceeds the amount filtered. As GFR falls, there is a progressive ↑ in tubular secretion until saturation occurs at SCr ~132–176 μmol/L (1.5–2.0 mg/dL); beyond this point, SCr rises as expected (see Fig. 1.6).
 - It undergoes extra-renal elimination by secretion and degradation in the GI tract. This becomes more important as GFR falls.
- When ↓ GFR is rapid, it takes time for a steady state to be reached and for SCr to ↑, i.e. SCr may initially be normal after a catastrophic renal insult.
- Traditionally measured using the Jaffé alkaline pictrate colorimetric assay. However, interference by non-creatinine chromogens created a tradition of overestimating Cr. Enzymatic methods on modern auto-analysers are generally more accurate, with less variability.
- Certain substances interfere with Cr, either through competitive inhibition of tubular secretion (cimetidine, trimethoprim, amiloride, spironolactone, triamterene) or assay interference (in the Jaffé reaction: bilirubin, ketoacids, vitamin C, glucose, and cephalosporins).

Creatinine clearance

CrCl is calculated as:

$$\text{CrCl} \times \text{plasma creatinine } (P_{Cr}) = \text{urine creatinine } (U_{Cr}) \times \text{volume } (V)$$

$$\therefore \text{CrCl} = (U_{Cr} \times V) / P_{Cr}$$

Example

- Serum Cr = 106 $\mu\text{mol/L}$
 - Urine Cr = 8800 $\mu\text{mol/L}$
 - Urine volume = 1.2L
 - $\text{CrCl} = (U_{Cr} \times V) / P_{Cr}$
 - $\text{CrCl} = (8800 \times 1.2) \div 106 = 99.6 \text{L/day}$
 - Conventionally, CrCl is shown in mL/min $\therefore \times 1000/1440$
 - $(99.6 \times 1000) / 1440 = 69.2 \text{mL/min}$
- (normal range: ♀: $95 \pm 20 \text{mL/min}$; ♂: $120 \pm 25 \text{mL/min}$)

⚠ Limitations

- Tubular secretion of Cr means that GFR is overestimated.
- Requires accurate urine collection.
- Heir to all the pitfalls inherent in Cr measurement.
- Even if collections are accurate, there is marked serial variation (15–20%).

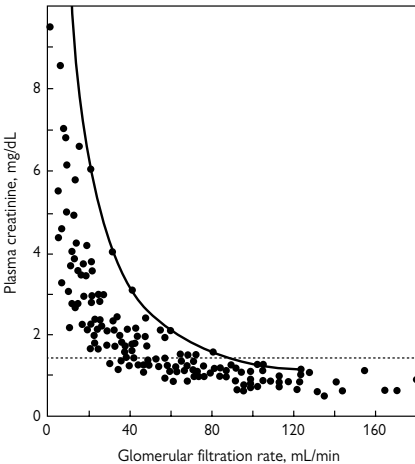


Fig. 1.6 The relationship between Cr concentration and GFR (measured as inulin clearance) in 171 patients with glomerular disease. The hypothetical relationship between GFR and Cr is shown in the continuous line, assuming that only filtration of Cr takes place. The broken horizontal line represents the upper limit of normal of serum Cr (1.4mg/dL or 115 $\mu\text{mol/L}$). It can be seen that, because of Cr secretion, serum Cr consistently overestimates GFR (reproduced from Shemesh O, Golbertz H, Kriss JP, et al. (1985) Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 28: 830–8, with permission from Nature Publishing Group.

eGFR

Introduction (see also p. 196)

In the last few years, it has become routine to estimate and classify kidney function and disease using equations based on the serum Cr. This is termed estimated or eGFR. Such equations attempt to correct for the confounding effects of body weight, age, sex, race, and muscle mass.

Limitations

Still based on Cr and do not take into account tubular secretion, extra-renal elimination, or differences in production between individuals of the same age and sex, or the same individual over time.

Cockcroft–Gault (CG)

$$\text{eGFR (mL/min)} = \frac{1.2 \times \{140 - \text{age (yr)}\} \times \text{weight (kg)}}{\text{Cr } (\mu\text{mol/L})}$$

Multiply $\times 0.85$ in ♀ to correct for reduced creatinine production.

MDRD

Widely used internationally and the current basis of CKD classification. Developed from data in the Modification of Diet in Renal Disease (MDRD) study. However, remains poorly validated in children (age <18 years), elderly (age >70 years), pregnancy, ethnic groups other than Caucasians and African Americans, and those without CKD.



eGFR, in mL/min per $1.73\text{m}^2 =$

$$(170 \times (P_{\text{Cr}} [\text{mg/dL}] \exp[-0.999]) \times (\text{Age} \exp[-0.176]) \times ((S_{\text{Urea}} [\text{mg/dL}] \exp[-0.170]) \times ((\text{Albumin} [\text{g/dL}] \exp[+0.318]))$$

- Multiply $\times 0.762$ if the patient is ♀
- Multiply $\times 1.180$ if the patient is black.
- Simplified version:

$$\text{eGFR} = 186.3 \times ((\text{serum creatinine}) \exp[-1.154]) \times (\text{Age} \exp[-0.203]) \times (0.742 \text{ if } \text{♀}) \times (1.21 \text{ if African American})$$

Notes: (i) to convert Cr from mg/dL to $\mu\text{mol/L}$, $\times 88.4$. To convert urea from mg/dL to mmol/L, $\times 0.357$; (ii) $\exp =$ exponential.

 CG tends to *overestimate* and MDRD *underestimate* GFR. Up to 25% of patients will be misclassified where either is used to categorize patients according to the KDOQI CKD scheme ( p. 192).

CKD-EPI equation

- The CKD Epidemiology Collaboration has pooled data from multiple studies to produce the CKD-EPI equation.
- Uses the same variables as MDRD.
- The study population included individuals with and without kidney disease over a wide range of GFRs.
- The equation provides a more accurate assessment of GFR in individuals with normal or only slightly ↓ GFR (particularly GFR >60mL/min), resulting in:
 - Lower estimates of population CKD prevalence.
 - More accurate prediction of adverse outcomes.
- There are still important limitations: ~50% will have an eGFR that is >16mL/min different from true measured GFR (although this represents a slightly improvement over MDRD).
- Although most laboratories currently report an MDRD eGFR, a move to adopt CKD-EPI for routine clinical use is likely to be increasingly advocated.

- The eGFR formulae are available as web-based and downloadable calculators.
 - <http://www.kidney.org/professionals/tools>
 - <http://www.renal.org/eGFRcalc>
- Several useful Apps are also available, e.g. National Kidney Foundation eGFR calculator, MedCalc, QxMD, MedMath, Epocrates.

Reciprocal of plasma creatinine

- There is an inverse relationship between GFR and SCr:
 $CrCl = \text{constant} / SCr$
- Plotting the reciprocal of SCr (1/SCr) against time will often, though not always, produce a straight line, the slope of the curve representing change in GFR with time.
- A logarithmic plot of SCr can be used in a similar way.
- This may be useful in two settings:
 - Extrapolation of the line can help predict when CKD is likely to reach ESRD and ∴ assist timely planning of RRT.
 - A change in the slope of the curve can be used to monitor treatment: a ↓ in the slope indicates slowed progression, while an ↑ may indicate a 2nd insult (acute-on-chronic kidney injury).

GFR measurement: other methods

Isotopic GFR

Several radiopharmaceuticals (^{51}Cr -EDTA, $^{99\text{m}}\text{Tc}$ -DTPA, ^{125}I -iothalamate) compare favourably to inulin for the measurement of GFR. Isotopic techniques are expensive.

Method

A single IV injection, followed by venous sampling at regular intervals (intervals \uparrow , as expected GFR \downarrow). Post-injection, plasma isotope activity \downarrow rapidly, as it distributes throughout the ECF. A slower exponential decline (renal elimination) then follows, allowing GFR to be determined. Protocols based on urine collection are also described.

With DTPA, renal elimination is often measured with a gamma camera positioned directly over the kidneys. While not as precise as venous sampling, it enables assessment of each individual kidney's contribution to total GFR (termed 'split function') (📖 p. 54).

Cystatin C

- The variable nature of Cr production has encouraged the search for alternative endogenous compounds that might help estimate GFR.
- Cystatin C, a 13kDa cysteine protease inhibitor, is the most developed of these.
- Produced by all nucleated cells and freely filtered at the glomerulus before tubular reabsorption and metabolism. Unlike Cr, it does not undergo tubular secretion, but a degree of extra-renal elimination is likely.
- Unfortunately, despite early optimism, several important 'non-GFR' determinants of cystatin C concentration have been identified.
 - Advancing age, male sex, diabetes, \uparrow BMI, \uparrow albumin, and \uparrow CRP are all associated with increased levels.
 - Relative high or low cell turnover, e.g. \uparrow/\downarrow thyroidism or steroid treatment (Δ transplant patients!), also cause variability.
- Several cystatin C-based eGFR equations have been formulated (as have equations that incorporate both cystatin C and SCr).
- At present, there remains considerable uncertainty as to any advantages for GFR estimation, both in the general population and existing CKD. Available data are frustratingly inconsistent.
- A shorter half-life and smaller volume of distribution led to an expectation that it might be a more useful marker in the non-steady state, particularly AKI. However, results have proved variable.
- There also appears to be no clear-cut advantage in the context of low muscle mass.
- Nonetheless, cystatin C appears to be a better predictor of adverse outcomes than either SCr or eGFR based on the SCr.
- There is also significant current inter-assay and inter-laboratory variability, although progress is being made toward standardization.
- Overall, it remains to be seen whether it will yet prove itself in selected circumstances and \therefore move into the clinical mainstream.

Urea

- Synthesized in the liver as a means of ammonia excretion.
- Rate of production not constant (unlike SCr).
- Inverse relationship with GFR.
- Influenced by a number of factors independent of GFR (see Table 1.4).
- Freely filtered at the glomerulus but reabsorbed in the tubules:
 - Urea movement is linked to water (under vasopressin influence) in the distal nephron.
 - ↓ renal perfusion → ↑ urea reabsorption → disproportionate ↑ urea compared to SCr.
 - May help to differentiate 'pre-renal' renal dysfunction (📖 p. 96).

Table 1.4 Influences on urea

↑ Ur	↓ Ur
<ul style="list-style-type: none"> ● High dietary protein intake ● GI bleeding ● Catabolic states <ul style="list-style-type: none"> • Haemorrhage • Trauma • Corticosteroids ● Tetracyclines 	<ul style="list-style-type: none"> ● Low protein diet ● Liver disease ● Pregnancy

Renal function in the elderly

The kidneys suffer significantly at the hands of the ageing process, with senescence associated with progressive glomerular and tubulointerstitial scarring, nephron loss, declining renal function, and downstream consequences for systemic haemodynamics. These changes begin (depressingly) in the 4th decade and hasten during the 5th and 6th, with increasing clinical relevance.

Pathology

Macroscopic features include thinning of the renal cortex and an overall decrease in renal size.

Glomerular

Basement membrane thickening, mesangial matrix expansion, capillary loop changes, periglomerular fibrosis, glomerular hypertrophy, glomerulosclerosis (~30% by age 80).

Tubular

Dilatation and atrophy (particularly in outer medulla), macrophage infiltration, and collagen deposition → interstitial fibrosis.

Vascular

Intimal hyperplasia (→ stiffness) of interlobular arteries and afferent arterioles.

Pathophysiology

- Glomerular hyperfiltration and hypertrophy → glomerular sclerosis and scarring → further glomerular hyperfiltration and hypertrophy.
- Intrarenal RAS activation → ↑ A2 → intrarenal (including podocyte) injury.
- Endothelial dysfunction → ↓ NO production → hypoxic and ischaemic damage.
- TGF- β overexpression → fibrosis.
- ↑ oxidative stress → tissue damage.
- AGE accumulation.
- Arteriolar hyalinosis → failure of autoregulation → glomerular injury.
- General biological senescence: telomere shortening, mitochondrial loss, and enhanced apoptosis.

Effect on renal function

GFR

The Baltimore longitudinal study (1958–1981) used serial measurements of CrCl to show a ↓ GFR of 0.75 mL/min/year. Recent studies have used inulin clearances to show that, although GFR progressively falls in older age groups (♂ > ♀), it is not necessarily an inevitability. There may be no demonstrable decline in normotensive, otherwise healthy, individuals, so it remains important to consider the effect associated comorbidities (↑ BP, vascular disease, CCF, etc.) may be having over and above age itself.

Assessment of GFR

SCr is less useful in the elderly because of (i) ↓ muscle mass and (ii) ↓ urinary Cr excretion. This means that formulae based on SCr (including MDRD, Cockcroft–Gault, and CKD-EPI) tend to underestimate GFR in those age >65 (and are not actually robustly validated in this population).

Additional effects of renal ageing

- ↓ renal plasma flow.
- Microalbuminuria and overt albuminuria more common.
- Regulation of Na⁺ balance is impaired (↓ excretion → contributes to ↑ BP in the context of a high-salt western diet).
- ↑ K⁺ more common (↓ excretion and ↓ aldosterone). The elderly are ∴ vulnerable to the effect of any medication interfering with K⁺ excretion (such as ACE-I).
- Water handling (both diluting and concentrating) ability is impaired. Potential consequences:
 - Nocturia is very common.
 - Inappropriately dilute urine (and reduced thirst response) despite ↑ plasma osmolality → dehydration.
 - Inadequate excretion following water load → hyponatraemia.
- Impaired distal tubular acidification (→ mild acidosis).
- ↑ EPO production (although the increase in response to a low Hb is actually blunted).
- Effects on mineral metabolism: ↑ PTH, ↓ calcitriol, and ↓ PO₄.

Clinical relevance

- ↓ muscle mass in the elderly → ↓ SCr.
- ► ↑ SCr in an elderly patient usually represents a significant ↓ GFR.
- Although age-related ↓ GFR is common anyway, it will be exaggerated in the presence of comorbidity, such as ↑ BP and vascular disease.
- ⚡ CKD is common in the elderly:
 - In NHANES (1999–2004), nearly ~45% of elderly subjects had CKD (📖 p. 194) by current criteria, with those aged >70 accounting for 50% of CKD overall.
 - However, is early CKD relevant in this age group? For example, GFR 50–59mL/min does not increase CV mortality in comparison to >60mL/min?
 - In view of this, many believe CKD is an unhelpful term in the majority of individuals in this age group.
 - The incidence and prevalence of ESRD is higher in the elderly (mean age of RRT is mid-60s).
- AKI and acute-on-chronic kidney disease are both more common.
- The elderly are more vulnerable to the effects of nephrotoxic drugs.
- The elderly are also more prone to electrolyte imbalances occurring through disease or inappropriate medical management (e.g. indisciplined perioperative fluid therapy).

Immunological and serological investigation

Introduction

Immunological and serological testing are widely (perhaps too widely) undertaken in the work-up of many forms of renal disease. Although helpful, such tests are rarely diagnostic in isolation and must always be interpreted in the context of a detailed clinical assessment.

There are a few common scenarios where the 'renal screen' is often performed (see Table 1.5):

- Unexplained AKI (📖 p. 119) or progressive CKD.
- For correlation with histology after a renal biopsy (📖 p. 82).
- During follow-up to assess disease activity or response to treatment.

Table 1.5 Immunological testing in kidney disease

Clinical context	Investigation
AKI where RPGN a possibility (📖 p. 71).	ANCA (📖 p. 640) Anti-GBM (📖 p. 656) ANA, anti-dsDNA (📖 p. 659) Complement components C3, C4
Microscopic haematuria	<i>Consider:</i> ANCA, anti-GBM
Proteinuria	<i>Consider:</i> ANA, anti-dsDNA C3, C4 <i>With consent:</i> HBV, HCV, HIV serology <i>Age >40:</i> Serum protein electrophoresis (SPEP) Urine protein electrophoresis (UPEP) Serum free light chains (SFLC)
Proteinuria with microscopic haematuria	As above, plus: ANCA, anti-GBM
Nephrotic syndrome (with or without evidence of a multisystem disease)	ANA, anti-dsDNA, C3, C4 <i>Age >40:</i> SPEP, UPEP, SFLC <i>With consent:</i> HBV, HCV, HIV serology
Unexplained CKD (particularly older age groups)	SPEP, UPEP
Suspected lymphoproliferative disorder	SPEP, UPEP, SFLC, cryoglobulins
Thrombotic microangiopathy (diarrhoea-negative)	Anti-ADAMTS13

Complement and the kidney

(See Tables 1.6 and 1.7.)

- Common investigations are immunoassays for C3 and C4 and a functional assay for the total haemolytic component (CH50).
- C3 and C4 measure circulating amount, while CH50 assesses activation (it measures the 50% red cell haemolysing dose of complement).
- C3 and C4 can be used to screen for classical and alternative pathway abnormalities, with diseases associated with high levels of circulating immune complexes associated with hypocomplementaemia.
- Low C3 implies tissue injury, with activation of either the classical or alternative complement pathway.
- Low C4 implies activation of the classical pathway (or a hereditary null allele).
- CH50 is a good screen for overall complement activity (e.g. a patient with recurrent infections).

C3 nephritic factor (C3Nef)

- A circulating IgG autoantibody against C3 convertase.
- It acts to stabilize C3 convertase to augment its function and increase the consumption of C3.
- Associated with MCGN type II (dense deposit disease).
- Measure when GN is associated with a persistently low C3.

Factor H

- An alternative pathway regulatory protein.
- Genetic deficiency is associated with familial haemolytic uraemic syndrome and predisposes to MCGN type II.

Table 1.6 C3, C4, and C50 in relation to kidney disorders

Disorder	C3 and C4
SLE	↓ C3, ↓ C4, ↓ CH50
Infective endocarditis	↓ C3, ↓ C4, ↓ CH50
Shunt nephritis	↓ C3, ↓ C4, ↓ CH50
Post-strep GN	↓ C3, ↓/↔ C4, ↓ CH50
Essential mixed cryoglobulinaemia	↔ C3, ↓ C4, ↓ CH50
MCGN type II	↓ C3, ↔ C4, ↓ CH50 ? C3 nephritic factor

Table 1.7 Antigens and their associations

Antigen	Association
Double-stranded DNA	SLE
Sm (Smith)	SLE
Ro/SSA and La/SSB	SLE, Sjögren's syndrome
Scl-70	Diffuse systemic sclerosis (SSc)
Centromere	Limited cutaneous SSc (CREST)
RNA polymerase	Renal involvement in systemic sclerosis
RNP	Mixed connective tissue disease

Diagnostic imaging: X-ray

Introduction

To select the most appropriate investigation (and maintain healthy relations with the radiology department), the requesting clinician should understand the indications and limitations of imaging in renal disease.

Plain X-ray

- 'KUB' (kidneys–ureter–bladder). Essentially, a supine AXR centred on the umbilicus.
- Main role is identification and surveillance of calcification (see Box 1.9). Lateral and oblique films may differentiate calcification *in line with*, as opposed to *in*, the renal tract.
- The medial edges of both psoas muscles are usually visible—disappearance suggests a perinephric mass or retroperitoneal collection.
- Tomography keeps one particular image plane in focus, blurring out images in front and behind. Moving the plane can produce serial 'cuts' that detect small calculi. Now largely superseded by CT.
- ⚠ Remember the radiation exposure of an AXR is 35 × that of a CXR.

Where are the kidneys on a plain AXR?

- Differences in attenuation between renal tissue and perinephric fat mean that the kidneys are (just) visible.
- Usually adjacent to the upper border of the T11 through to the lower border of L3.
- Normal renal size is 11–15cm (in adults). Kidneys appear bigger on an AXR than on ultrasound.
- Right kidney usually shorter than the left (upper limit of variation in length between right and left 1.5cm).

Box 1.9 Causes of renal tract calcification

Urinary calculi

Most are radio-opaque to some degree; exceptions are pure uric acid and xanthine stones.

Localized calcification

- Tuberculosis.
- Tumours.

Nephrocalcinosis

Medullary:

- Disturbed calcium metabolism:
 - Hyperparathyroidism.
 - Sarcoidosis.
 - Vitamin D excess.
 - Idiopathic hypercalciuria.
 - Oxalosis.*
- Tubular diseases:
 - Distal renal tubular acidosis.
 - Bartter's syndrome.
- Other:
 - Medullary sponge kidney.
 - Papillary necrosis.

Cortical:

- Trauma.
- Cortical necrosis.
- Oxalosis.*

*Causes both medullary and cortical calcification.

Diagnostic imaging: ultrasound

Introduction

A front-line investigation in many forms of renal disease. *Pros*: provides real-time two-dimensional images, non-invasive, relatively quick, and requires little patient preparation. *Cons*: operator-dependent, poor pelvi-ureteric detail, no functional information, may miss small stones and masses, and only limited 'snapshot' images are usually stored for later review.

Main uses

- Document one or two kidneys.
- Diagnosis of obstruction (pelvicalyceal dilatation).
- Measurement of renal size in CKD (see Table 1.8 for causes of abnormal renal size).
- Evaluation of renal masses (cystic vs solid).
- Screening for polycystic disease.
- Identify nephrocalcinosis and calculi.
- Evaluate bladder emptying.
- Estimate prostate size (may require a transrectal approach).
- Guide percutaneous procedures (e.g. renal biopsy, nephrostomy).
- Doppler USS can be used to evaluate arterial and venous blood flow. Widely used for transplant assessment, but role as a screening tool in renovascular diseases uncertain (📖 p. 586). (See Fig. 9.1 for USS of obstructed kidney.)

Normal appearances

- Renal length 9–12cm.
- Smooth outline.
- Cortex >1.5cm.
- Echotexture:
 - Medulla darker than cortex.
 - ↓ Corticomedullary differentiation with ↑ age and parenchymal disease (e.g. acute GN) (⚠ often over-reported and over-interpreted).
- Pelvicalyceal (PC) system poorly visualized.
- Bladder examined when full. Normal bladder wall thin and hard to delineate.

Table 1.8 Causes of abnormal renal size on imaging**Large kidneys**

- Unilateral:
 - Tumour.
 - Cyst.
 - Unilateral hydronephrosis.
 - Compensatory hypertrophy.
- Bilateral:
 - Polycystic kidney disease (and other cystic diseases).
 - Infiltration (e.g. lymphoma).

Small kidneys

- Unilateral:
 - Congenital hypoplasia.
 - Renal artery stenosis.
- Bilateral:
 - Small smooth kidneys:
 - Chronic glomerulonephritis.
 - Chronic interstitial nephritis.
 - Virtually any chronic renal disorder, except diabetic nephropathy.
 - Small irregular kidneys:
 - Reflux nephropathy.
 - Congenital dysplastic syndromes.
 - TB.
 - Renal infarction.

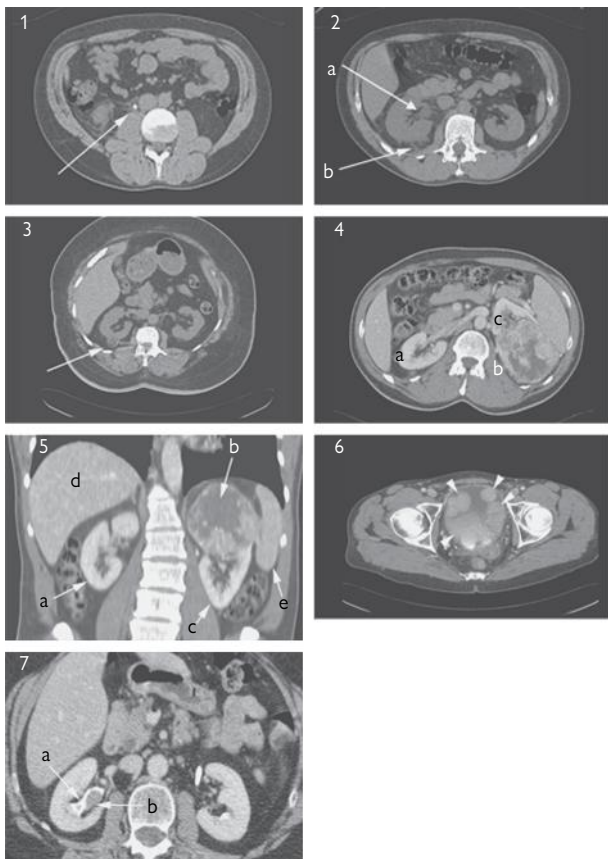


Fig. 1.7 CT scanning in renal disease. 1. Abdominal CT scan without contrast showing a calculus in the mid-ureter with stranding around it (arrow). 2. CT scan without contrast showing (a) a dilated pelvis and (b) perirenal stranding. 3. CT scan without contrast demonstrating a small solid lesion (arrow) containing fat (low attenuation), therefore, most likely to be an angiomyolipoma. 4. CT scan with contrast demonstrating (a) a normal right kidney, (b) a left renal tumour, and (c) remaining normal renal parenchyma on the left. 5. Reconstructed CT scan with contrast demonstrating (a) a normal right kidney, (b) a renal tumour in the left upper pole, (c) normal lower pole of the left kidney, (d) normal liver, and (e) spleen. 6. CT scan demonstrating multiple bladder tumours (arrowheads). 7. CT urogram demonstrating (a) contrast in the right collecting system and (b) a filling defect in the collecting system, consistent with a transitional cell carcinoma. Reproduced from Barrett, J, Harris, K, Topham, P. *Oxford Desk Reference of Nephrology* (2008), with permission from Oxford University Press.

Diagnostic imaging: CT and MRI

CT

Increased availability, better image resolution, and progressively shorter scanning times have significantly increased the routine use of CT for the investigation of the urinary tract (see Fig. 1.7 for CT scans).

Indications

- Characterization of a renal or perirenal mass:
 - Differentiation of simple cysts from tumours (📖 p. 742).
- Tumour staging.
- Delineation of renal or perirenal collections and abscesses.
- Detection of renal and ureteric calculi (CT-KUB) (📖 p. 724).
- Trauma: defines extent of renal and associated intra-abdominal injuries.
- Retroperitoneal disease:
 - Abdominal aorta, adrenal glands, retroperitoneal masses, fluid collections, lymphadenopathy.
 - Investigation of choice in retroperitoneal fibrosis (📖 p. 739).
- Obstruction: presence, level, and aetiology (📖 p. 732).
- Parenchymal infection:
 - Pyelonephritis may not show on USS or IVU.
 - Exclude associated pyonephrosis.
- 🏠 Renovascular disease (📖 p. 586).

Standard renal CT with contrast

Performed for the majority of the indications.

⚠ See Box 1.10, Contrast media (📖 p. 53).

CT-KUB

Performed without contrast to identify calculi.

CT-IVU

Contrast scan with sequences that focus on PC system and ureters.

Renal CT angiography (CTA)

Software reconstructs 3D images of the intra-abdominal vasculature.

Electron beam CT (EBCT)

Specialist tool for monitoring vascular, especially coronary, calcification (📖 p. 242).

MRI

Indications

- Evaluation of a renal mass and tumour staging:
 - In selected cases, e.g. venous invasion.
- MR urography (the MR equivalent of an IVU).

- Renal insufficiency:
 - Gadolinium is not nephrotoxic and is also safe if there has been a previous allergic reaction to iodinated contrast. ► However, gadolinium has been associated with the development of nephrogenic systemic fibrosis (NSF).
- MR angiography:
 - 📖 Detection of renovascular disease (📖 p. 586).

Gadolinium and nephrogenic systemic fibrosis

- The MR contrast agent gadolinium (Gd) has been implicated in the development of nephrogenic systemic fibrosis (NSF).
- NSF is a rare, painful, and often disabling, skin lesion that can progress to involve internal organs (including muscle, heart, and lungs). It was first described in the late 1990s and only occurs in renal failure.
- The dermatopathy appears scleroderma-like: erythema, plaques, induration, and peau d'orange, with the lower legs and forearms initially affected. Subsequent periarticular tissue involvement leads to contractures and immobility.
- Pathology: CD34 +ve fibrocyte proliferation, with dermal thickening. Gd may be detected in the lesions. Exact pathophysiology uncertain; however, Gd tissue deposition, with TGF- β -induced fibrosis and fibrocyte collagen production, appears important.
- Gd exposure has been implicated in >95% cases:
 - Free Gd is relatively water-insoluble (and highly toxic) so requires chelation for *in vivo* use.
 - These chelates may be ionic or non-ionic and linear or cyclical.
 - Ionic and cyclic forms bind Gd more avidly, perhaps explaining an apparent variance in risk between preparations, e.g. higher for gadodiamide and gadopentetate.
 - Gd chelates are renally excreted, so half-life is GFR-dependent.
 - NSF incidence increases greatly below GFR <30mL/min.
 - Most reports have been in dialysis patients.
 - Peritoneal dialysis (PD) patients may be at higher risk.
 - Risk is probably <5% for an ESRD patient exposed to Gd.
- Prevention:
 - If GFR <30mL/min (and especially GFR <15mL/min), Gd exposure should be limited to situations where it is deemed essential.
 - Avoid chelates that are more strongly associated with NSF, and limit the administered dose.
 - If already on maintenance haemodialysis, many dialyse the patient immediately after exposure (and again at 24h). This reduces Gd half-life, but additional evidence of benefit is lacking.
 - 📖 Some advocate haemodialysis for patients with stage 5 CKD (eGFR <15mL/min), even if not already established on maintenance RRT.
- In confirmed disease, transplantation offers the best chance of improvement.
- Cases should be reported to the International NSF Registry (📖 <http://www.icnfd.org>).

Diagnostic imaging: IVU

Intravenous urography

Provides a good overview of the urinary tract, particularly the PC system and ureters. Good for detecting calculi. However, the growth of CT, including CT urography, has seen a very significant decline in use (see Fig. 1.8 for IVU scan).

The procedure

- Ensure good bowel prep, NBM for 4h pre-procedure. If GFR normal, a fluid restriction of ~500mL/prior 24h assists contrast concentration (⚠ dangerous if ↓ GFR ∴ often avoided).
- Includes (film sequence altered, according to clinical situation):
 - Plain control film (? opacities pre-contrast).
 - Post-contrast: bilateral nephrograms (delayed: poor perfusion, obstruction, ATN, venous thrombosis), renal outline (? ischaemic scars, reflux, TB).
 - Further exposures at 5 and 10min (PC filling defects: clot, tumour, sloughed papilla, stone. PC deformity: reflux).
- Mild abdominal compression delays contrast excretion and may improve PC system views.
- Post-voiding film to assess bladder outflow.
- Delayed films (2, 6, 12, and 24h) may establish a level of obstruction.

Modifications

- *IVU with furosemide*: furosemide exaggerates and distinguishes PUJ obstruction from normal anatomical variants ('baggy' pelvis).
- *High-dose IVU*: used if ↓ GFR limits contrast excretion. Largely redundant where USS and CT are available.

Metformin

There is often apprehension that continued metformin use prior to IV contrast administration may contribute to contrast-induced AKI (CI-AKI) (📖 p. 148) post-procedure.

It is important to remember that metformin is not nephrotoxic. However, it does undergo renal excretion and may accumulate, potentially causing a severe lactic acidosis, if GFR deteriorates post-contrast.

The pre-contrast withdrawal of metformin does not reduce the risk of CI-AKI, but, if CI-AKI develops, metformin should be stopped immediately—with glycaemic control achieved by other means until GFR recovers.

Those with pre-existing significant renal impairment (eGFR <30mL/min) who are at particular risk of CI-AKI should almost certainly not be taking metformin anyway. This can be clarified with the responsible clinician. An eGFR of 30–60mL/min is a grey area, but there is no current recommendation to stop metformin, as long as the patient is supervised appropriately through the contrast procedure (📖 p. 149).

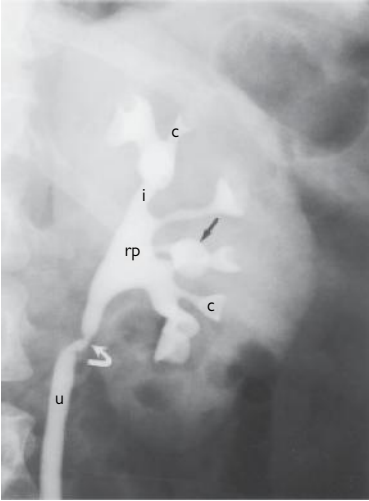


Fig. 1.8 IVU: magnified view of the left kidney. Calyx (c), infundibulum (i), renal pelvis (rp), proximal ureter (u). Calyx which projects posteriorly is seen *en face* (arrow). Normal fold of the ureter at the ureteropelvic junction (curved arrow). Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P *et al.* (eds) (2005). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford: Oxford University Press.

Box 1.10 Contrast media

- Organic radio-opaque iodides excreted by glomerular filtration.
- Modern non-ionic, iso-osmolar agents are better tolerated than their ionic, hyperosmolar (~1500mOsmol/kg) predecessors.
- Minor contrast reactions (urticaria, itching, nausea, vomiting, sneezing, metallic taste) common (5–10%), especially if history of allergy. Usually self-limiting, but antihistamines may help. Not necessarily associated with reaction on re-challenge.
- ► Severe reactions: ↓ BP, shock, pulmonary oedema, bronchospasm, and anaphylaxis. ►► Access to resus equipment is mandatory. Mortality historically estimated as 1 in 30,000 to 1 in 75,000 but lower with non-ionic media.
- Corticosteroids (e.g. prednisolone 30mg bd for 24h pre- + post-procedure) are often used if history of atopy or asthma (⚠ but do not guarantee non-reaction).
- Nephrotoxicity is dose-dependent and ↑ if dehydration, DM, pre-existing ↓ GFR, ↑ age, poor CV function (📖 p. 148).
- Prevention of nephrotoxicity and AKI is discussed on 📖 pp. 148–151.

Diagnostic imaging: nuclear medicine

Introduction

Nuclear techniques provide functional, as well as structural, information and can complement other imaging modalities. Three types:

- GFR estimation (e.g. $^{51}\text{Cr-EDTA}$) (📖 p. 36).
- Dynamic (e.g. $^{99\text{m}}\text{Tc-DTPA}$, $^{99\text{m}}\text{Tc-MAG 3}$): serial scans track renal uptake, transit, and excretion of an isotope. A time-activity curve is generated.
- Static (e.g. $^{99\text{m}}\text{Tc-DMSA}$): isotope is taken up and retained within functioning tissue. Demonstrates non-functioning ('scarred') renal tissue.
See Fig. 1.9 for diuretic renogram.

Radiopharmaceuticals

- $^{99\text{m}}\text{Tc-DTPA}$. Filtered at the glomerulus and neither reabsorbed nor secreted by the tubules. A good marker of GFR but limited utility in more severe renal impairment (e.g. $\text{SCr} > 200 \mu\text{mol/L}$ (~2.2mg/dL)).
- $^{99\text{m}}\text{Tc-MAG 3}$. Principally excreted by tubular secretion so useful if \downarrow GFR. Less background uptake than DTPA but more expensive.
- $^{99\text{m}}\text{Tc-DMSA}$. Filtered at the glomerulus, then reabsorbed and retained in the proximal tubules. Subsequent excretion is slow. Used for parenchymal imaging.

Applications

- Function of each kidney (termed 'split function') (DTPA, MAG 3, DMSA).
- Congenital abnormalities (DMSA), e.g. horseshoe kidney, ectopic pelvic kidneys.
- Chronic pyelonephritis and vesicoureteric reflux (DMSA) (📖 p. 712):
 - Focal scarring (more than one cause).
 - DTPA-cystogram: reflux follow-up and sibling screening.
- Renal transplantation: perfusion and obstruction.
- Acute kidney injury (📖 p. 120).
- Dilated vs obstructed renal pelvis:
 - A dilated pelvis may not indicate true obstruction.
 - Diuretic renography (DTPA or MAG 3) may differentiate the two.
- Arterial occlusion (DTPA, MAG 3): failure of perfusion.
- Captopril renography in renovascular disease (📖 p. 586):
 - In renal artery stenosis (RAS), perfusion and \therefore GFR are maintained by A2-mediated efferent arteriolar constriction. ACE-I administration will block this and alter the uptake and excretion of DTPA or MAG 3.
 - A positive scan suggesting RAS:
 - Asymmetry of size and function.
 - Delayed time to peak activity.
 - Cortical isotope retention.

- Sensitivity ↓ if bilateral disease, ↓ GFR, or pre-existing ACE-I therapy (stop 4–5d prior).
- Progressively superseded, as image reconstruction in CT and MR angiography has improved.

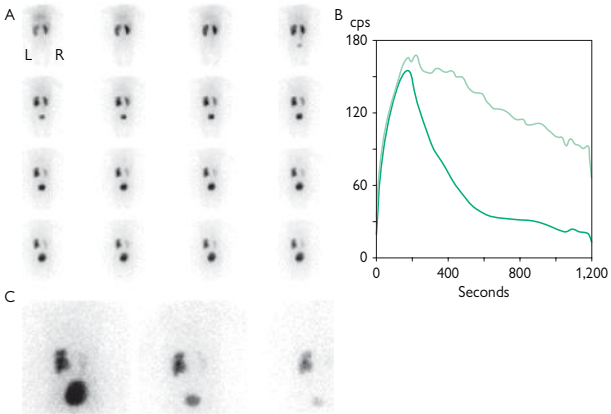


Fig. 1.9 Diuretic renography. Posterior views after 1 minute demonstrate preserved parenchymal function. The right kidney is normal, but the left appears dilated (A). The left (upper trace) and right (lower trace) renograms confirm nearly symmetric uptake of tracer, but abnormal outflow on the left (B). Images obtained after 20 min, post micturition and 50 min (from left to right) show residual activity within the left renal pelvis (C). Adapted from the *Journal of Nucl Med* 2006; 47, 11 (p1823) with the kind permission of the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

Diagnostic imaging: angiography and uroradiology

Renal angiography

Remains the gold standard investigation in renovascular disease, despite increasing promise within the chasing pack.

Technique

A retrograde catheter is passed under fluoroscopic guidance via a femoral puncture. A flush aortogram reveals number and location of renal arteries before selective catheterization (intravenous digital subtraction angiography (IVDSA) is generally inadequate). Contrast nephrotoxicity (📖 p. 148) is a concern, and CO₂ has been used as an alternative to iodinated media.

Indications

- Renovascular disease:
 - Invasive ∴ not an ideal screening test (📖 p. 586).
 - May be preferred when clinical suspicion for RAS is high, and there is an intention to proceed immediately to angioplasty and endovascular stenting.
- Acute renal ischaemia:
 - Acute emboli or thrombosis, traumatic occlusion, dissection.
 - Therapeutic intervention (e.g. thrombolysis) may be possible.
- Unexplained haematuria:
 - Vascular lesions (e.g. AVM, angioma). May allow embolization.
- Classical polyarteritis nodosa (PAN) (📖 p. 652):
 - Intrarenal microaneurysms.
- Renal transplantation:
 - Evaluation of donor anatomy prior to live kidney donation (📖 p. 374), although most now perform CT angiography in this situation.
- Bleeding post-renal biopsy:
 - Identify bleeding source (± therapeutic embolization).

Uroradiology

Urethrography and cystography

- Contrast → urethra ± bladder.
- Indications: trauma, urethral stricture, bladder diverticulae or fistulae.
- CT cystography increasingly used.

Micturating cystourethrography (MCUG)

- A contrast-filled bladder and urethra are visualized during voiding.
- Gold standard for diagnosis of VUR (📖 p. 712).
- Demonstrates reflux and dilatation/distortion of the ureters and PC system.
- Pressure-flow videocystometrography involves measurement of bladder pressures and urine flow rate, in addition to imaging.

Retrograde ureteropyelography

- The ureteric orifices are cystoscopically cannulated and contrast injected under fluoroscopic screening.
- Ureter, PUJ, and PC system can be visualized.
- May precede insertion of a retrograde ureteric stent.

Antegrade ureteropyelography (percutaneous nephrostomy)

- A needle is placed percutaneously into the renal pelvis under fluoroscopic or USS guidance.
- Contrast media is injected to evaluate PC, ureteric, and bladder anatomy.
- Urine → culture and cytology.
- Pressure studies can be undertaken in suspected PUJ obstruction (Whitaker test) (📖 p. 736).
- Indications: relief of urinary obstruction (📖 p. 734), dilation of ureteric strictures, antegrade stent placement, removal of calculi.


Ileal loopography

- The loop is filled with contrast, following the introduction of a Foley catheter.
- Upper tract dilatation is common after ileal diversion and free reflux of contrast into the ureters is almost universal—if not present, obstruction at the ureteric insertion (most common site) should be suspected.

Cystourethroscopy, ureteroscopy, and ureterorenoscopy

- Cystourethroscopy or cystoscopy involves a visual inspection of the inside of the urethra and bladder, using either a flexible (outpatient, no need for anaesthetic, little capacity to biopsy) or rigid (inpatient, anaesthetic, can biopsy if necessary) cystoscope.
- Undertaken by urologists, rather than radiologists.
- Indications include:
 - Investigation of micro- and macroscopic haematuria.
 - Recurrent UTIs.
 - Unexplained lower tract symptoms.
 - Surveillance of bladder tumours.
- Flexible ureterorenoscopy involves passing a small flexible fiberoptic transurethral endoscope through the bladder and as far up as the renal pelvis.
- Rigid ureteroscopy does not generally reach this distance and generally requires a general anaesthetic, although it does allow biopsies to be taken.


Clinical syndromes: proteinuria— introduction

Protein excretion <150mg/d is normal. ~30mg of this is albumin; the rest is LMW protein, including β_2 microglobulin, enzymes, and peptide hormones. A small proportion is secreted by the renal tubules, including Tamm–Horsfall mucoprotein (uromodulin) (see Table 1.9; see also  p. 20).

Why is abnormal proteinuria important?

- It is a marker of intrinsic renal disease, particularly glomerular injury.
- It is a risk factor for the progression of renal insufficiency.
- It is an independent risk factor for CV morbidity and mortality

What is the relevance of a positive dipstick for protein?

- Dipsticks predominantly detect albumin ( p. 20). They are generally +ve if protein excretion >300mg/d.
- Dipstick proteinuria has a prevalence of around 5% in healthy individuals (usually *trace* to *1+* range).
- Further evaluation is mandatory to distinguish 'benign' from 'pathological' proteinuria.

What is pathological proteinuria?

- Persistent protein excretion >150mg/d implies renal/systemic disease.
- The amount and composition depend on the nature of renal injury.
- Urinary electrophoresis can distinguish the source.

Glomerular

Failure of the glomerular barrier allows passage of intermediate and high MW protein. The most important cause of proteinuria in clinical practice. The predominant protein is albumin.

Tubular

LMW proteins, such as immunoglobulin light chains and β_2 microglobulin, normally pass through the glomerulus and are reabsorbed by proximal tubular cells. Damage to the proximal tubule disrupts this cycle and results in tubular proteinuria. \triangle This is not detectable on dipstick examination.

Overflow

Overproduction of LMW plasma proteins exceeds the capacity of the normal proximal tubule to reabsorb them. Causes: (i) immunoglobulin light chains in myeloma; (ii) lysozyme in monomyelocytic leukaemia. Dipstick examination will be negative; specific assays are required.

Secretory proteinuria

Protein added to the urine lower in the urinary tract (e.g. bladder tumour, prostatitis). Blood (>50mL/24h) will also cause proteinuria (but not albuminuria).

Table 1.9 Causes of protein excretion

Daily protein excretion	Cause
0.15–1.0g/24h	Mild glomerulopathies
	Orthostatic proteinuria
	Tubular proteinuria
	Overflow proteinuria
1.0–3.0g/24h	Probably glomerular
>3.0g/24h	Virtually always glomerular

NB Proteinuria >3g does not necessarily result in the nephrotic *syndrome* but is often referred to as nephrotic *range*. Proteinuria with accompanying microscopic haematuria strongly suggests glomerular disease.

When may proteinuria be ‘benign’?

Transient

- Fever.
- Exercise.
- Extreme cold.
- Seizures.
- CCF.
- Severe acute illnesses.

Persistent

- Postural (orthostatic) proteinuria:
 - Normal subjects demonstrate a small ↑ in protein excretion on standing. Postural proteinuria is an exaggeration of this.
 - Relatively common in young adults (~3–5%). Rare age >30.
 - Usually <1g/24h.
 - Diagnose with a ‘split’ urine collection: 16h daytime and 8h overnight collection (simpler: –ve dipstick (or uPCR) on waking, +ve at night).
 - Renal function remains normal, even after prolonged follow-up.
 - Remits with time (remains in ~50% cases at 10 years and <25% at 20 years).
 - Possible mechanisms: (i) trivial glomerular lesion; (ii) ↑ circulating A2 and noradrenaline when upright → ↑ glomerular permeability; (iii) renal vein entrapment between aorta and superior mesenteric artery → local haemodynamic disturbance (‘nutcracker’ syndrome—also a possible cause of microscopic haematuria).

Clinical syndromes: proteinuria

What is microalbuminuria?

- The term microalbuminuria describes albuminuria above the normal range (>30mg) but below the threshold of traditional dipsticks (<300mg).
- A misleading term, implying the albumin is of lower molecular weight. This is not the case—the ‘micro-’ prefix is simply meant to reflect the low amount.
- This has led to newer terminology, such as ‘moderately increased albuminuria’ for microalbuminuria and ‘severely increased albuminuria’ for macroalbuminuria.
- It is a sensitive indicator of:
 - Early renal disease.
 - CV risk in DM, ↑ BP, and several other conditions.
- It is detected by spot microalbumin/creatinine ratio, ultrasensitive dipstick, or radioimmunoassay on a 24h urine collection (📖 p. 20).

Clinical consequences

Mild proteinuria does not produce clinical sequelae. When more severe (>3–5g/d), a distinct clinical entity—the nephrotic syndrome—may result. Heavy proteinuria may cause frothy urine (↓ surface tension).

The nephrotic syndrome (📖 p. 554)

Urine albumin loss → ↓ serum albumin → oedema (through a variety of mechanisms). The concomitant loss of other serum proteins → hyperlipidaemia, thrombotic tendency, ↑ susceptibility to infection.

Selectivity of proteinuria

- This refers to size discrimination at the glomerulus.
- Highly selective → albumin and proteins of similar MW.
- Non-selective → larger proteins, including immunoglobulins.

Selectivity is calculated by comparison of IgG and albumin (or transferrin) clearance. This requires a sample of plasma and ‘spot’ urine specimen.

$$\text{Selectivity index} = \frac{\text{serum IgG} \times \text{urine Alb}}{\text{urine IgG} \times \text{serum Alb}} \times 100$$

≤10%, highly selective.

11–20%, moderately selective (limited discriminatory value).

≥21%, poorly selective.

- Limited clinical utility and rarely performed in practice.
 - May have a limited prognostic value—non-selective proteinuria suggests more severe injury to the glomerular apparatus.
 - In children: can identify the highly selective proteinuria of minimal change disease and potentially avoid the need for a renal biopsy.

Microalbuminuria and cardiovascular risk

- Microalbuminuria (or ‘high albuminuria’) is a marker of CV risk.
- This applies to the general population, not just DM or \uparrow BP.
- The mechanisms underpinning this association are poorly understood, but microalbuminuria, endothelial dysfunction, and chronic inflammation are interrelated processes that develop and progress together.
- Microalbuminuria can be correlated to the risk of stroke, MI, LV dysfunction, PVD, and death, e.g. in the HOPE (Heart Outcomes Prevention Evaluation) trial and follow up of the Framingham cohort.
- BP reduction is the key to microalbuminuria reduction—RAS blockade with ACE inhibitors or ARBs (or both) appears to be the treatment of choice.
- There is no present consensus on microalbuminuria screening in non-diabetics, though screening of hypertensive patients (and other high-risk groups) is advocated by some authorities; e.g. the American College of Cardiology (ACC) and American Heart Association (AHA).
- See Fig. 1.10 for management.

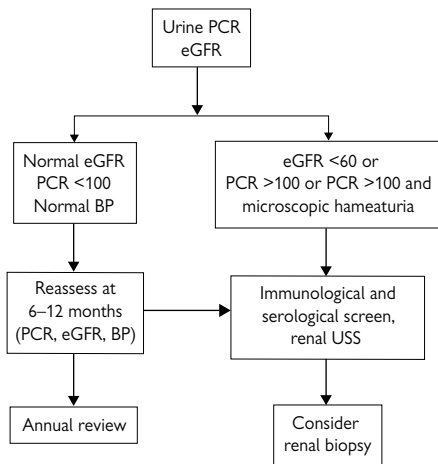


Fig. 1.10 Suggested outline management of proteinuria. NB Immunological and serological screen see p. 40.

Clinical syndromes: haematuria— introduction and classification

Introduction

Can result from bleeding at any site in the urinary tract, from the kidney to the tip of the urethra. Causes range from benign to serious (see Table 1.10).

Classification

Macroscopic vs microscopic

- *Macroscopic*:
 - Blood is visible to the naked eye. Gross haematuria startles the patient and ∴ presents early.
 - The patient may not recognize blood and report discoloration (pink, smoky, cola, or tea-like).
 - ► Macroscopic haematuria always requires investigation (presenting complaint in ~85% of bladder and ~40% of renal tumours).
 - Heavy bleeding with clot formation almost never occurs in glomerular disease.
- *Microscopic* (📖 p. 66):
 - Blood only visible under high-powered microscopy.
 - Often detected on dipstick examination in an asymptomatic patient.

Glomerular vs non-glomerular

Provides a framework for considering pathology. Both can present with macro- or microscopic bleeding (particularly non-glomerular haematuria). Always assume bleeding is non-glomerular (particularly age >40) until investigation proves otherwise. Locally agreed nephrological and urological referral and management pathways are highly desirable, particularly for microscopic haematuria.

Transient haematuria

- Exercise ('joggers' nephritis').
- Menstruation.
- Sexual activity.
- Viral illnesses.
- Trauma.

Table 1.10 Important causes of haematuria by age and source

Origin	Age <40	Age ≥40
Glomerular	IgA nephropathy Thin basement membrane disease Alport's syndrome Focal GN (e.g. post-streptococcal) Other GN (e.g. variably present in membranous and diabetic nephropathies)	
Non-glomerular	Renal stones	Renal stones
Upper urinary tract	Pyelonephritis Polycystic kidney disease Medullary sponge kidney Hypercalciuria/ hyperuricosuria ± stones Renal trauma Papillary necrosis Ureteral stricture and hydronephrosis Sickle cell trait or disease Renal infarction or arteriovenous malformation Renal TB (? HIV) Renal vein thrombosis	Transitional cell tumour Renal cell carcinoma Polycystic kidney disease Pyelonephritis Papillary necrosis Renal infarction Ureteral stricture and hydronephrosis Renal TB Renal vein thrombosis
Lower urinary tract	Cystitis, prostatitis, and urethritis Benign bladder, ureteral polyps, and tumours Bladder cancer Prostate cancer Urethral stricture <i>Schistosoma haematobium</i>	Cystitis, prostatitis, and urethritis Bladder cancer Prostate cancer Benign prostatic hypertrophy Benign ureteral/bladder tumours
Uncertain source	Exercise haematuria Unexplained haematuria Over-anticoagulation Factitious haematuria	

Clinical syndromes: haematuria assessment

Clinical assessment

History

- How much bleeding? Is the urine discoloured or frankly bloody?
- Recent trauma? May be relatively trivial, e.g. contact sports.
- Previous episodes?
- History of stone disease?
- Relevant medications? Anticoagulants should not cause haematuria if the INR is in the required range.
- Recent instrumentation of the urinary tract?
- Any associated urinary symptoms? Urinary infection?
- Pain?
 - Sudden onset of colicky flank pain suggests a stone.
 - Suprapubic pain may indicate infection or clot colic.
 - ► Painless macroscopic haematuria indicates a tumour until proved otherwise.
- What part of the stream?
 - Initial haematuria suggests an anterior urethral lesion.
 - Terminal haematuria usually arises from the posterior urethra, bladder, bladder neck, or trigone.
 - Continuous haematuria usually originates at, or above, the level of the bladder.
 - Cyclical haematuria in ♀ suggests endometriosis of the urinary tract.
- Risk factors for urothelial malignancy (📖 p. 750)?
- Recent skin or throat infection—post-streptococcal GN.
- Episodic macroscopic haematuria with throat infections is a classical presentation of IgA nephropathy (📖 p. 544).
- Recent travel? Schistosomiasis is the most common cause of haematuria worldwide (resist the temptation to swim in Lake Malawi!).
- Systemic symptoms, e.g. arthralgia, rashes, suggestive of an underlying inflammatory disorder?
- Family history of deafness (Alport's) or other renal disease?

Physical examination (signs usually scarce)

- Haemodynamically stable?
- Anaemia.
- Bruising/bleeding 2° bleeding diathesis.
- Skin or throat infections (→ post-infectious GN).
- Rashes, swollen joints (→ inflammatory condition, e.g. vasculitis).
- Cardiorespiratory:
 - Stigmata of endocarditis.
 - ↑ BP and oedema (→ glomerular disease).

- Abdomen:
 - Flank tenderness (→ stone disease, pyelonephritis).
 - Masses.
 - Bruit (→ AVM).
 - Prostate.
 - Consider testicular examination and VE (? misinterpreted vaginal bleeding).

Investigation of macroscopic haematuria

- Urinalysis:
 - ⚠ A -ve dipstick in a patient with documented macroscopic haematuria should not stop further investigation.
 - In heavy bleeding, the dipstick often tests +ve for protein: interpret with caution.
- Urine M,C+S: infection? Ova of *Schistosoma haematobium*?
- Urine cytology: malignant cells? Casts and dysmorphic red cells?
- FBC, U&E, clotting, G&S (± cross-match when severe), PSA, Hb electrophoresis in black patients.
- Imaging: CT, with and without contrast, is the investigation of choice. If unavailable, USS + IVU.
- Cystoscopy (in virtually all patients):
 - ± ureterography or ureteroscopy.
- Angiography (rarely). May demonstrate a vascular lesion.

Clinical syndromes: microscopic haematuria

Microscopic haematuria

Definition

Arbitrary. >2 red cells/hpf (📖 p. 22) (~10⁷ red cells/24h). However, it is usually a +ve dipstick, not a cell count that triggers investigation (dipsticks detect 2–5 cells/hpf).

Epidemiology

Reported prevalence varies widely (0.18–16.1%), reflecting differences in the definition used and population screened (particularly with respect to age). Common in both adults and children.

Predictive value

The proportion that has (or develop) significant disease depends on the group studied and thoroughness of investigation. Overall risk of malignancy (2–10%) is less than macroscopic haematuria (5–22%) but ↑ with age (see Table 1.11).

Table 1.11 Risk of malignancy

↑ Chance of malignant lesion	↑ Chance of glomerular lesion
Age >40	Proteinuria
History of gross haematuria	Dysmorphic red cells and red cell casts (📖 p. 22)
Analgesic abuse	Renal impairment
Smoking	↑ BP
Alcohol abuse	
Occupational exposures (📖 p. 750)	
Pelvic irradiation	
Previous cyclophosphamide treatment	

Evaluation

- Pay attention to risk factors in Table 1.11. See Fig. 1.11.
- Casts and dysmorphic cells (📖 p. 22).
- Imaging:
 - CT is the investigation of choice.
 - If unavailable, a combination of USS (alone: may miss small stones and renal tumours <3cm diameter) and IVU (alone: may miss tumours not involving the PC system) is generally used.
- Nephrology work-up: measure BP, FBC, U&E, eGFR; quantify proteinuria (uACR/uPCR); consider immunological and serological ('nephritic' or 'renal' screen (📖 p. 40) ± renal biopsy (📖 p. 82).

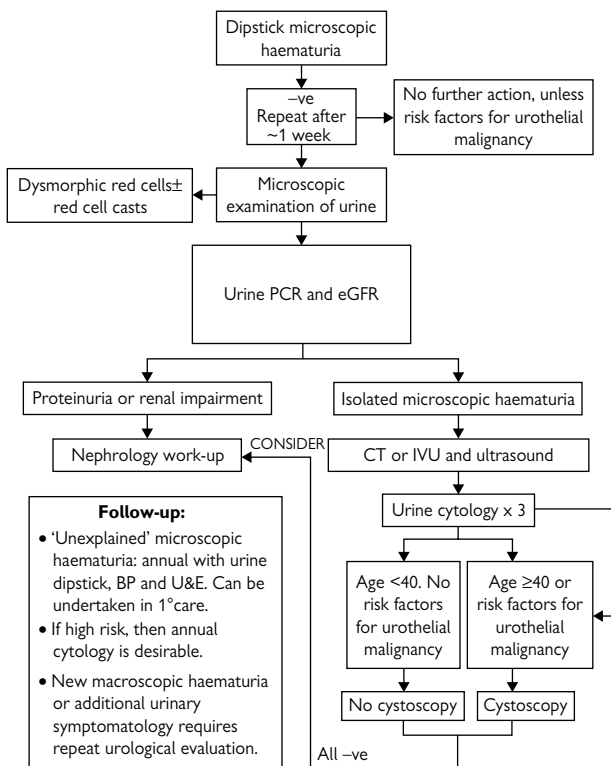


Fig. 1.11 Suggested management of microscopic haematuria. See notes on p. 66.

Clinical syndromes: microscopic haematuria screening

See Table 1.12 for causes of isolated microscopic haematuria.

Should we screen for microscopic haematuria?

• Two-thirds of physicians include dipstick examination for haematuria in health checks, but the benefits of screening are yet to be established.

Argument for

- Dipstick examination is easy, acceptable to patients, and inexpensive.
- It may assist early diagnosis of urological malignancies (where early intervention may be lifesaving) and intrinsic renal disease (where intervention may delay or prevent progression to ESRD).

Argument against

- Basic criteria for screening are not fulfilled.
- Dipstick testing is not sufficiently specific, and predictive values for both malignancy and renal disease are relatively poor.
- Benefits of early detection have not been established for either.

Microscopic haematuria and the risk of ESRD

- A recent longitudinal study of 1.2 million young individuals (aged 16–25) presenting for military service in Israel* found an initial 0.3% prevalence of persistent microscopic haematuria (with normal SCr and proteinuria <200mg/day).
- Males were affected twice as commonly as females.
- During 21 years' follow-up, ESRD developed in 0.7% of those with (and 0.045% of those without) initial microscopic haematuria.
- This gave an adjusted hazard ratio of 18.5.
- The mean age of ESRD treatment was earlier (34 vs 38) in the haematuria cohort and attributed mainly to glomerular disease.
- While the relevant advisory bodies do not presently advocate population screening, these recent data have led to a call for selected screening of younger patients so that they can be followed up more closely for the development of overt renal disease.

*Vivante A, Afek A, Frenkel-Nir Y, et al. (2011). Persistent asymptomatic isolated microscopic hematuria in Israeli adolescents and young adults and risk for end-stage renal disease. *JAMA*, 306, 729–36.


Table 1.12 Causes of isolated microscopic haematuria

Finding	Prevalence in 1689 adults (%)
Cancer	5.1
Stones	5.0
UTI	4.3
Renal disease	2.2
No source found	43.0

Sutton JM (1990). Evaluation of hematuria in adults. *JAMA*, **263**, 2475–80.

Clinical syndromes: CKD, AKI, and the nephritic syndrome

Chronic kidney disease (see Chapter 3)

The end result of any process causing renal parenchymal loss or damage. CKD implies an irreversible reduction in the number of functioning nephrons and is characterized by a progressive inability of the kidneys to fulfill their homeostatic responsibilities.  Always ensure that reversible factors have been excluded.

Classification


Previously termed chronic renal failure, with an arbitrary definition. The NKF-KDOQI classification is now almost universally used internationally (see Table 1.13).

Table 1.13 CKD: a brief primer (see  Chapter 3)


Stage	Description	GFR (mL/min/1.73m ²)
1	Asymptomatic urinary abnormalities	>90
2	Mild CKD*	60–89*
3	Moderate CKD	30–59
4	More severe CKD (complications more likely)	15–29
5 and 5D	Approaching or at ESRD	<15 or on dialysis (D)

* Patients with a GFR >60mL/min should not be considered to have CKD, unless there is concomitant evidence of kidney damage, e.g. urinary abnormalities (proteinuria, haematuria), structural abnormalities (e.g. abnormal imaging), genetic disease (e.g. APKD), or biopsy-proven disease.

Older nomenclature

Uraemia (or *uraemic syndrome*): the constellation of symptoms and signs produced as GFR declines (originally chosen to imply retention of urine in the blood). A multisystem disorder with a complex pathophysiological basis ( p. 212). Correlation of Ur and SCr with symptomatology is poor, so the diagnosis is part clinical, part biochemical.

Azotaemia: a term previously popular in the USA and used to imply retention of nitrogenous compounds. Typically refers to early CKD, sparing *uraemia* for symptomatic patients. Also attempts to play down the role of urea itself.

End-stage renal disease (ESRD): generally defined as a GFR ≤5mL/min. The initiation of renal replacement therapy (RRT) is generally required to maintain the patient's continued well-being (Note: RRT does not have to wait until the patient is symptomatically *uraemic*,  p. 267).

Acute kidney injury (AKI)

(📖 Chapter 2.)

The nephritic syndrome (📖 p. 536)

Acute post-infectious GN, particularly following pharyngitis or cellulitis with group A β -haemolytic streptococci, provides the historical prototype for this condition and remains relatively frequent in developing countries. Now commonly associated with a variety of other glomerular conditions (📖 p. 548).

Clinical features

- Haematuria (usually microscopic).
- Proteinuria.
- \uparrow BP.
- Circulatory overload and oedema.
- Oliguria.
- \downarrow GFR.

▶ Rapidly progressive glomerulonephritis (RPGN)

- The dramatic end of the nephritic spectrum, with rapid \downarrow GFR and (usually) oligo-anuria.
- Caused by an aggressive glomerular lesion, with extensive crescent formation (📖 p. 532).
- Other renal diseases can produce an identical clinical picture (e.g. acute thrombotic microangiopathy).
- ►► Seek expert help. This is a life-threatening fulminant illness, and recovery of renal function is rare without early treatment.

Hypertension (📖 Chapter 5)

The kidney has been described as both 'villain and victim' in \uparrow BP.

Hypertension in renal disease

- Underlying renal disease is found in a minority of patients with \uparrow BP, although the possibility should always be considered (an abnormal urine dipstick provides a simple clue).
- \uparrow BP may be a feature of any renal disease, although particularly common in glomerular and vascular diseases.
- Hypertension has an extremely important bearing on the progression of renal disease (📖 p. 203).

Renal disease in hypertension

- The normal kidney plays an important role in the pathogenesis of essential hypertension (📖 p. 452).
- The kidney is an important site of end-organ damage caused by \uparrow BP.

Clinical syndromes: pulmonary renal syndromes

Introduction

The combined presentation of an acute GN with pulmonary haemorrhage is one of the most dramatic scenarios in clinical medicine.

Causes

ANCA +ve vasculitis (📖 p. 640) ~60% cases. Anti-GBM or Goodpasture's disease (📖 p. 656) ~20%. Also SLE (📖 p. 658), Henoch–Schönlein purpura (📖 p. 650), cryoglobulinaemia (📖 p. 634), and rheumatoid vasculitis (📖 p. 669).

History

- The first report of a condition simultaneously affecting lungs and kidney was presented in 1919 by Ernest Goodpasture, following post-mortem studies during the 1918–19 influenza pandemic.
- Four decades later, the eponymous term Goodpasture's syndrome was adopted to describe comparable clinicopathological presentations.
- Subsequent realization that pulmonary renal syndromes are not a single clinical entity brought about further refinements to the nomenclature.
- Goodpasture's *disease* is now reserved for lung haemorrhage and crescentic GN in the context of anti-GBM disease (📖 p. 656).
- With hindsight, it is more likely that Goodpasture's original patient had a systemic vasculitis and not the disease that now bears his name.

Clinical features

- Acute nephritic syndrome (rapidly progressive renal failure with an active urinary sediment).
- Features of an underlying systemic condition may be present (e.g. cutaneous vasculitis, sinusitis, arthritis).
- Pulmonary haemorrhage:
 - Cough.
 - Dyspnoea.
 - Haemoptysis (extensive bleeding).
 - Anaemia (and iron deficiency).
 - Hypoxaemia and respiratory failure.
 - CXR: diffuse or patchy alveolar shadowing (indistinguishable from pulmonary oedema/ARDS).
 - CT: confirms air space filling.
 - Lung function: ↑ diffusion capacity for carbon monoxide (KCO).
 - Bronchoscopy: bloody bronchoalveolar lavage.

Other 'pulmonary renal' syndromes

Pulmonary haemorrhage is rare, but respiratory dysfunction and/or radiological abnormalities are common in AKI.

- Volume overload with pulmonary oedema.
- Infection:
 - AKI may accompany pneumonia and vice versa.
 - A vasculitis patient receiving immunosuppressive therapy will be at risk of opportunistic infections, including fungi, viruses, and TB.
 - Hantavirus.
- Pulmonary emboli.
- Acid–base disturbances.
- Acute respiratory distress syndrome (ARDS).

Hantavirus

- Members of the Hantavirus family are widely distributed globally and responsible for several clinical syndromes—often collectively referred to as 'haemorrhagic fever with renal syndrome'.
 - Puumala virus (Scandinavia, Western Europe) → milder renal disease.
 - Hantaan virus (Russia, China) and Dobrava virus (Central and Western Europe) → more severe renal disease.
 - Sin Nombre virus (North America) and Andes virus (South America) → cardiopulmonary syndrome.
- Spread: inhalation or contact (urine, faeces) with infected rodents (vectors include mice, voles, shrews as well as rats). Person-to-person transmission rare.
- Infection can be associated with significant morbidity and mortality, although <25% cases are severe (~0.5% mortality for milder European forms, reaching 5–10% for some others).
- Outbreaks can occur, e.g. during the Balkan war in the late 1990s.
- Clinical features:
 - Fever.
 - Respiratory failure (non-cardiogenic pulmonary oedema).
 - Systemic sepsis (and shock).
 - AKI (proteinuria, haematuria, vascular endothelial damage, acute tubulointerstitial inflammation).
- Diagnosis: clinical suspicion in endemic areas, serological testing, immunohistochemistry of biopsy material (including renal).
- Management: supportive. No specific antiviral therapy is effective.

Clinical syndromes: urine volume and urinary tract pain

Changes in urine volume

- Polyuria: >3L/24h.
- Oliguria: <400mL/24h.
- Anuria: <100mL/24h.

Polyuria

Excretion of a urine volume in excess of normal; >3L/day is an arbitrary cut-off. H₂O excretion is tightly controlled, so daily volumes vary widely in an individual.

It is usually frequency of micturition (especially overnight) 2° to the larger volume, rather than the volume itself, that causes the patient to present (although most patients with frequency do not have polyuria). Obtain a 24h urine collection for volume before undertaking further investigation.

Polyuria is seen in three clinically important situations (see Table 1.14):


- Excessive fluid intake.
- Increased tubular solute load, e.g. hyperglycaemia.
- Failure of the renal tubules to concentrate the urine (diabetes insipidus,  p. 789).

Table 1.14 Conditions associated with polyuria

↑ Fluid loss

Renal tubular	Nephrogenic diabetes insipidus, acquired tubular defect (e.g. caused by pyelonephritis, post-obstruction, chronic ↓ K ⁺ , ↑ Ca ²⁺), nephrotoxins (e.g. aminoglycosides, cisplatin, lithium), diuretics, Bartter's syndrome, polyuric recovery phase of AKI
Endocrine	Central diabetes insipidus, Addison's disease, hyporeninaemic hypoaldosteronism
Osmotic diuresis	Glycosuria, mannitol, contrast agents

↑ Fluid intake

Psychological	Psychogenic polydipsia
---------------	------------------------

Oliguria

Passage of a urine volume inadequate for excretion of the end products of metabolism. <400mL/24h (~20mL/h). The causes of oliguria (and anuria) are analogous to those of AKI.

Anuria

Passage of <100mL/24h or the absence of urine flow.

► Address the following questions urgently if anuria:

1. Is the bladder catheter blocked?
2. Is the urinary tract obstructed?
3. Are the kidneys perfused?

Pain

Loin pain

- Renal pain is usually experienced in the loin near the costovertebral angle.
- Anterior radiation may cause confusion with intraperitoneal pain.
- May also radiate to the genitalia.
- Usually associated with distension of the renal capsule and described as a constant dull ache.
- Differential: nerve root irritation (commonly T10–T12).
- ► An aggressive and a destructive renal disease may be painless.

Ureteric colic

- Sudden onset, extremely severe (pale, distressed, unable to settle) colic.
- Caused by a combination of ureteral stretching, local inflammation, and hyperperistalsis (spasm of ureteral smooth muscle).
- Pain may not completely fade between exacerbations.

Causes

- Passage of a stone (common), blood clot, or sloughed papillae.
- Ureteral pathology that develops slowly or produces only partial obstruction may be painless (small stone → excruciating colic; large, non-obstructing staghorn calculus → no pain).
- Pattern of referred pain can sometimes help to determine the level of ureteric obstruction:
 - Upper ureter → loin
 - Mid-ureter → ipsilateral iliac fossa (may → testicle in ♂, labium in ♀, and upper thigh in both).
 - Lower ureter → bladder irritability (frequency, dysuria, urgency) and suprapubic discomfort (may → urethra and tip of penis).

The bladder

Suprapubic pain

- Usually overdistension of the bladder (acute retention) or local inflammation (cystitis).
- Cystitis: signs of bladder irritability (below) and sharp, stabbing pain towards the end of voiding (strangury).
- Slowly progressive distension (e.g. neurogenic bladder) may cause no pain.
- Constant suprapubic pain, unrelated to retention, may not originate in the bladder. In ♀, consider gynaecological causes.

Bladder irritability

- Dysuria, frequency, and urgency among the commonest symptoms encountered in clinical practice.
- Urinary infection, causing inflammation of the urethra, trigone, and bladder, is (by far) the most frequent cause (📖 p. 706).
- ⚠ About one-third of patients with bladder cancer present with bladder irritability.

Clinical syndromes: tubular syndromes

Introduction

A degree of tubular dysfunction may occur with any renal injury (though the clinical picture is usually dominated by \downarrow GFR). Several distinct clinical syndromes result from tubular defects in the context of a normal GFR.

Generalized tubular dysfunction (Fanconi syndrome)

Multiple tubular defects produce a distinct clinical phenotype referred to as the Fanconi syndrome (unrelated to Fanconi's anaemia). Components may be present to a variable degree.

Causes

- *Acquired*: drugs (aminoglycosides, sodium valproate, ifosfamide, nucleoside reverse transcriptase inhibitors) and toxins (ethanol, cadmium, uranium, lead, mercury), myeloma, SLE, Sjögren's. Mild forms of the syndrome are more common than was previously thought.
- *Inherited*: cystinosis, tyrosinaemia, fructose intolerance, galactosaemia, glycogen storage disorder type I, cytochrome c oxidase deficiency (all autosomal recessive). There is also an autosomal dominant idiopathic form of Fanconi syndrome. Dent's disease and Lowe syndrome are X-linked Fanconi-like disorders.

Features

- *Phosphaturia and bone disease*:
 - Impaired PO_4 reabsorption \rightarrow phosphaturia \rightarrow hypophosphataemia.
 - This, and impaired 1α hydroxylation (activation) of 25-hydroxyvitamin D_3 in proximal tubular cells, produces skeletal abnormalities, including rickets (children), osteomalacia (adults), and osteoporosis.
- *Aminoaciduria*:
 - Amino acids are usually filtered at the glomerulus before reabsorption by multiple transport carriers in the proximal tubule.
 - Fanconi syndrome \rightarrow all amino acids appear in the urine in excess.
 - No clinically significant sequelae and supplementation unnecessary.
- *Glycosuria*:
 - Amount varies but serum glucose usually normal.
 - Clinical sequelae are rare, though hypoglycaemia occurs in some forms (e.g. Fanconi–Bickel syndrome/glycogenosis).
- *Renal tubular acidosis (RTA)*:
 - Defective bicarbonate reabsorption in the proximal tubule results in systemic acidosis (a form of type II RTA, [p. 824](#)).
- *Na^+ loss*:
 - If severe \rightarrow postural \downarrow BP, \downarrow Na^+ , and metabolic alkalosis result.
 - Salt supplementation occasionally necessary.
- *Hypokalaemia*:
 - \uparrow delivery of Na^+ to the distal tubule \rightarrow Na^+ reabsorption at the expense of K^+ excretion.

- Acidosis and RAS activation by volume depletion also → K^+ loss.
- Clinical sequelae common (muscle weakness, constipation, polyuria, cardiac arrhythmias) and supplementation often required.
- **Proteinuria:**
 - LMW proteinuria is common (β_2 microglobulin, lysozyme, and other tubular proteins), though excretion rates are usually low–moderate.
- **Polyuria:**
 - Polyuria, polydipsia, and dehydration can be prominent.
 - Caused by ↓ K^+ and impaired concentrating ability in the distal tubule.
- **Hypercalciuria:**
 - Rarely → nephrolithiasis/calcinosis (? protective effect of polyuria), although these may be precipitated by treatment with vitamin D metabolites (further ↑ urinary Ca^{2+}).
 - Serum Ca^{2+} usually normal.

Isolated tubular defects

Renal glycosuria

- ↓ proximal tubular glucose reabsorption → glycosuria (despite normal blood glucose).
- Clearance studies allow differentiation into different patterns implicating several defective tubular transport mechanisms.
- The amount can be quite significant (normally 1–30g/24h) but generally a benign condition with no clinical sequelae.
- ⚠ Always needs to be distinguished from DM.
- Genetic mechanisms involved but inheritance unpredictable.

Aminoaciduria

- Causes:
 - Inborn error of metabolism → ↑ plasma levels and ‘overflow’.
 - Renal aminoaciduria secondary to defective tubular transport mechanisms.
 - Amino acid transport is complex, involving transporters specific to single or chemically related groups of amino acids.
- The most important isolated aminoaciduria is cystinuria, an autosomal recessive cause of recurrent cystine stone formation (📖 p. 719).

Phosphaturia

- Defective phosphate transport → phosphaturia, hypophosphataemia, and disorders of the skeleton.
- Several described, including X-linked hypophosphataemic rickets (vitamin D-resistant rickets) and autosomal dominant hypophosphataemic rickets.
- FGF-23 excess, causing inhibition of phosphate reabsorption, is now known to underpin many of these disorders (📖 p. 236).

Clinical syndromes: bladder outflow obstruction

Introduction

- Main causes are shown in Box 1.11. The likelihood of each is influenced by age and sex. Presentation is with:
 - Acute retention of urine.
 - Lower urinary tract symptoms (LUTS).
- LUTS are divided into two groups. Symptoms correlate poorly with underlying urinary pathology, so it is best to remain as descriptive as possible (see Table 1.15).
- ⚠ Bladder outflow obstruction (BOO) can be clinically silent in some patients, despite significant residual bladder urine volumes and eventually progressive urinary obstruction.

Table 1.15 Symptoms of bladder outflow obstruction

Obstructive (voiding) symptoms	Storage (filling) symptoms*
Impaired size or force of stream	Nocturia
Hesitancy or straining	Daytime frequency
Intermittent or interrupted flow	Urgency
Sensation of incomplete emptying	Urge incontinence
	Dysuria


* Also called irritative.

'Prostatism' is no longer preferred to describe outflow symptoms (age-matched ♀ report similar symptoms).

Examination

Palpate for bladder enlargement; rectal examination, pelvic examination in ♀; examine the legs neurologically, and test anal tone/sensation.

Investigations

- Urine M,C+S, U&E, and PSA (in males >40 years,  p. 772).
- *Imaging.* Bladder USS to measure residual volume post-micturition (correlation to outflow obstruction is poor).
- *Uroflowmetry.* Full bladder emptied into a flow meter to generate a flow curve (rate vs time). Normal max flow >20mL/s. Further urodynamic assessment will distinguish non-obstructive causes of low flow (e.g. detrusor failure).
- *Pressure-flow studies (cystometrography).* More sensitive and specific but invasive. Bladder and rectal catheters record filling and voiding bladder pressures (normograms relate pressure to flow).
- *Videocystometrography.* Fluoroscopic screening of the ureters, bladder, and urethra. Useful in the investigation of neurological bladder dysfunction.
- *Retrograde urethrography.* ? urethral stricture.

Box 1.11 Causes of bladder outflow obstruction

- Congenital:
 - Urethral valves and strictures.
- Structural:
 - Benign prostatic hyperplasia (📖 p. 758).
 - Carcinoma of the prostate (📖 p. 766).
 - Bladder neck stenosis.
 - Urethral stricture.
- Functional:
 - Bladder neck dyssynergia.
 - Neurological disease—spinal cord lesions, MS, diabetes.
 - Drugs—anticholinergics, antidepressants.

Prostatic enlargement (📖 p. 758)

- Prostate size correlates poorly with degree of obstruction on urodynamic assessment.
- Impaired flow is a function of two separate components:
 - Dynamic: ↑ sympathetic tone of prostatic smooth muscle.
 - Static: mass effect of enlargement.

Renal biopsy: introduction

Despite improvements in other diagnostic techniques, renal biopsy and examination of histology retain pivotal roles in nephrology.

Renal transplant biopsy is considered separately (📖 p. 407).

Indications (📖 p. 82)

- Unexplained acute or chronic kidney disease with normal renal size.
- Histology is likely to influence treatment.
- Histology is likely to offer prognostic information.
- Information concerning the activity (and potential reversibility) and/or chronicity of a previously identified lesion is desirable.

Preparation for renal biopsy

- ⚠ Renal biopsy is an invasive procedure. An evaluation of the risk-benefit ratio is required in every case.
- Imaging: confirm two normal-sized, unobstructed kidneys with normal parenchyma.
- BP <160/90mmHg; preferably <140/90mmHg.
- Hb ideally >100g/L.
- Normal clotting (PT and APTT <1.2 × control). Platelet count >100 × 10⁹/L.
- Send group and save.
- Antiplatelet agents and anticoagulants stopped >5 days prior to procedure. Ideally, do not restart for 7 days post-biopsy.
- Sterile urine.
- Informed consent. Give appropriate written or visual patient information.
- If renal impairment, the risk of bleeding increases ~2–3-fold.
- Most units will have their own policy, e.g. if urea ≥20mmol/L (55mg/dL) or SCr ≥250μmol/L (2.8mg/dL) or bleeding time >10min, give DDAVP 0.4 micrograms/kg IV 2–4h pre-biopsy (⚠ not if recent or ongoing angina).

Contraindications

- Uncorrected bleeding tendency (absolute contraindication).
- Chronic kidney disease with small kidneys.
- Multiple cysts.
- Suspected renal malignancy (📖 p. 743).
- Hydronephrosis.
- Active urinary infection.
- Uncontrolled hypertension (>160/95mmHg).
- Hypotension.
- Significant anaemia.
- Uncooperative patient.
- Solitary kidney (only a relative contraindication).

Technique

- Performed percutaneously under LA via a posterior approach.
- Sedation is generally avoided, as patient cooperation is essential.
- Patient lies prone, with a pillow under the abdomen to straighten the spine.
- USS locates the kidneys, determines their size, and identifies cysts.
- Either kidney may be biopsied.
- A lower pole biopsy reduces the risk of piercing a major vessel.
- USS is used to directly guide the needle to the kidney 'real time'.
- LA is infiltrated down to the renal capsule, using a spinal needle.
- Non-real-time techniques, after the kidneys have been marked on the surface, also remain in use.
- CT guidance is an alternative when USS visualization is inadequate.
- Disposable TruCut® needles or spring-loaded biopsy guns are generally used (e.g. 16-gauge; larger needles may ↑ complication rate). An initial stab incision at the skin can ease passage of the needle. The patient is required to hold their breath when the needle enters the kidney.
- Where possible, two cores of tissue are obtained to increase diagnostic yield. Avoid >4 passes with the biopsy needle. Call for a more experienced operator after two unsuccessful passes.
- Routine processing includes light, immunofluorescence (or immunohistochemistry), and EM. Biopsy material is divided, as different fixatives are required for the different techniques, e.g. glutaraldehyde for EM.
- Patient remains on bed rest, with a good fluid intake for 6–8h. Pulse and BP are monitored regularly and urine inspected for haematuria.
- The patient is advised not to undertake heavy lifting or strenuous exercise for 4 weeks.
- Day case biopsy is now common. ⚠ These should be deemed low risk, as complications actually occur after 6–8h in ~1/3 cases.
- High risk ∴ not for day case: SCr >200µmol/L (2.2mg/dL), BP >140/90mmHg, small renal sizes (📖 p. 84).

Open renal biopsy

- May be considered if the percutaneous approach carries an unacceptable risk or has been unsuccessful.
- Allows direct visualization of the kidney and easier control of bleeding.
- More tissue can potentially be obtained.
- The risk of a GA may actually exceed that of a percutaneous biopsy.
- Laparoscopic techniques have been described.

Transvenous renal biopsy

- An endovascular technique developed in hepatology and not widely available. The kidney is approached via a transjugular or transfemoral route. Usually performed by interventional radiologists.
- The renal capsule is not punctured, and the risk of perinephric bleeding is reduced.
- High success rates demonstrated (i.e. renal tissue obtained), but complication rates appear similar.
- Potential uses: morbid obesity, comatose patient, uncorrected coagulopathy, failed percutaneous approach.

Renal biopsy: indications

Clinical syndromes: when to biopsy?

► There is no such thing as a 'routine' renal biopsy.

📖 *Microscopic haematuria* (p. 66)

- Practice varies, but most do not biopsy, unless there is associated proteinuria and/or renal impairment (either at presentation or during the course of follow-up). Isolated microscopic haematuria generally has an excellent prognosis, and histology will not influence management.
- Possible exceptions: suspected systemic condition (e.g. SLE, vasculitis), potential live kidney donors, or for insurance or employment reasons.

Proteinuria

📖 *Non-nephrotic proteinuria* (<3.5g/24h)

- Many recommend a biopsy at modest levels of proteinuria to ensure potentially treatable lesions, e.g. primary FSGS and membranous GN, are not overlooked.
- Others argue that the benign prognosis of these conditions, when urinary protein excretion is low, means that a biopsy is unnecessary.
- Some clinicians use an arbitrary 'cut-off' level of proteinuria to guide their decision-making (e.g. biopsy if >1g/24h—uPCR >100mg/mmol), particularly if treatment with an ACE-I or ARB does not reduce the proteinuria below this threshold (p. 61).
- The presence of renal insufficiency weighs in favour of a biopsy.

Nephrotic range proteinuria

- A biopsy is generally recommended. Two exceptions:
 - Minimal change disease in childhood. In this situation, an initial trial of steroids may be appropriate.
 - Diabetic nephropathy (p. 611).

Acute nephritic syndrome

The need to confirm diagnosis and adapt treatment, according to the type and severity of the renal lesion, mandates a biopsy in the majority of cases, even when the diagnosis is suggested by serological tests (e.g. anti-GBM disease or ANCA +ve vasculitis).

📖 *Acute kidney injury* (p. 121)

- Unexplained AKI, particularly with an active urinary sediment (i.e. possible RPGN), or AKI that does not behave as expected, e.g. failing to recover.

Chronic kidney disease

The most important determinants of the appropriateness of a biopsy are:

- *Renal size.* If <9cm, a biopsy is technically more demanding and histology is more likely to show chronic, non-specific, irreversible change (with the original insult not identifiable).
- *Clinical context.* A high pre-test probability may circumvent the need to obtain histology, e.g. diabetic nephropathy.

- *Degree of proteinuria.* A treatable glomerular lesion is less likely if urinary protein excretion is low (e.g. $<1\text{g}/24\text{h}$ or $\text{uPCR} <100\text{mg}/\text{mmol}$).

Systemic disease potentially involving the kidney

- Immunological or serological testing (📖 p. 40) may provide important diagnostic clues (e.g. ANCA +ve vasculitis, anti-GBM disease), but renal biopsy will confirm the diagnosis and assess the degree of activity and potential reversibility. This aids decision-making around the type and duration of treatment.
- This is particularly true of lupus nephritis where classification of the renal lesion is a cornerstone of management.
- In some conditions, demonstrable renal involvement may be an important determinant of the need for systemic treatment, e.g. myeloma.
- Other important systemic conditions that often precipitate a renal biopsy include sarcoidosis and amyloidosis.

Renal biopsy: complications

Introduction

In general, percutaneous kidney biopsy is a safe procedure, and serious complications are uncommon. However, less serious sequelae, such as pain and mild bleeding, are relatively common, so it is important to explain the potential for these to the patient pre-procedure.

Higher risk¹

- Uncorrected bleeding tendency (▶▶ do not biopsy).
- ↑ BP (>130mmHg systolic).
- ↓ GFR, especially if SCr >177mmol/L (2.0mg/dL).
- Small renal sizes (<10cm).
- Hb <120g/L.
- Older age (>40).
- Use of larger (e.g. 14-gauge) biopsy needle.

Complications

- Pain:
 - Dull ache around the needle entry point and tract is almost universal once LA effect wears off.
 - Simple analgesia is often necessary.
 - Severe pain raises the possibility of a significant perirenal bleed and should prompt assessment to determine the extent of the problem (as well as additional analgesia).
 - Pain is usually short-lived but may be persistent >12h in <5%, meriting further investigation for a haematoma.
- Bleeding:
 - Bleeding is the main complication of renal biopsy.
 - Three potential sites:
 - Collecting system (→ haematuria).
 - Within the renal capsule (→ pain).
 - Perinephric space (→ haematoma).
 - A degree of capsular or perirenal bleeding accompanies almost every renal biopsy.
 - A Hb drop ≤10g/L is common.
 - Asymptomatic haematomas can be detected on USS in up to 30% patients.
 - A larger capsular haematoma (pain, significant drop in Hb) occurs in ~2%.
 - A large capsular haematoma may tamponade and compress the kidney, causing high renin hypertension (known as a 'page' kidney).
 - Transient microscopic haematuria is present in virtually all patients.
 - Macroscopic haematuria in ~3.5%.
 - Gross haematuria may cause painful clot colic ± ureteral obstruction.
 - Transfusion required in ~1%.
 - Endovascular intervention to control bleeding in 0.6%.
 - Nephrectomy to control bleeding in 0.01%.

- Arteriovenous fistula:
 - ~18% on Doppler but rarely symptomatic; may cause persistent haematuria and (rarely) hypertension.
 - Most resolve spontaneously within 12–24 months.
 - Embolization may be an option in those that remain symptomatic.
- Incorrect tissue obtained:
 - Usually muscle, fat, liver, spleen.
- Colonic perforation.
- Perirenal infection (0.2%).
- Peritoneal-calyceal fistula.
- Death (0.02%).

► Management of significant bleeding

- Seek expert help.
- Bed rest.
- Regular pulse, BP, and O₂ saturations (every 15min).
- Ensure adequate IV access and commence fluid resuscitation as necessary.
- Reassure the patient, and ensure adequate analgesia.
- Check Hb, and repeat after 2, 4, 8, and 12h as a minimum.
- Cross-match at least 2 units of blood, and transfuse as necessary.
- Repeat clotting studies post-biopsy. Correct coagulopathies.
- Maintain a high urine flow with IV fluids to prevent ureteral obstruction and clot colic.
- Consider a 3-way urethral catheter for irrigation if clot retention and bladder outflow obstruction.
- Inform surgical team.
- Do not move the patient for imaging until they are stabilized. An ultrasound is unlikely to be of value beyond the identification of a haematoma. A contrast CT may identify ongoing active bleeding, but the patient's clinical status may already imply this.
- If severe or persistent, consider arteriography to localize source of bleeding ± embolization to stop it.
- Surgical intervention may allow control of the bleeding point, but an emergency nephrectomy may be necessary.

Reference

1. Corapi KM, Chen JL, Balk EM, Gordon CE (2012). Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. *American Journal of Kidney Diseases*, **60**, 62–73.

Acute kidney injury (AKI)

- Definition 88
- Epidemiology 92
- Biomarkers of AKI 94
- Causes and classification 96
- Prevention of AKI 98
- Pre-renal AKI 102
 - Causes of pre-renal AKI 104
 - Causes of intrinsic renal AKI 105
- Acute tubular necrosis (ATN) 106
 - Pathophysiology of ATN 108
- AKI: recognition 110
- AKI: priorities 112
- Assessing AKI: clinical clues 114
- Assessing AKI: urinalysis 116
- Assessing AKI: blood tests 118
- Assessing AKI: imaging 120
- Assessing AKI: histology 121
- AKI management: a checklist 122
- AKI management: volume replacement—which fluid? 124
- AKI management: volume replacement—how much? 126
- AKI management: hyperkalaemia 130
- AKI management: pulmonary oedema 134
- AKI management: electrolytes and acidosis 136
- AKI management: other strategies 138
- AKI management: nutrition 140
- AKI management myths 144
- AKI: hope for the future? 146
- Contrast-induced AKI (CI-AKI) 148
- Rhabdomyolysis 152
 - Rhabdomyolysis: management 154
- AKI in cirrhosis 156
- Management of HRS 158
- Tumour lysis syndrome 160
- Abdominal compartment syndrome (ACS) 162
- AKI in the developing world 164
- AKI in sepsis 166
- Managing septic shock and AKI 168
- Renal replacement therapy in AKI 172
 - RRT in AKI: modalities 174
 - RRT in AKI: choosing modality? 176
 - RRT in AKI: prescription 178
 - RRT in AKI: anticoagulation 182
 - RRT in AKI: citrate regional anticoagulation 186
- Peritoneal dialysis (PD) in AKI 188

Definition

Introduction

Acute kidney injury (AKI) (formerly acute renal failure) is the syndrome arising from a rapid fall in GFR (over hours to days). It is characterized by retention of both nitrogenous (including Ur and Cr) and non-nitrogenous waste products of metabolism, as well as disordered electrolyte, acid–base, and fluid homeostasis.

▶▶ There is evidence that even relatively small acute reductions in kidney function are associated with poorer outcomes, including increased mortality, higher risk of long-term dialysis, and longer hospital stay.

Historical limitations

- Despite a relative insensitivity to acute changes in GFR, most definitions of acute renal dysfunction have been based on serum Cr, either as an absolute value or as a change from baseline. Other definitions have incorporated urine output (UO) or the need for dialysis support.
- A 2004 survey of 598 participants at a critical care nephrology conference revealed 199 different criteria to define AKI and 90 for the initiation of renal replacement therapy.¹
- This lack of consensus had implications for collection and comparison of epidemiological data, and consistency of clinical practice.

The RIFLE criteria for AKI

- In response, the Acute Dialysis Quality Initiative established a multilayered definition of AKI called the RIFLE criteria.
- AKI is stratified into five stages, based on severity and duration of renal injury: **R**isk, **I**njury, **F**ailure, **L**oss, and **E**nd-stage disease (see Table 2.1).
- Many studies (>0.5 million patients) have validated these criteria.
- RIFLE-defined AKI is associated with significantly reduced survival (with increasing RIFLE stage leading to greater risk of death).

Acute Kidney Injury Network (AKIN) classification

- More recently, AKIN (an international network of AKI experts) modified RIFLE to incorporate small changes in SCr occurring within a 48h period and to remove changes in GFR as diagnostic criteria (see Table 2.1).

KDIGO AKI definition (2012)

- AKI, classified by either of the earlier listed criteria, may identify slightly different patients: RIFLE may not detect ~10% of AKIN-identified cases, and AKIN may miss ~25% RIFLE cases.
- KDIGO have recently produced a definition that incorporates the key elements of both, and it is likely that this definition will become the accepted standard.

Key elements of KDIGO AKI definition

- Increase in SCr by $\geq 26.5 \mu\text{mol/L}$ ($\geq 0.3 \text{mg/dL}$) within 48h.
- Increase in SCr by $\geq 1.5 \times$ baseline (known or presumed to have occurred within prior 7d).
- Urine volume $< 0.5 \text{mL/kg/h}$ for 6h.

(Only one criterion needs to be present to fulfill the definition.)

Table 2.1 The evolving definition of AKI

(a) RIFLE classification¹

RIFLE category	SCr/GFR criteria	Urine output criteria
Risk	\uparrow SCr ≥ 150 – 200% (1.5–2-fold) OR decrease of GFR $>25\%$	$< 0.5 \text{mL/kg/h}$ for 6h
Injury	\uparrow SCr > 200 – 300% (> 2 – 3 -fold) OR decrease of GFR $>50\%$	$< 0.5 \text{mL/kg/h}$ for 12h
Failure	\uparrow SCr $> 300\%$ (> 3 -fold) from baseline OR decrease of GFR $>75\%$ OR SCr $\geq 350 \mu\text{mol/L}$ ($\geq 4.0 \text{mg/dL}$) with an acute rise of at least $45 \mu\text{mol/L}$ (0.5mg/dL). Or on RRT.	$< 0.3 \text{mL/kg/h}$ for 24h OR anuria for 12h
Loss	Complete loss of renal function for > 4 weeks	
End-stage kidney disease	Need for RRT for > 3 months	

(b) AKI network classification²

AKIN stage	Serum creatinine criteria	Urine output criteria
1	SCr $\geq 26.4 \mu\text{mol/L}$ (0.3mg/dL) in ≤ 48 h OR \uparrow SCr ≥ 150 – 200% (1.5–2-fold) from baseline	$< 0.5 \text{mL/kg/h}$ for > 6 h
2	SCr > 200 – 300% (2–3-fold) from baseline	$< 0.5 \text{mL/kg/h}$ for > 12 h
3	SCr $\geq 300\%$ (3-fold) from baseline OR SCr $\geq 354 \mu\text{mol/L}$ ($> 4 \text{mg/dL}$) with an acute rise of $\geq 44 \mu\text{mol/L}$ (0.5mg/dL) OR treatment with RRT	$< 0.3 \text{mL/kg/h}$ for 24h OR anuria for 12h

(c) KDIGO classification³

Stage	Serum creatinine criteria	Urine output criteria
1	1.5–1.9 times baseline OR $\geq 0.3 \text{mg/dL}$ ($> 26.5 \mu\text{mol/L}$) in ≤ 48 h	$< 0.5 \text{mL/kg/h}$ for 6–12h
2	2–2.9 times baseline	$< 0.5 \text{mL/kg/h}$ for ≥ 12 h
3	≥ 3 times baseline OR increase in SCr to $\geq 4.0 \text{mg/dL}$ ($354 \mu\text{mol/L}$) OR initiation of RRT	$< 0.3 \text{mL/kg/h}$ for ≥ 24 h OR anuria for ≥ 12 h

GFR, glomerular filtration rate; RRT, renal replacement therapy; SCr, serum creatinine. Only one criterion needs to be met to be classified as AKI; if both are present, the criterion which places the patient in the higher stage of AKI is selected.

¹ R. Bellomo, et al. Critical Care, vol. 8, no. 4, pp. R204–R212, 2004.

² R. L. Mehta, et al. Critical Care, vol. 11, article R31, 2007.

³ <http://www.kdigo.org/>

Acute kidney disease (AKD)

- Strict adherence to definitions of both acute (AKI) and chronic (CKD) renal disease may miss individuals with functional or structural abnormalities present for <3 months but who may benefit from active intervention to restore kidney function (∴ avoiding permanent damage and adverse outcomes).
- For this reason, KDIGO have proposed the term AKD to include not only those with AKI, but also those with GFR <60mL/min/1.73m² for <3 months or a decrease in GFR by ≥35% or an increase in SCr by >50% for <3 months.

Reference

1. Ricci Z, Ronco C, D'Amico G, et al. (2006). Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. *Nephrology Dialysis Transplantation*, **21**, 690–6.

Epidemiology

Incidence

Depends on the population studied and the definition used, meaning few studies historically have been able to provide accurate incidence data. However, the more recent use of AKIN/RIFLE criteria has improved this. It remains important to recognize the limitations imposed by the use of SCr and urine output for the detection of AKI. It is hoped that, in the future, sensitive biomarkers of renal cell injury will improve earlier identification.

Hospital

- 5–10% of general admissions.
- 20–25% of patients with sepsis and ~50% with septic shock.
- 50% of all ITU admissions (where it acts as an independent risk factor for mortality of 20–60%, depending on AKI stage).

Community

- KDIGO estimate a worldwide AKI prevalence of ~2,100 pmp, the majority of which are community-acquired.
- The burden of AKI may be highest in developing countries.
- Community-based studies in the UK (SCr >300 μ mol/L or 3.4mg/dL) estimate 486–620 pmp. This is age- and comorbidity-related (17 pmp aged <50 and 949 pmp aged 80–89).
- Restricting the evaluation to changes in SCr, particularly large changes, will miss many cases.
- Individuals with CKD are at increased risk of AKI (and AKI is a risk factor for progression of CKD).
- Incidence of dialysis-dependent AKI: ~200 pmp annually.

Prognosis

► There is increasing evidence for the adverse outcomes associated with AKI (even after apparent resolution), including longer hospital length of stay, significant complication rates (including infection), risk of CKD (including ESRD), development of CV disease, and higher mortality.

Mortality

- Outcomes for the new AKIN criteria by stage are shown in Table 2.2.
- Prompt improvement (<24h) in renal, cardiovascular, or respiratory function is associated with a better chance of survival.
- Outcomes for patients with sepsis in an ICU setting are linked to timely AKI resolution (► indicating a therapeutic window where outcomes for these patients may be improved).
- Despite improvements in many aspects of clinical care (particularly nutrition and renal replacement therapy), overall mortality in AKI requiring RRT remains >50% (reflecting a high incidence in the elderly and those with multi-organ failure).
- The underlying cause will play a role, e.g. lower for nephrotoxin-driven AKI (<30%) vs higher for sepsis- and trauma-related AKI (~60%).

Table 2.2 AKI mortality by AKIN stage

Rise in SCr	Odds ratio for hospital mortality
≥27µmol/L (0.3mg/dL)	4.1
≥45µmol/L (0.5mg/dL)	6.5
≥90µmol/L (1.0mg/dL)	9.7
≥180µmol/L (2.0mg/dL)	16.4

Chertow G M, Burdick E, Honour M, et al. (2005). Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of American Society of Nephrology*, **16**, 3365–70.

Renal recovery

Recovery of renal function will depend on underlying diagnosis. For ATN, ~50% will have some degree of residual renal impairment. This will be irreversible, dialysis-dependent renal failure in ~5% (~10% in the elderly). The risk of worsening or *de novo* CKD and death following an episode of AKI (even if function appears to return to normal) is high.² The future healthcare impact of this is currently uncertain but could be significant, as more patients survive to hospital discharge following serious illness.

Reference

2. Bucaloiu ID, Kirchner HL, Norfolk ER, et al. (2012). Increased risk of death and *de novo* chronic kidney disease following reversible acute kidney injury. *Kidney International*, **81**, 477–85.

Biomarkers of AKI

Introduction

Driven by the recognition that even relatively small increases in SCr were associated with a poor outcome and increased healthcare costs, the 2005 American Society of Nephrology Renal Research Report assigned the highest research priority to the discovery of new biomarkers of AKI and their validation in different patient populations and clinical settings.

SCr is a suboptimal biomarker of AKI. \uparrow SCr is delayed, making it insensitive for early diagnosis (\rightarrow missed therapeutic opportunities). It is also unable to differentiate pre-renal AKI from ATN.

Novel biomarkers include: (i) LMW proteins that undergo glomerular filtration prior to reabsorption in the proximal tubule (damaged tubules \rightarrow \uparrow urinary excretion); (ii) enzymes that are released into the urine after tubular cell injury (\rightarrow markers of tubular damage); and (iii) inflammatory mediators released by renal cells or infiltrating inflammatory cells (\rightarrow markers of site and degree of injury) (see Fig. 2.1).

Use in clinical practice

The ideal biomarker should provide additional information not available from clinical evaluation and traditional tests. The main problem to date is that studies have been performed either in defined clinical settings (where the timing of the renal insult is understood, e.g. after cardiopulmonary bypass, coronary angiography, or following renal transplantation) or in children (where there are no confounding comorbidities, such as CKD, diabetes mellitus, and chronic inflammatory disease). As a result, currently available data cannot necessarily be generalized to more heterogeneous populations, such as critically ill patients in ICU. However, it is hoped that ongoing studies will demonstrate the utility of novel biomarkers to improve recognition, management, and outcomes for AKI.

Putative biomarkers under study

Neutrophil gelatinase-associated lipocalin (NGAL)

A 25kDa glycoprotein produced by epithelial tissues in several organs. Excreted via glomerular filtration and completely reabsorbed by tubular cells. Also produced in distal tubular cells (renal ischaemia \rightarrow \uparrow NGAL expression). Appears to be anti-apoptotic and to upregulate heme oxygenase-1. Urinary NGAL is sensitive and specific for early ATN (no \uparrow in pre-renal AKI). Rises 2–4h post-AKI; common confounders: sepsis, malignancy, CKD, COPD, pancreatitis. Clinical utility now tested in many scenarios, including cardiac surgery and contrast toxicity. Plasma NGAL may also help to predict likelihood of renal recovery.

Cystatin C

A 13kDa cysteine protease inhibitor produced by all nucleated human cells and released into plasma at a constant rate (📖 p. 36). Freely filtered in glomeruli and completely reabsorbed in the proximal tubule. Detectable in urine 12–24h after renal injury. Results confounded by systemic inflammation, malignancy, thyroid disorders, smoking, glucocorticoid deficiency and excess.

Interleukin-18

An 18kDa proinflammatory cytokine. Released from proximal tubular cells. Rises 6–24h after renal injury. Confounders: inflammation, sepsis, cardiac failure.

Kidney injury molecule-1 (KIM-1)

A transmembrane glycoprotein, produced by proximal tubular cells after ischaemic or nephrotoxic injury (it sheds an extracellular domain that can be measured in urine). No systemic source. Rises 12–24h after renal injury. Confounders: renal cell carcinoma, adult polycystic kidney disease, chronic proteinuria.

N-acetyl- β -D-glucosaminidase (NAG)

A lysosomal enzyme (>130kDa), produced in many cells, including proximal and distal tubular cells. Detectable in urine 12h after tubular injury.

Retinol-binding protein (RBP)

A 21kDa single-chain glycoprotein. Undergoes glomerular filtration before reabsorption by proximal tubular cells. Detectable in urine within 12h.

Liver-type fatty acid-binding protein (L-FABP)

A 14 kDa intracellular lipid chaperone, produced in various organs as well as proximal tubular cells. Freely filtered by glomeruli and reabsorbed in proximal tubular cells. Detectable in urine within 1h, i.e. soon after injury.

α glutathione S-transferase (α GST) and η glutathione S-transferase

47–51kDa cytoplasmic enzymes, produced in distal tubular cells. Urinary levels increase within 12h.

Other promising biomarkers

Urinary insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) are both markers of cell cycle arrest. Several microRNAs (ribonucleotides that regulate gene expression) are upregulated during AKI, e.g. miR-210. Proteomic profiling and other techniques have identified many other candidates, including the Na⁺/H⁺ exchanger (NHE3), perforin, granzyme B, and monocyte chemoattractant protein (MCP)-1.

It is hoped that combining biomarkers into an 'AKI panel' will further improve sensitivity and clinical utility.

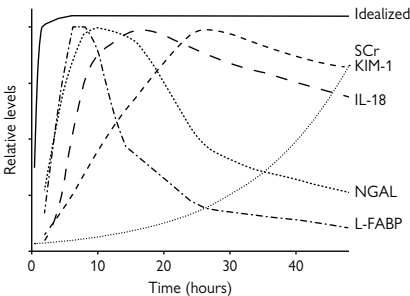


Fig. 2.1 Temporal relationship of studied AKI biomarkers to injury. The characteristics of an ideal biomarker are also shown.

Causes and classification

Introduction

- It is crucial to remember that AKI is neither a diagnosis nor a disease. Rather, it is a clinical syndrome that is caused by, or complicates, a wide range of disorders. (See Fig. 2.2)
- The introduction of the new nomenclature has propagated a tendency for AKI to be conceptualized as a 'standard' or homogenous disorder.
- While this may have benefits, clinical practice must always reflect the heterogeneity and complexity of the syndrome and its context.
- The goals are to: (i) identify patients earlier—when simple interventions may make an important difference to outcome; (ii) consider the multiple possible causes of renal injury; (iii) anticipate complications before they arise.

Three dependable clinical syndromes can be used to help categorize AKI and \therefore to direct diagnosis and therapy.

Pre-renal AKI

- \downarrow renal blood flow (RBF) \rightarrow \downarrow GFR.
- \downarrow RBF may be 2° to hypovolaemia per se, \downarrow effective RBF (\downarrow cardiac output, vasodilatation in sepsis), or intrarenal vasomotor changes (e.g. NSAIDs and ACE-I).
- Potentially reversed by restoration of RBF.
- Kidneys remain structurally normal.

Intrinsic renal AKI

- The renal parenchyma itself sustains damage through injury to the renal vasculature, glomerular apparatus, or tubulointerstitium.
- The commonest cause (by far) is acute tubular necrosis (ATN), itself the end-product of an ischaemic or a nephrotoxic injury (📖 p. 106).
- The diagnosis of ATN implies:
 - Glomerular, vascular, and other interstitial diseases are not responsible for AKI. Be cautious; these disorders often require specific treatment, and a delay in their diagnosis can have significant consequences for long-term kidney function. They may also coexist with ATN. ► Seek expert help if you are uncertain.
 - Recovery of renal function should occur if supportive measures are adequate (so make sure that they are adequate).
 - A potentially reversible phase has passed during which ATN may have been avoided.

Post-renal AKI

- The kidneys produce urine, but there is obstruction to its flow.
- \uparrow back pressure \rightarrow \downarrow tubular function.
- Obstruction may occur at any level in the urinary tract.
- AKI results when both kidneys are obstructed or when there is obstruction of a solitary kidney.
- Obstruction eventually causes structural (and \therefore permanent) damage.

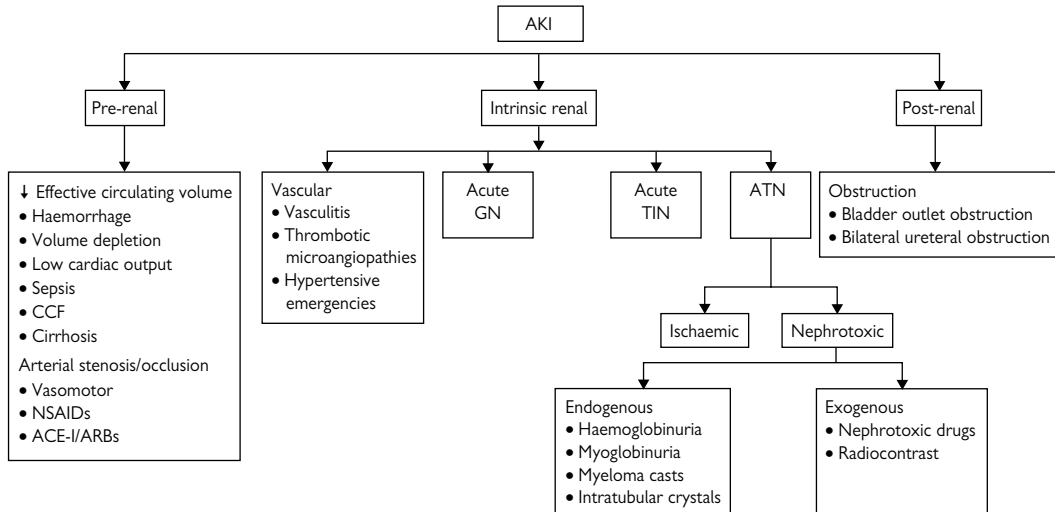


Fig. 2.2 Classification and major causes of acute kidney injury.

Prevention of AKI

►► Many cases of AKI can be prevented or reversed at an early stage.

Who is at risk?

- ↑ age.
- Pre-existing CKD:
 - ↑ SCr, ↓ eGFR, or proteinuria.
- Surgery (esp. if with another risk factor):
 - Trauma and burns surgery (hypovolaemia, sepsis, myoglobinuria).
 - Cardiac surgery (poor LV function, intra-operative haemodynamic instability, cardiopulmonary bypass, use of aprotinin).
 - Vascular surgery (e.g. suprarenal aortic cross-clamping) and endoluminal intervention (e.g. an endovascular stent occludes a renal artery orifice) can disturb renal perfusion ± cause atheromatous emboli to kidneys). Pre or intra-operative contrast administration. Risk of emergency AAA repairs > elective (25% vs <5% AKI).
 - Hepatic and biliary surgery (over 70% of hepatic transplants complicated by AKI); biliary surgery also high risk.
- Diabetes mellitus (esp. if established diabetic nephropathy with ↓ eGFR).
- Volume depletion (NBM, bowel obstruction, vomiting, burns).
- LV dysfunction and other cardiac disease.
- Other causes of ↓ effective arterial volume (cirrhosis).
- Drugs that cause renal vasomotor changes (NSAIDs, ACE-I, ARB).
- Hyperbilirubinaemia and frank jaundice.
- Multiple myeloma (☹️ may just be that these patients are often dehydrated, with a degree of renal insufficiency to start with). Precipitation of casts with tubular injury is the concern (📖 p. 622).

Common nephrotoxins (see 📖 p. 898)

The kidneys are particularly susceptible to nephrotoxic injury because of their rich blood supply and a propensity to concentrate toxic substances within their cortex.

- NSAIDs (including COX-2 inhibitors).
- Diuretics, ACE-I, ARB (esp. in volume-depleted patients).
- Antimicrobials: aminoglycosides, vancomycin, amphotericin (lipid preparation is ONLY ~50% less nephrotoxic and may still cause AKI).
- Immunosuppressants (e.g. ciclosporin, tacrolimus) and chemotherapeutic agents (e.g. cisplatin).
- IV contrast (📖 p. 148).

Using nephrotoxic drugs

⚠️ Recognizing the potential for nephrotoxicity is the critical step:

- Is it a definite indication?
- Is there a therapeutic alternative?
- Have all precautions to ↓ toxicity been undertaken (e.g. hydration)?
- Have you arranged for renal function to be monitored closely?
- Is therapeutic drug monitoring necessary (e.g. gentamicin/vancomycin)?

Reducing AKI risk perioperatively

Three principles

1. Avoid dehydration.
 2. Avoid nephrotoxins (Δ contrast, NSAIDs, aminoglycosides).
 3. Review clinical (esp. volume) status and renal function if at risk.
- Optimize volume status preoperatively:
 - No patient should ever go to theatre dehydrated.
 - Review daily weights, chart input/output; check postural heart rate and BP.
 - Calculate losses, esp. in patients NBM.
 - Δ CVP: intermittent measurement does not correspond to volume status in many studies. Seek expert help prior to undertaking.
 - IV fluid replacement \rightarrow use balanced crystalloid solutions unless hyperkalaemic and/or anuric (seek expert help if present) (GIFTASUP guidelines).¹
 - Optimize blood sugar control in diabetics (\rightarrow sliding scale).
 - Optimize nutrition (with par/enteral nutrition, if indicated).
 - Consider bladder catheter for those with prostatic disease.
 - Avoid surgery, if possible, immediately after a contrast procedure.
 - Stop antihypertensives (esp. diuretics, ACE-I/ARB) for 24–48h, as BP allows.
 - Find out how the procedure and patient progressed in theatre. Check intraoperative records for blood loss and fluid and drugs administered.
 - Review the patient early post-op. Consider need for level 2 and 3 care.
 - There is no role for dopamine, furosemide, or other diuretics in the prevention of perioperative AKI.

¹ http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf

STOP AKI checklist

The London AKI network (LAKIN) is a regional collaborative that aims to collate available evidence, clinical standards, and national guidelines into accessible practical advice and well-defined clinical pathways.

The guidelines are designed for those managing AKI in general ward areas and aims to facilitate the interaction between general wards, local critical care teams, and regional kidney unit services. (See Fig. 2.3)

LAKIN advocates the following **STOP** (**S**epsis; **T**oxicity; **O**bstruction; **P**arenchymal disease) checklist to help improve awareness of the causes of AKI.

- *Sepsis and hypotension:*
 - Severe sepsis.
 - Haemorrhage.
 - Dehydration.
 - Cardiac failure.
 - Liver failure.
 - Renovascular insult.
- *Toxicity:*
 - Nephrotoxic drugs.
 - Iodinated radiological contrast.
- *Obstruction:*
 - Bladder outflow.
 - Stones.
 - Tumour.
 - Surgical ligation of ureters.
 - Extrinsic compression (lymph nodes).
 - Retroperitoneal fibrosis.
- *Parenchymal kidney disease:*
 - Glomerulonephritis.
 - Tubulointerstitial nephritis.
 - Rhabdomyolysis.
 - Haemolytic uraemic syndrome.
 - Myeloma.
 - Malignant hypertension.

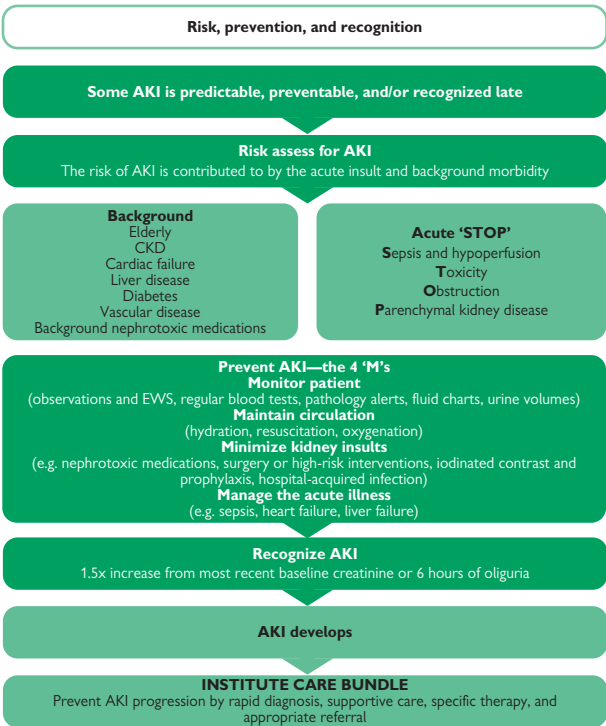


Fig. 2.3 AKI risk, prevention and recognition. Reproduced from London AKI network manual (2012), with permission. <http://www.londonAKI.net/clinical>

Pre-renal AKI

Any cause of *apparent* volume depletion may compromise renal perfusion, as \downarrow RBF \rightarrow \downarrow GFR. The kidneys are structurally intact but functionally compromised. As a general rule, the metabolically susceptible proximal tubule can withstand relative underperfusion (and hypoxia) for a period of days (as many as 5) before true cellular injury supervenes (ATN). (See Fig. 2.4 for algorithm detailing sequence of events.)

Hypoperfusion

Hypoperfusion is *not* the same as volume depletion. Renal perfusion is a product of effective circulating volume, cardiac output, and peripheral vascular resistance.

△ Any cause of a fall in effective arterial blood volume (p. 104) can cause pre-renal AKI, regardless of the hydration status of the patient:

- Hypovolaemia.
- Cardiogenic shock (or cardiac failure).
- Systemic vasodilatation (as in sepsis).

Physiological response to hypoperfusion

Systemic response

Systemic hypoperfusion is sensed as a \downarrow in arterial BP by carotid and arteriolar baroreceptors. Activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) as well as \uparrow vasopressin (ADH) release act in concert to maintain BP and preserve blood flow to vital organs. This is accomplished by:

- Vasoconstriction in 'dispensable' vascular beds (e.g. cutaneous).
- \uparrow cardiac output and heart rate.
- \uparrow thirst and \downarrow sweating.
- \uparrow renal conservation of salt and water.

Renal response (*renal autoregulation*)

GFR is initially maintained because intraglomerular pressure is preserved despite the fall in systemic BP through renal autoregulation. This is dependent on the balance between dilatation of the pre-glomerular afferent arteriole (\rightarrow prostaglandins and NO) and constriction of the efferent post-glomerular arteriole (\rightarrow mainly angiotensin II).

If perfusion continues to fall, pre-renal AKI will result. As RBF drops, so glomerular filtration and urine output fall as well. Below a mean arterial pressure (MAP) of \sim 80mmHg, GFR \downarrow rapidly. However, lesser degrees of hypotension may provoke pre-renal AKI in susceptible individuals:

- The elderly.
- Pre-existing afferent arteriolar pathology (e.g. hypertensive nephrosclerosis or diabetic nephropathy).
- ACE-I or ARB therapy where constriction of the efferent arteriole is blocked.
- Patients on NSAIDs with afferent arteriolar constriction.

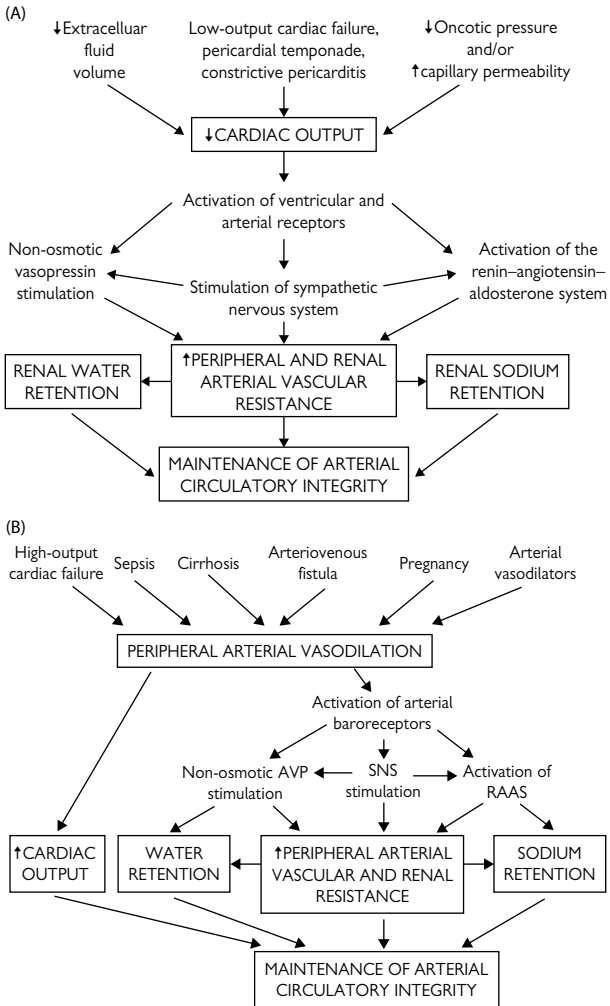



Fig. 2.4 (A) Sequence of events in which reduced cardiac output initiates renal sodium and water retention. (B) Sequence of events in which peripheral arterial vasodilatation initiates renal sodium and water retention. Reproduced from Schrier RW et al. (2004). *Neuroscience*, **129**, 897–904. With permission from Elsevier.



Causes of pre-renal AKI

Hypovolaemia


Any cause of ↓ intravascular volume.

- ECF depletion (usually both Na⁺ and H₂O depletion—when losses are predominantly H₂O, ECF volume is usually preserved until late).
 - Inadequate fluid intake: limited access to fluid (children, elderly patients with poor mobility, endurance sports), NBM, inadequate IV fluids (everyone on a drip is at risk).
 - GI losses: D&V, NG drainage, GI bleeding.
 - Renal losses: diuretic therapy, uncontrolled DM (osmotic diuresis), salt-losing nephropathy (rare— p. 583), post-relief of urinary obstruction, diabetes insipidus.
 - Skin losses: excessive sweating, febrile patients, burns.
- Haemorrhage:
 - Trauma, surgery (and surgical drains), GI bleeding.
- ‘Third space’ compartmental losses*:
 - Intestinal obstruction, peritonitis, pancreatitis, major fractures.



Impaired cardiac output

- Cardiac pump failure → ↓ BP → ↓ RBF.
 - Ischaemic heart disease → angina or MI.
 - Dysrhythmias (incl. uncontrolled AF).
 - New or established LV dysfunction (incl. myocarditis and cardiomyopathy of any cause).
 - Pericardial disease:  tamponade.
- In CCF, the ECF volume may be normal or ↑ (with oedema and ascites), but the kidneys respond as though it were inadequate (↓ ‘effective circulating volume’). See  p. 102 and p. 778.

Peripheral vasodilatation

- The pathophysiology of septic shock is complex but causes failure of peripheral circulatory control ( p. 166).
- Interactions between intraglomerular vaso-dilating and—constricting mediators resulting from sepsis also contribute to ↓ GFR.

Intrarenal vasomotor changes

- NSAIDs impede prostaglandin-mediated afferent arteriolar dilatation.
 - ▶ Post-op patient prescribed NSAIDs.
- ACE-I and ARB oppose angiotensin II-induced efferent arteriolar constriction. ▶ Dehydrated elderly patient still taking an ACE-I.
- Contrast administration ( p. 148).
- Renovascular disease ( p. 586).

* ‘Third space’ was originally coined to refer to a fluid compartment that is not in equilibrium with the ECF.

Causes of intrinsic renal AKI

Encompasses all causes of AKI in which the renal parenchyma has been damaged. ► ATN accounts for 80–90% of all intrinsic AKI.

⚠ Exclusion or correction of pre-renal ± post-renal factors is an essential part of the diagnosis. (See Fig. 2.5)

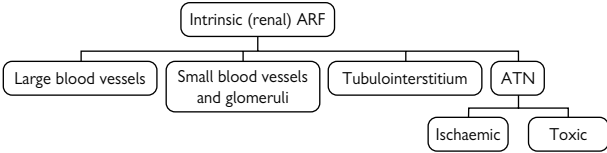


Fig. 2.5 Classification of intrinsic AKI.

Differential diagnosis of intrinsic AKI

- Larger renal vessels:
 - Renal artery occlusion due to thrombosis or dissection.
 - Cholesterol emboli (📖 p. 590).
 - Renal vein thrombosis (📖 p. 590).
 - ACE-I + bilateral renovascular disease (📖 p. 586).
- Diseases involving the small renal vessels and glomeruli:
 - Glomerulonephritis (📖 p. 536).
 - Vasculitis (📖 p. 638).
 - Thrombotic microangiopathies (📖 p. 574).
 - Malignant hypertension (📖 p. 518).
 - Scleroderma renal crisis (📖 p. 666).
- Diseases of the tubulointerstitium:
 - Acute interstitial nephritis (📖 p. 580).
 - Cast nephropathy (complicating multiple myeloma) (📖 p. 622).
 - Contrast nephrotoxicity (📖 p. 148).
 - Tumour lysis or acute urate nephropathy (📖 p. 160).
- Acute tubular necrosis (ATN) (📖 p. 106):
 - May complicate prolonged pre-renal AKI or accompany any of the disorders listed here.

Acute tubular necrosis (ATN)

ATN is, by far, the most commonly encountered cause of intrinsic AKI. It is widely seen in hospitalized patients and is predictable in high-risk clinical scenarios (so it is often preventable).

The diagnosis implies that pre-renal and post-renal factors have been excluded (or corrected) and that other causes of intrinsic AKI, such as vasculitis or TIN, are deemed unlikely. It also suggests that recovery of renal function can be achieved—but only if the causative insult is removed and adequate supportive measures are put in place. (See Box 2.1.)

Box 2.1 ATN subdivided by cause

Ischaemic (incl. septic)

ANY cause ↓ renal perfusion:

- Hypotension.
- Shock:
 - Haemorrhagic.
 - Cardiogenic.
 - Septic.
- Devascularization (incl. aortic cross-clamping).

Nephrotoxic

- Myoglobin.
- Haemoglobin.
- Aminoglycosides.
- Contrast.
- Amphotericin.
- Cisplatin.
- Many others (📖 p. 7).

Presentation

- ATN presents as AKI: ↓ GFR → uraemia and disordered salt, water, and electrolyte homeostasis.
- ► ATN may be oliguric or non-oliguric.
- It represents a continuum from pre-renal failure but with progression to:
 - Actual structural injury to the renal parenchyma.
 - Limited (or no) immediate resolution upon restoration of renal perfusion.
- Differentiation between pre-renal AKI and ATN can be difficult.
- Helpful features include (*not* uniformly present):
 - Clear evidence of sepsis, hypotension, or nephrotoxin exposure.
 - Bland urine on dipstick (or minor proteinuria).
 - Urine biochemistry (often *not* helpful and rarely performed in practice, 📖 p. 116).

Histology

► A kidney biopsy is rarely necessary for diagnosis.

ATN is a misnomer—frankly necrotic tubular cells are uncommon. Acute tubular injury (ATI) is an increasingly popular alternative term.

There may be few histological changes, even with marked functional renal impairment. Typical features: tubular cell flattening, wide spacing of tubules 2° to interstitial oedema, tubular cell vacuolation, loss of proximal tubular cell brush border, tubular cell sloughing into the lumen (\rightarrow obstruction), mitotic figures in regenerating epithelial cells \pm and leucocyte infiltration. Glomeruli are normal. (See Fig. 2.6)

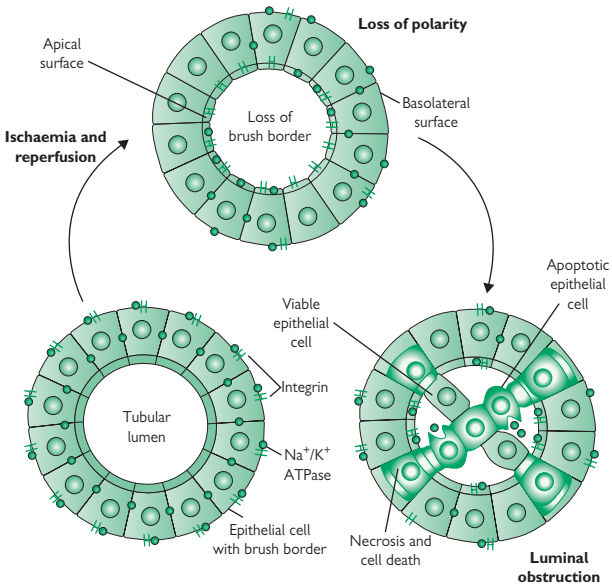


Fig. 2.6 Tubular changes in the pathophysiology of ischaemic acute tubular necrosis (p. 108). After ischaemia and reperfusion, morphological changes occur in the proximal tubules, including loss of polarity, loss of the brush border, and redistribution of integrins and sodium/potassium ATPase to the apical surface. Cell death, resulting from necrosis and apoptosis, causes cell shedding and luminal obstruction. Reproduced with permission from Schrier RW *et al.* (2004). *Neuroscience*, 129, 897–904.

Prognosis

- AKI 2° ATN imparts a significant in-hospital mortality (p. 92).
- The renal prognosis:
 - 50% will be left with some degree of renal impairment.
 - 5–10% will eventually require long-term renal replacement therapy.

Pathophysiology of ATN

(See Fig. 2.7)

Vessels and endothelium

- Blood flow is not uniform within the kidney— pO_2 falls progressively from cortex (6.65–13.3kPa) to medulla (1.3–2.9kPa) despite higher metabolic activity in the latter. ► The proximal tubular S3 segment and the medullary thick ascending loop of Henle are found in the medulla.
- Any cause of ↓ RBF or endothelial injury may ↓ delivered O_2 , rendering vulnerable segments of the nephron relatively hypoxic.
- As a result of endothelial cell injury:
 - ↑ afferent arteriolar cytosolic Ca^{2+} → ↑ sensitivity to vasoconstrictor and sympathetic stimulation → impaired glomerular autoregulation.
 - Endothelial cell swelling compounds ↓ flow → ↓ O_2 delivery.
 - Injured endothelium (or endothelium under the influence of proinflammatory mediators (TNF- α , IL-18) → ↓ endothelial adhesion molecules (ICAM-1, VCAM, P-selectin) → ↓ leucocyte-endothelial interaction → medullary vascular congestion → medullary hypoxia.
 - Activated leucocytes → local inflammation and local injury.
 - ↓ endothelial nitric oxide production + ↑ endothelin and prostaglandin synthesis → enhanced vasoconstriction, further ↓ RBF.
- The net result is impeded blood flow and ↓ O_2 delivery to metabolically active and relatively hypoxic tubular segments. In effect, demand exceeds supply.

Tubular cells

- Hypoxic proximal tubular cells (PTC) now become ↑ energy-deplete.
- Injured PTC generate proinflammatory mediators → recruitment of leucocytes into the interstitium, with subsequent inflammation.
- ↓ O_2 delivery leads to ↑ Ca^{2+} entry into energy-depleted cells.
- ↑ Ca^{2+} -dependent cysteine protease activity → actin breakdown → cytoskeletal disruption → loss of cell polarity.
- Loss of polarity → ↓ basolateral Na^+/K^+ ATPase pumps and ∴ ↓ proximal Na^+ absorption.
- More Na^+ is delivered to the distal nephron and sensed at the macula densa. This triggers *tubuloglomerular feedback* (p. 920) → ↓ GFR.
- Apical relocation of integrins → loss of cell–cell adhesion → tubular cell desquamation and cast formation → tubular obstruction → ↓ GFR.
- Desquamation of PTC exposes the basement membrane and provides a route for misdirected filtrate, with further ↑ interstitial congestion.
- Necrosis ± apoptosis (both are present—ATN is a misnomer):
 - ATP depletion + ↑ reactive O_2 species + intracellular acidosis + ↑ cytosolic Ca^{2+} + ↑ phospholipase activity → cell necrosis.
 - Apoptotic stimuli → caspase activation → cell apoptosis.
- Nitric oxide:
 - Hypoxia → ↑ PTC iNOS expression → NO release → cell death.
 - NO scavenged by O_2 radicals → toxic peroxynitrite generation.
 - (eNOS in the afferent arteriole protects against ischaemic injury).

Repair

- Post-reperfusion, sublethally injured cells → repair and proliferation.
- Non-viable cells die (necrosis and apoptosis) and exfoliate.
- Poorly differentiated epithelial cells appear (? a population of renal stem cells).
- Viable cells enter the cell cycle under regulation of cyclin-dependent kinase inhibitors (especially p21).
- Growth factors (IGF-1, EGF, HGF, TGF- β) → proliferation and differentiation of tubular cells, restoring the epithelium to health.

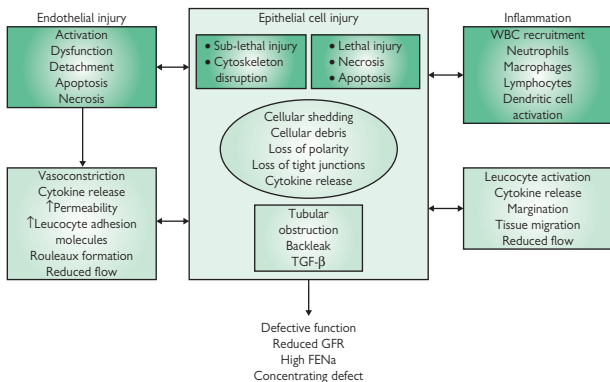


Fig. 2.7 Pathophysiology of ATN. Reproduced from Asif A. Sharfuddin & Bruce A. Molitoris, Pathophysiology of ischemic acute kidney injury. *Nature Reviews Nephrology* 7:189–200 (2011), with permission from Nature Publishing Group.

Organ cross-talk in ischaemic AKI

Distant organ dysfunction has long been recognized as part of the AKI syndrome. Mechanisms underpinning this apparent systemic proinflammatory state include altered expression of cellular adhesion molecules, abnormal lymphocyte trafficking, cytokine and chemokine release, and the dysregulation of immune responses.

- **Heart:** LV dysfunction associated with myocyte apoptosis, neutrophil infiltration, and ↑ local cytokine expression (TNF- α , IL-1, ICAM-1).
- **Lung:** acute lung injury (▶ high mortality) with ↑ microvascular permeability resulting from various proinflammatory and pro-apoptotic pathways (→ downregulation of alveolar epithelial transporters, e.g. ENaC and aquaporins).
- **Liver:** inflammation, hepatocyte apoptosis, lipid peroxidation, decreased antioxidant activity → tissue injury.
- **CNS:** confusion and encephalopathy. Neutrophil recruitment and several mediators (e.g. G-CSF and glial fibrillary acidic protein) have been implicated in neuronal injury.

AKI: recognition

Introduction

There is a lot to get to grips with in a patient with AKI. It occurs in the context of a wide range of underlying conditions, and the patient can be anywhere on a clinical spectrum from asymptomatic to critically unwell. You are not alone, however. ► Consult locally agreed AKI protocols; seek specialist help early, and make use of helpful aids, such as the free smartphone app designed by London AKI network (LAKIN), or internet resources, e.g. 📞 <http://www.londonAKI.net/clinical>.

Recognize the problem

Patients may be asymptomatic during the early stages of AKI, despite nearly non-functioning kidneys, and may be very unwell by the time the diagnosis is apparent (► emphasizing why it is so important to be familiar with high-risk patients and high-risk situations (📖 p. 98)).

Presenting features of AKI

Usually

- ↑ Ur and ↑ SCr.
- ↓ UO (UO <400mL/d is frequent (~50%) but not invariable).

Frequently

- Volume depletion OR
- Volume overload → pulmonary oedema.
- Hyperkalaemia (→ arrhythmias or cardiac arrest).
- Non-specifically sick, often deteriorating, patient.

Rarely

- Uraemic symptoms (📖 p. 213).

- Check renal function and K⁺ in all acutely unwell patients, esp. if:
 - Falling or low UO, or anuria.
 - Persistent nausea and vomiting, or prolonged NBM.
 - Drowsiness or impaired conscious level.
 - Signs of systemic sepsis.
 - Hypertension or hypotension, particularly if severe.
 - Pulmonary ± peripheral oedema.
 - Puzzling ECG abnormalities (► T wave changes and conduction delays).
 - Metabolic acidosis.

AKI or CKD?

Patients are often found to have \uparrow SCr or \downarrow eGFR \pm oliguria at the time of their presentation, with unrelated medical or surgical conditions. Differentiating true AKI from stable (long-standing) CKD, or even an acute deterioration of pre-existing renal impairment, is clearly very important.

Much has traditionally been made of the ability to distinguish the two after initial clinical assessment and blood tests. However, many of these features—even if present—are, at best, suggestive and, at worst, misleading.

The only two consistently useful discriminators are:

1. Previous measurements of renal function:

- Where might this be documented? Can the patient remember previous blood tests?
- Previous hospital admissions?
- Search your pathology system, and pull hospital notes.
- Ask the patient's GP to check their records.

2. Ultrasound:

- Long-standing renal disease leads to loss of renal parenchyma and \downarrow renal size.
- Small ($< 9\text{--}10\text{cm}$ length), echo bright, often cystic kidneys are characteristic of CKD.

► Normal-sized kidneys should arouse suspicion of AKI. A common exception is diabetic nephropathy (📖 p. 604).

Lab findings suggesting AKI, rather than CKD

These are *rarely* as helpful as textbooks imply. Err on the side of caution (i.e. assume AKI until proven otherwise).

- Anaemia might suggest chronic undersynthesis of erythropoietin by scarred kidneys: a *normal* Hb \therefore argues against CKD, but anaemia occurs in both AKI and CKD.
- \downarrow Ca^{2+} and \uparrow PO_4 suggest established CKD-MBD (📖 p. 232). Not so: disturbances of mineral metabolism can occur rapidly in AKI.
- In many situations, particularly when renal size is normal, a kidney biopsy may be necessary to determine the nature of the renal lesion and the extent of reversibility (📖 p. 121).

AKI: priorities

Make the patient safe

Evaluate as for any critically unwell patient: airway, breathing, and circulation. The standard priorities of resuscitation initially override thoughts regarding underlying cause. ► Does the patient require urgent level 2 or 3 care?

Two additional specific questions must be addressed urgently:

- ► How high is the K^+ ?
- ► What is the volume status?

Hyperkalaemia (📖 p. 130) and pulmonary oedema (📖 p. 134) may prove rapidly lethal, if untreated. ►► Call for expert help.

Care bundles and protocols, such as that provided by LAKIN (see Fig. 2.8), provide a helpful framework for prioritizing management.

Look for a reversible cause

Once the patient is stabilized, consider the following questions, as they may identify situations where relatively straightforward interventions can have a significant impact.

- Is it pre-renal (📖 p. 114)?
 - Is the patient septic?
 - Are there predisposing factors in the history?
 - Carefully assess the patient's volume and haemodynamic status.
 - Is invasive monitoring needed? Involve your critical care team if it is.
- Is it post-renal (📖 p. 115)?
 - Are there predisposing factors in the history?
 - Is there a palpable bladder or significant urinary tract symptoms?
 - What does the urine look like—any haematuria?
 - Arrange an urgent USS.
- What is on the drug chart (📖 p. 7)?
 - Stop all nephrotoxins, if possible.
- Has any radiocontrast been administered?
- Have you dipsticked the urine (📖 p. 116)?
 - ► Do it now—you may forget later.

AKI care bundle

Institute in all patients with a 1.5 × rise in creatinine or oliguria (0.5 mL/kg/h) for >6 hours

This is a medical emergency

**Full set of physiological observations
Assess for signs of shock/hypoperfusion
If MEWS triggering, give oxygen, begin resuscitation,
and contact critical care outreach team**

Fluid therapy in AKI

Assess heart rate, blood pressure, jugular venous pressure, capillary refill (should be <3 s), conscious level.
If hypovolaemic, give bolus fluids (e.g. 250–500 mL) until volume replete with regular review of response. Middle grade review if >2 litres filling in oliguria.
If the patient is euvoalaemic, give maintenance fluids (estimated output plus 500 mL) and set daily fluid target.

Monitoring in AKI

Do arterial blood gas and lactate if venous bicarbonate is low or evidence of severe sepsis or hypoperfusion. Consider insertion of urinary catheter and measurement of hourly urine volumes. Measure urea, creatinine, bone, other electrolytes, and venous bicarbonate at least daily while creatinine rising. Measure daily weights, keep a fluid chart, and perform a minimum of 4-hourly observations. Perform regular fluid assessments and check for signs of uraemia.

Investigation of AKI

Investigate the cause of all AKI unless multi-organ failure or obvious precipitant Urine dipstick.
If proteinuria is present, perform urgent spot urine protein creatinine ratio (PCR).
USS should be performed within 24 hours unless AKI cause is obvious or AKI is recovering or within 6 hours if obstruction with infection (pyonephrosis) is suspected. Check liver function (hepatorenal), CRP, and CK (rhabdomyolysis). If platelets low, do blood film/LDH/Bili/retics (HUS/TTP). If PCR high, consider urgent Bence-Jones protein and serum free light chains.

Supportive AKI care

Treat sepsis—in severe sepsis, intravenous antibiotics should be administered within 1 hour of recognition. Stop NSAID/ACE/ARB/metformin/K-sparing diuretics, and review all drug dosages. Give proton pump inhibitor and perform dietetic assessment. Stop antihypertensives if relative hypotension. If hypovolaemic, consider stopping diuretics. Avoid radiological contrast if possible. If given, follow prophylaxis protocol.

Causes Think 'STOP AKI'

Sepsis and hypoperfusion, **T**oxicity (drugs/contrast), **O**bsturbation, **P**arenchymal kidney disease (acute GN)

Fig. 2.8 The LAKIN AKI care bundle. Reproduced from London AKI network manual (2012), with permission. <http://www.londonAKI.net/clinical>

Assessing AKI: clinical clues

Pre-renal AKI

History (📖 p. 104)

- Any cause of ↓ intravascular volume?
 - Inadequate fluid intake, haemorrhage, GI losses, renal losses, skin losses, third-space losses.
- Any cause of cardiac pump failure?
- Any evidence for sepsis?

Clinical examination (📖 p. 12)

- Assessment of volume status is fundamental to diagnosis:
 - BP: check lying and standing, if possible.
 - Heart rate: check lying and standing, if possible.
 - Peripheral perfusion:
 - Warm with bounding pulse → vasodilatation (? sepsis).
 - Cold and shut down with ↓ capillary refill → volume depletion or low cardiac output.
 - ↓ JVP: hypovolaemia or vasodilatation (may be ↑ with pump failure).
 - Peripheral and pulmonary oedema.
 - Urine output.

Poor signs of volume depletion

- Dry mucous membranes (most sick patients mouth-breathe).
- ↓ skin turgor (better sign in children).

Classically

1. Volume depletion (hypovolaemic or haemorrhagic shock):

- (Postural) hypotension.
- May be peripherally shut down.
- JVP ↓.

2. Poor cardiac output (cardiogenic shock):

- Hypotension with narrow pulse pressure.
- Peripherally shut down (often very).
- JVP ↑.

3. Systemic vasodilatation (septic shock):

- Hypotension with ↑ pulse pressure.
- Peripherally warm.
- JVP ↓.

Intrinsic renal AKI

Large renal vessels

History

- Cardiovascular:
 - CV risk: smoking, diabetes, lipids, ↑ BP, age.
 - CV disease: claudication and PVD, stroke, IHD.
 - CV intervention: invasive/endovascular radiological procedures, vascular surgery.

- Source of emboli: AF, prosthetic valve, cardiomyopathy, thrombophilia tendency.
- Nephrotic syndrome: renal vein thrombosis (📖 p. 590).

Examination

AF, missing pulses, dilated heart, bruits, aortic aneurysm, ischaemic toes, ↑ BP (though very non-specific), oedema (? nephrotic).

Small renal vessels and glomeruli

History

No other cause evident; recent infection, particularly skin or throat (post-streptococcal GN); symptoms suggesting a deep-seated infection (fevers, night sweats); known systemic disorder, e.g. SLE, scleroderma, vasculitis; symptoms suggesting an underlying connective tissue disorder or vasculitis (📖 p. 5).

Examination

Rash, ↑ BP, oedema, synovitis, arthropathy, uveitis, mouth ulcers, epistaxis, hearing loss, stigmata of endocarditis, evidence of scleroderma or other connective tissue disorder, abnormal respiratory findings (pulmonary-renal syndrome).

Investigations

Urinalysis (📖 p. 116), abnormality in immunological/serological testing ('renal' or 'nephritic/myeloma' screen) (📖 p. 119), and renal biopsy may be required (📖 p. 121).

Tubulointerstitium

History

Drugs (📖 p. 7); systemic infection: many are associated, including TB (📖 p. 698). Systemic diseases: myeloma, sarcoidosis, Sjögren's syndrome, SLE, uveitis (tubulointerstitial nephritis and uveitis (TINU) syndrome (📖 p. 581)).

Examination

Fever or rash, easy bruising in multiple myeloma.

Investigations

Eosinophiluria on urine microscopy/cytology, eosinophilia in peripheral blood (neither are universal).

Post-renal (📖 p. 730)

History

LUTS, prostate disease, urothelial cancer, stones, pain, haematuria.

Examination

Palpable bladder? Visible haematuria?


Investigation

Early urinary tract imaging (usually USS) is essential.

Assessing AKI: urinalysis

► The only excuse for not performing a urine dipstick is if a patient is completely anuric!

Urinalysis findings can point to a diagnosis, particularly for glomerulonephritis and other intrinsic renal lesions (see Fig. 2.9).

- Perform a dipstick (yourself), and *document the result*.
 - If there is significant blood and protein on dipstick: (i) exclude a UTI; (ii) consider an immunological/serological screen ('renal' or 'nephritic/myeloma' screen,  p. 119). ► Seek expert help.

Note: Δ blood will often be present post-catheterization.

- Send an MSU for microscopy and culture.
- uPCR or uACR if significant dipstick protein.

Urine biochemistry

Included here for completeness only. While still beloved of postgraduate examiners, urine biochemistry is of limited value in everyday practice. (See Table 2.3.)

In pre-renal AKI, tubular function is intact with avid salt retention, whereas, in established ATN, the resorptive and concentrating capacity of the kidney is lost. Urinary biochemical indices can \therefore differentiate the two.

- 'Typical' pre-renal AKI: \downarrow u- Na^+ , \uparrow Ur, \uparrow SCr in the urine; u-osmolality high.
- 'Typical' ATN: \uparrow u- Na^+ , \downarrow Ur and \downarrow SCr in the urine; u-osmolality relatively low.

Δ Problems

- Not sufficiently sensitive or specific. Rarely influences management.
- Diuretics confound the analysis (\rightarrow dilute urine with \uparrow Na^+ content).
- There are exceptions that biochemically appear pre-renal but are not: hepatorenal syndrome, contrast nephropathy, early obstruction, acute GN, and vasculitis.

Table 2.3 Urine biochemistry in urinalysis

Urine biochemistry	Pre-renal	ATN
Urine specific gravity	>1.020	<1.010
Urine osmolality (mOsm/kg H_2O)	>500	<350
Urine:plasma osmolality	>1.5	<1.1
Urinary Na^+ (mmol/L)	<20	>40
Fractional Na^+ excretion % (FE_{Na^+}) ¹ best index!	<1	>2
Fractional urea excretion % (FE_{urea})	<35	>35
Plasma urea:creatinine ratio	>10	<15
Urine:plasma urea ratio	>8	<3
Urine:plasma creatinine ratio	>40	<20
Renal failure index ²	<1	>1

¹ (urine Na^+ /plasma Na^+)/(urine Cr/plasma Cr) \times 100.

² urine Na^+ /(urine creatinine/plasma creatinine) \times 100.

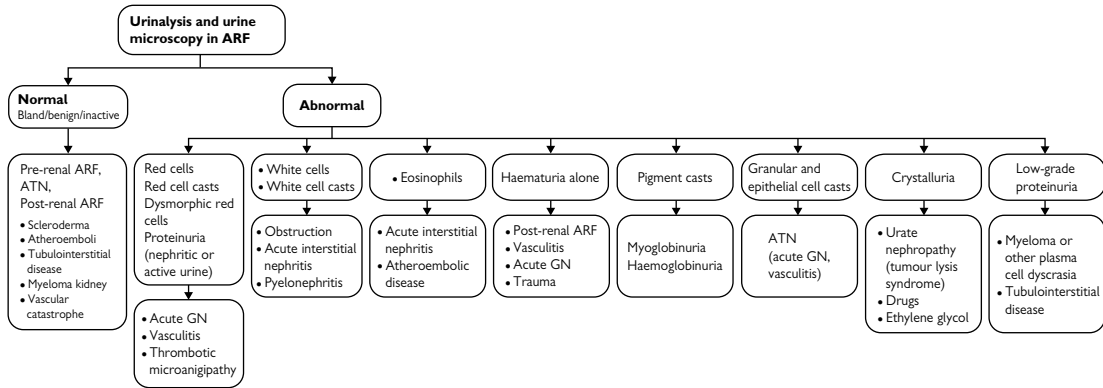


Fig. 2.9 The findings on urinalysis and urine microscopy in AKI.

Assessing AKI: blood tests

Managing AKI requires regular and informed testing. Order investigations sensibly and cumulatively—do not just request everything listed here.

Haematology

- FBC:
 - ↓ Hb develops early, typically 80–100g/L. ⚠ Haemolysis, GI bleeding.
 - ↑ WCC: infection (rarely tissue infarction or vasculitis). Eosinophilia is a rare feature of TIN and cholesterol emboli. ↓ WCC: severe sepsis (rarely SLE).
 - ↓ plt: DIC or thrombotic microangiopathy (→ check clotting and ask for a blood film). ↑ plt: inflammatory disorder, e.g. vasculitis.
 - Pancytopenia: ? marrow infiltration (? myeloma or other malignancy).
- Clotting:
 - ? Liver disease (↑ INR) or DIC (↑ PT, ↑ APTT, ↑ D-dimers).
- Group and save if anaemic.
- ↑ ESR with any inflammatory condition but esp. myeloma and SLE.
- Blood film if ↓ plts or ? microangiopathy:
 - Fragmented red cells. If found, send LDH, haptoglobins, reticulocyte count.

Biochemistry

- U&E:
 - ↑ plasma Ur:Cr ratio may indicate pre-renal AKI (but see 📖 p. 37).
 - ↑ K⁺. ▶▶ Needed urgently.
 - Na⁺ usually normal; ↓ Na⁺ occurs if volume overload or diuretics.
 - ↓ venous HCO₃⁻ → metabolic acidosis (if normal with normal O₂ saturation, then ABG may not be necessary).
- LFTs:
 - ↓ albumin may imply proteinuria and GN.
 - ? ↑ bilirubin, ? hepatorenal syndrome (📖 p. 156)? paracetamol overdose.
 - ⚠ ↑ transaminases may be of muscle origin → check the CK.
- Ca²⁺ and PO₄:
 - ↑ Ca²⁺ is a cause of AKI (? myeloma, sarcoidosis, malignancy).
 - ↓ Ca²⁺ and ↑ PO₄ are present in most cases.
- CRP for infection or inflammation. Procalcitonin if available.
- Creatine kinase (CK) if rhabdomyolysis likely.
- Urate if tumour lysis or pre-eclampsia possible.
- Lactate to assess tissue ischaemia or underperfusion.

Microbiology

Culture urine and blood if any clinical suspicion of sepsis.

Arterial blood gas

ABG and lactate are necessary if venous HCO₃⁻ is low (or unavailable) or there is evidence of sepsis, hypotension, or clinical deterioration.

Minimum AKI panel

- Urine dipstick.
- FBC, U&E, Ca²⁺, phosphate, albumin, LFT, CK, and CRP.
- Venous HCO₃⁻ or ABG.

Immunological/serological testing (the 'renal' or 'nephritic/myeloma' screen)

(Some) of these may be needed if intrinsic AKI (besides ATN) is suspected (e.g. active urine \pm systemic symptoms). However, common sense is required. There is no role for the reflex ordering of these in the majority of AKI (costly and require careful clinical correlation).

Anti-nuclear antibodies (ANA)

The serological hallmark of many autoimmune diseases. Further defined by specific target antigens. Where clinical suspicion is strong, the specific assay may be necessary despite a negative ANA (📖 p. 42). ⚠ False +ve ANAs are common.

Anti-neutrophil cytoplasmic antibodies (ANCA)

Autoantibodies directed against components of neutrophil cytoplasm, characteristic of small vessel vasculitis (📖 p. 642). Two patterns:

- Cytoplasmic (cANCA): antigen usually proteinase 3 (PR3).
- Perinuclear (pANCA): antigen usually myeloperoxidase (MPO).

Anti-glomerular basement membrane antibody (anti-GBM)

Highly sensitive and specific for anti-GBM disease (📖 p. 656).

Anti-streptolysin O titres (ASOT)

Post-streptococcal GN is the historical prototype for the acute nephritic syndrome, though incidence is falling (📖 p. 548). Sensitive for the diagnosis of streptococcal pharyngitis but less so for skin infections.

Protein electrophoresis (serum and urine)

Plasma cell dyscrasias: serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum free light chains (SFLC).

Immunoglobulins (IgG, IgA, and IgM)

Diffuse increase in vasculitis, SLE (and other connective tissue disorders), and HIV infection. Immune paresis in myeloma.

Rheumatoid factor (Rf)

May be +ve in RA associated vasculitis (📖 p. 669) or cryoglobulinaemia (📖 p. 634).

Viral serology

Hep B is associated with PAN (📖 p. 652), hepatitis C with mixed essential cryoglobulinaemia (📖 p. 686). HIV may present in many ways involving the kidney. ► It is desirable to know the viral status prior to haemodialysis.

Cryoglobulins (📖 p. 634)

Consider if unexplained rash, peripheral neuropathy, hypocomplementaemia, known hep C, known lymphoproliferative disorder, or +ve Rf (a useful screening test). The sample needs to be transported at 37°C, so bleed the patient and transport the sample yourself (in a water bath—an armpit is 2nd best) within minutes. Warn the lab it is coming.

Antiphospholipid antibodies

Associated with the primary antiphospholipid syndrome (📖 p. 664). Liaise with your haemostasis laboratory.

Assessing AKI: imaging

CXR

▶▶ Perform a CXR (urgently if tachypnoea, ↓ O₂ sats, haemoptysis, suspected infection, or significant associated primary lung disease).

The key findings are pulmonary oedema, respiratory infection, and pulmonary haemorrhage (all → air space shadowing that may look identical).

However, additional useful information may be gathered:

- Cardiac contour—? LVH consistent with long-standing ↑ BP, ? pericardial effusion.
- Hilar lymphadenopathy, lytic lesions.

Renal ultrasound

▶▶ Perform an USS of the renal tract as soon as possible (within hours if suspected pyonephrosis).

Imaging rarely makes a specific diagnosis but has two principal aims:

- To exclude obstruction (📖 p. 732).
- To confirm the presence of two kidneys and measure renal length.

Renal length is used as a surrogate for the time course of renal impairment. Long-standing CKD → parenchymal scarring, loss of renal volume and length.

- >10–11cm = normal (∴ probable AKI).
- <8–9cm (± acquired cysts) suggests CKD.

Isotope studies in AKI

- Certainly not first-line but (very) occasionally helpful:
 - Acute loss of renal perfusion associated with renal artery occlusion or embolism can be diagnosed with nuclear renography (e.g. MAG 3 scan).
 - Cortical necrosis (after severe haemorrhagic shock, particularly post-partum) will be demonstrated.
 - AKI accompanying early vascular complications in the immediate post-transplantation setting can be evaluated.
 - In experienced hands, recovery from ATN can be assessed, though it is rarely clinically useful.
 - In partial obstruction, delayed transit in the ureteric phase can be helpful.

Assessing AKI: histology

Role of the renal biopsy in AKI (see also p. 82)

Required in a minority of cases only. Consider once pre- and post-renal factors have been addressed and where 'non-ATN' intrinsic AKI is suspected. In ATN, the prognosis for renal recovery is generally good, and histological verification will not alter management.








The principal aims of biopsy are to:

- Establish a tissue diagnosis.
- Assess prognosis (is renal function salvageable?).
- Guide therapy.


Potential indications

- Unexplained AKI (initial work-up unhelpful/equivocal).
- Suspected glomerular disease:
 - Haematuria \pm casts, significant proteinuria, marked \uparrow BP (Δ control BP first).
- Serological or other evidence of systemic disease:
 - For example, ANCA, ANA, anti-GBM, paraprotein.
- Suspected thrombotic microangiopathy (HSP/TTP).
- Presumed ATN persists (e.g. >2 weeks, esp. if dialysis-dependent).
- Pre-existing glomerular disease.
- Suspected TIN/drug allergy.
- Suspected atheroembolic disease.













'Non-ATN' intrinsic renal disease presenting as AKI

- Acute primary GN ( p. 536).
- Systemic vasculitis affecting the kidney ( p. 638).
- Infection-associated GN ( p. 548).
- Thrombotic microangiopathies ( p. 574).
- Acute TIN ( p. 580).
- Myeloma cast nephropathy ( p. 622).
- Atheroembolic disease ( p. 590).

AKI management: a checklist

Despite a multitude of potential causes, several general principles apply to the management of AKI. See AKI bundle on  p. 113.

Where can I find information on...?

- Resuscitating volume deplete pre-renal AKI? ( p. 124)
- Managing hyperkalaemia? ( p. 131)
- Managing volume overload and pulmonary oedema? ( p. 134)
- Managing acidosis? ( p. 136)
- Maintaining nutrition? ( p. 140)
- Instituting dialysis? ( p. 172)
- Specific causes of AKI:
 - ATN? ( p. 106)
 - Hepatorenal syndrome? ( p. 156)
 - Contrast nephrotoxicity? ( p. 148)
 - Tumour lysis? ( p. 160)
 - Septic shock and AKI? ( p. 168)
- Post-renal failure and acute obstruction? ( p. 730)

Have you...

- Seen the result of the serum K^+ and acted appropriately?
- Assessed the patient's volume status and:
 - Satisfied yourself that, clinically and radiologically, the patient is not in pulmonary oedema?
 - Adequately corrected volume depletion?
- Taken a full history and examined the patient from head to toe?
- Excluded a palpable bladder?
- Seen a list of *all* the patient's drugs? If they are an inpatient, have you checked their drug chart, including the 'prn' side?
- Stopped nephrotoxins, if possible?
- Performed a urinalysis and sent an MSU for M,C+S?
- Arranged an urgent ultrasound?
- Checked the Hb \pm sent a group and save?
- Tried to find any historical tests of renal function?
- Checked serum Ca^{2+} and $PO_4 \pm$ written up a phosphate binder?
- Checked acid-base status and intervened appropriately?
- Arranged for the patient to be nursed in a sufficiently high dependency environment, with strict monitoring of fluid intake and output?
- Spoken to your dietitian?
- Discussed the patient with your local renal unit if needs be?
- If intrinsic AKI is suspected, sent off a nephritic and myeloma screen?

Questions you will be asked when referring to a renal unit

- What's the story?
- What's the potassium?
- What's the patient's volume and haemodynamic status? Are they dehydrated, overloaded, or about right? How do you know?
- Is there anything else of note on clinical examination?
- What's the patient's acid–base status?
- What drugs has the patient been on?
- What did the urine dipstick show?
- Has the patient had a renal ultrasound?
- Is the patient passing urine? How much?
- Do you have any record of a previous eGFR/serum creatinine?
- What comorbidity does the patient have?
- Is the patient fit for transfer? Are you sure (see Fig. 2.10 below)?

See Fig. 2.10 for LAKIN guidelines on transferring to a renal unit.

Transfer from ward to kidney unit (interhospital transfer)

The following is a guideline for whether patients are safe to transfer from a ward to a kidney unit in another hospital.
All AKI 3 patients or patients with complications should also be assessed as safe for transfer by a middle grade doctor and, if necessary, by the home critical care team

Hyperkalaemia

No ECG changes.
K < 6.0 mmol/L.

If K lowered to < 6.0 after presentation this must be potentially sustained (e.g bicarbonate therapy or dialysis/CVVH) not transient therapy (insulin and dextrose).

Renal acidosis

pH > 7.2.
Venous bicarbonate > 12 mmol/L.
Lactate < 4 mmol/L.

Respiratory

Respiratory rate > 11 and < 26/min.
Oxygen saturations > 94% on not more than 35% oxygen.
If patient required acute CPAP must have been independent of this treatment for 24 hrs.

Circulatory

Heart rate > 50/min and < 120/min.
Blood pressure > 100 mmHg systolic.
MAP > 65 mmHg.
Lactate < 4 mmol/L.
(Lower BP values may be accepted if it has been firmly established these are pre-morbid.)

Neurological

Alert on AVPU score or GCS > 12.

If criteria not met, emergency referral to local critical care

Once stabilized follow ITU to acute kidney unit transfer policy.

Fig. 2.10 LAKIN guidelines for transfer to a renal unit. Reproduced from London AKI network manual (2012), with permission. <http://www.londonAKI.net/clinical>

AKI management: volume replacement—which fluid?

Prompt fluid resuscitation reverses pre-renal AKI. However, there is increasing evidence that fluid overload is harmful and ∴ needs to be avoided. ► The key to achieving euvolaemia is repeated clinical assessment of a patient's volume status.

Which fluid?

Crystalloids

See Table 2.4 for composition of crystalloids.

Isotonic saline

0.9% isotonic remains the benchmark against which other solutions are measured. However, despite its other pseudonyms, it is neither 'normal' nor 'physiological'. In fact, there is evidence that it may be harmful. Excessive use of saline can result in hyperchloraemic acidosis. ⚡ Although the morbidity associated with this condition is probably low (isotonic saline has been in use for 50 years), it has informed a move towards the use of balanced solutions.

Balanced crystalloids

Refer to solutions with an electrolyte composition closer to plasma. The 2009 British consensus guidelines on intravenous fluid therapy for adult surgical patients recommended the use of balanced crystalloids over saline. Furthermore, the recent UK AKI consensus statement includes the recommendation that balanced crystalloids are used, unless patients are hypochloraemic or hyperkalaemic (balanced crystalloid solutions, such as Hartmann's and Ringer's solutions, contain 5mmol/L K^+ and must be used with caution). ⚡ Critics of such guidelines say that, while the move to balanced crystalloids is unlikely to cause harm, benefits are likely to be marginal only.

Hypotonic crystalloids

0.45% ('half normal') saline and 5% glucose distribute rapidly throughout total body water and are of limited use for the restoration of intravascular volume. Avoid unless true water depletion (hypernatraemia, 📖 p. 788).

Sodium bicarbonate

'Weak' $NaHCO_3$ solutions (e.g. 1.26% or 1.4%) can be useful in volume-depleted, acidotic ($pH < 7.15$) ± hyperkalaemic patients (📖 p. 131). Use with crystalloid, e.g. in a ratio of 1L $NaHCO_3$ to every 2–3L of NaCl. ⚠ Avoid stronger (4.2% or 8.4%) solutions, and monitor for ↓ Ca^{2+} .

Table 2.4 Composition (mmol/L) of commonly available crystalloids

Electrolyte	Plasma (typical)	Isotonic saline	Example balanced crystalloid, e.g. Hartmann's, Ringer's lactate
Sodium	140	154	131
Potassium	5	0	5
Chloride	100	154	111
Calcium	2.2	0	2
Magnesium	1	0	1
Bicarbonate	24	0	0
Lactate	1	0	29

Synthetic colloids

Solutions contain oncologically active ingredients (e.g. hydroxyethyl starch or gelatin) that remain in the intravascular compartment and pull in extravascular water. Effective volume expanders, but evidence suggests that starch-containing solutions may worsen AKI. Examples include Gelofusine® and Haemaccel®—both gelatin-based. The use of ≥ 1000 –1500 mL may deplete clotting factors and \uparrow bleeding risk. Severe allergic reactions have been reported to all types of colloid.

► The recent UK consensus statement on AKI and guidelines from the European Society of Intensive Care Medicine recommends that colloid (including gelatin-based) solutions be avoided.

Human albumin solutions

'Physiological colloid'. Expensive. Although a Cochrane meta-analysis concluded that its use was associated with \uparrow mortality in the critically ill, the more recent (and well-designed) SAFE study suggested equivalence with saline (and benefit in the subgroup of patients with sepsis). Many favour its use when volume depletion occurs in the context of hypoalbuminaemia. Proven benefit also in AKI in the context of cirrhosis with spontaneous bacterial peritonitis (p. 158). The results of the Albumin in Severe Sepsis and Septic Shock (ALBIOS) study, in which patients with severe sepsis were randomized to either albumin or crystalloid for resuscitation, will be available in 2013.

- Isotonic (4–5%). Usually 100–500 mL bottles. Used to restore circulatory volume.
- Concentrated (20–25%). Usually 50–100 mL bottles. Used to expand circulatory volume when general salt and water restriction is desirable, i.e. an oedematous, hypoalbuminaemic patient who is intravascularly depleted (e.g. nephrotic syndrome, cirrhosis).

AKI management: volume replacement—how much?

See Figs 2.11 and 2.12 for guidelines on fluid therapy and AKI complications, respectively.

How much fluid?

The volume required to restore euvolaemia is the volume that improves clinical signs of fluid depletion. These include:

- Reducing tachycardia.
- Improved peripheral perfusion.
- Rising BP (► check for postural drop, if possible). If ↓ BP, despite apparently adequate filling, consider cardiogenic or septic shock.
- Visible JVP.
- Improving UO.

⚠ Beware volume overload: ↑ P, ↑ BP, ↑ RR, basal lung crackles, ↓ O₂ sats.

How quickly?

Resuscitation

See 📖 p. 168 for initial management of severe sepsis and sepsis-induced shock. In other situations, the aim is to infuse fluids (± blood products) rapidly to restore BP and tissue perfusion. If in doubt, trial of 200–300 mL crystalloid fast IVI, and reassess clinical parameters. Repeat, as required.

Replacement

If the patient is not shocked, the optimal infusion rate depends on: (i) degree of hypovolaemia; (ii) ongoing losses; (iii) whether oligo-anuric; (iv) CV status.

The following is a *rough* guide to getting things underway (⚠ slower in the elderly and in those with poor LV function):

- First litre over 2h, *then reassess*.
- Second litre over 4h, *then reassess*.
- Third litre over 6h, *then reassess*.

In the face of ongoing losses (e.g. diarrhoea), input should aim to exceed measured and unmeasured (insensible, ~30mL/h) losses by 100mL/h. If you think you may have overdone it, stop fluids and reassess the patient.

Maintenance

Once euvolaemic, and assuming no other losses, match UO + 30mL on an hourly basis. Insensible losses will be higher in a febrile patient. ► Reassess the patient at least twice a day.

When do you need a central line?

- Not often; however, bedside assessment can be problematic. Although generally straightforward when the patient is profoundly volume-depleted, it is much more difficult to judge when a patient is at the point of euvoaemia and \therefore no longer in need of fluid.
- Despite this, clinical assessment remains the cornerstone—it is an important skill and improves with practice.
- If you are not experienced enough to assess volume status clinically, then you are unlikely to be experienced enough to use invasive monitoring correctly. If in doubt, speak to your critical care.
- Stand-alone CVP measurements do not correlate well with intravascular volume status (although trends following a fluid bolus may be helpful).
- ► Putting a central lines into a hypovolaemic patient is not easy and offers a significant risk of complication.
- The UK consensus AKI statement does not advocate a CVP line for the routine management of AKI.

However, a CVP may be useful in AKI in conjunction with:

- Septic shock and capillary leak.
- Cardiogenic shock or where the CV status is precarious and you feel it would be dangerous, or unwise, to give significant fluids without a more accurate baseline and continuous monitoring.
- The need for vasoactive medications (e.g. noradrenaline).
- There are other non-invasive tests that are being increasingly used to assess volume status, e.g. IVC diameter on ultrasound (📖 p. 13.)

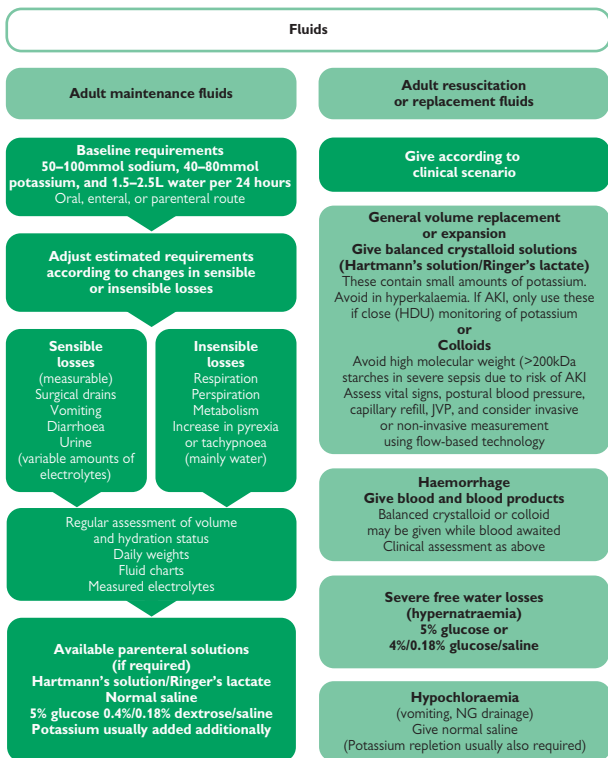


Fig. 2.11 AKI fluid therapy. Reproduced from London AKI network manual (2012), with permission.  <http://www.londonAKI.net/clinical>

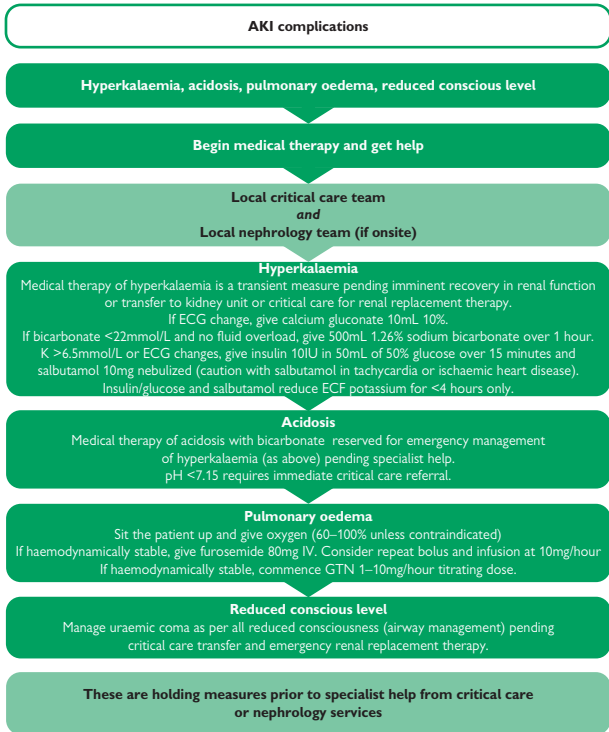



Fig. 2.12 AKI complications from London AKI network manual. Reproduced from London AKI network manual (2012), with permission.  <http://www.londonAKI.net/clinical>

AKI management: hyperkalaemia

In excitable tissues, $\uparrow K^+ \rightarrow$ depolarization of the membrane resting potential $\rightarrow Na^+$ channel inactivation $\rightarrow \downarrow$ membrane excitability \rightarrow neuromuscular depression and cardiac dysrhythmias.

What represents a dangerous $\uparrow K^+$?

- Chronically hyperkalaemic patients may tolerate $\uparrow K^+$ of 6.0–7.0mmol/L (▶ but treat if >6.5 mmol/L).
- ⚠ However, an acute $\uparrow K^+$ in AKI is much less likely to be tolerated, particularly if: (i) elderly; (ii) associated cardiac disease (esp. arrhythmias); (iii) oliguria (cannot excrete $\uparrow K^+$).
- Closely monitor (\rightarrow cardiac monitor, repeat serum K^+ 2–4-hourly) all patients with $\uparrow K^+$ acutely >6.0 mmol/L, and commence treatment to enhance K^+ wasting.
- ▶▶ Treat to urgently lower serum K^+ if ≥ 6.5 mmol/L.

⚠ Although U&E are often repeated to exclude haemolysis or artefact, this should cause delays \rightarrow put on a cardiac monitor, and start treatment.

The hyperkalaemic ECG

ECG manifestations of $\uparrow K^+$ are manifold (see Fig. 2.13). ⚠ Mild ECG changes can progress to life-threatening disturbances very quickly. All may be exacerbated by coexisting $\downarrow Ca^{2+}$ and acidosis. ⚠ A normal ECG does *not* rule out cardiac instability.

- Peaking of T waves ('tenting').
- Flattening and disappearance of P waves.
- Prolonged PR interval (1° heart block).
- Progressive widening of the QRS complex.
 - Deepened S waves and merging of S and T waves.
- Idioventricular rhythm.
- Sine wave pattern.
- VF and asystolic cardiac arrest.

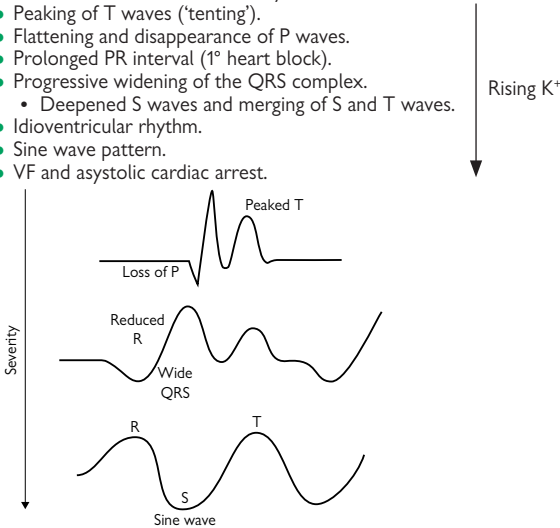


Fig. 2.13 The ECG changes of hyperkalaemia.

►► Treatment of dangerous hyperkalaemia

The following ↓ *serum* K^+ acutely but DO NOT ↓ overall elevated *total body* K^+ . Additional measures, described on [book icon] pp. 132–133, are ∴ also required.

Calcium

- If $K^+ \geq 6.5$ mmol/L or ECG changes.
- ► Ca^{2+} is cardioprotective—it does not ↓ K^+ .
- Antagonizes membrane K^+ effects by poorly understood mechanisms.
 - 10 mL 10% calcium gluconate (usually 1 ampoule—calcium gluconate contains 220 μ mol Ca^{2+} /mL), or
 - 5 mL 10% calcium chloride (usually half an ampoule— $CaCl_2$ contains 680 μ mol Ca^{2+} /mL).
- Give over 2–5 min. Repeat if no ECG improvement after 5 min (up to 40 mL calcium gluconate).
- Acts within minutes, but *protective effect lasts < 1h*.
- ⚠ Can induce digitalis toxicity (→ a pragmatic approach: halve the initial dose, and give more slowly if taking digoxin).

Insulin and glucose

- If $K^+ \geq 6.5$ mmol/L or ECG changes.
- Insulin binds to its cellular receptor and ↑ Na-K-ATPase activity, moving K^+ into cells. Glucose alone will ↓ K^+ through endogenous insulin release, but insulin/glucose is more effective.
- 10–15 IU of soluble insulin (e.g. Actrapid®) in 50 mL of 50% glucose IVI over 10 min (alternative: 5 IU of soluble insulin in 50 mL 20% glucose over 15 min by syringe pump and repeated).
- 50% glucose is extremely viscous and irritant. Find a large vein, and flush with saline afterwards.
- Effect within 15–30 min (peak ~60 min), lasts for 2–4 h. Expect a ↓ of 0.5–1.5 mmol/L. Can be repeated after 4 h.
- Check BMs regularly for 6 h, and infuse 10% glucose IVI if ↓ glucose.

Sodium bicarbonate

- If ↑ K^+ in the presence of acidosis ($HCO_3^- < 16$) and volume depletion.
- ↑ Na^+/H^+ exchange → ↑ intracellular Na^+ → ↑ Na-K-ATPase activity (i.e. K^+ in for Na^+ out). Additional pH-independent mechanisms operate.
- 1.26% or 1.4% solutions as 200–500 mL over 15–60 min IVI.
- In cardiac arrest: 50 mL of 8.4% (1 ampoule) IVI.
- ⚠ CAUTION: do not infuse bicarbonate solutions into the same cannula as calcium gluconate/carbonate unless thoroughly flushed.
- Action within hours, not minutes.
- Involves an appreciable Na^+ load (150 mmol Na^+). ⚠ Volume overload.
- Rapid correction of acidosis in a patient with ↓ Ca^{2+} may induce tetany and seizures, as ionized calcium drops rapidly as pH ↑.

β 2-agonists (salbutamol, etc.)

- 10–20mg (i.e. a large dose) of nebulized salbutamol will \downarrow K^+ by up to 1mmol/L but has limited additive benefit beyond insulin/glucose (it acts via the same Na-K-ATPase and has a slower onset of action).
- Δ It may also precipitate angina or arrhythmias in those with underlying cardiac disease and can cause an increase in lactate acid (\rightarrow worsening acidosis).

Once (if) the immediate arrhythmic danger is past, the aim should be to reduce total body potassium to prevent further hyperkalaemic episodes.

Urinary K^+ wasting: diuretics

- Only useful in patients expected to pass urine and \therefore urine into which K^+ can be excreted. Particularly useful if coexisting volume overload.
- Act on the renal tubule— K^+ loss as one of several effects.
- Furosemide 40–120mg IVI as a slow bolus or 10–40mg/h to a maximum of 1000mg/day. Bumetanide offers a better absorbed oral alternative.
- Effect depends on onset of diuresis. Can lose substantial amounts of K^+ over 24h, with a UO >2 L/day.
- *Much less effective, as GFR deteriorates.*

Gut K^+ wasting: cation exchange resins

Overused, particularly orally.

- Exchange Na^+/Ca^{2+} for K^+ in the gut so actually removes K^+ , rather than just redistributing it.
- Calcium polystyrene sulfonate (CPS) (Calcium Resonium[®]) or sodium polystyrene sulphonate (SPS) (Resonium A[®] or Kayexalate[®]). Can give 15g orally (supplied as a powder to be suspended in water) up to qds or 15–30g suspended in 2% methylcellulose and 100mL water rectally up to qds, retained for at least 2 (preferably >4) hours. May require saline irrigation through a catheter to remove the resin from the colon.
- Rectal route is more effective, as there is more K^+ available for exchange: colonic $[K^+] = 60\text{--}90\text{mmol/L}$, whereas upper GI tract = $5\text{--}10\text{mmol/L}$.
- The constipating effect of these agents given orally may paradoxically prevent K^+ losses in the stool—equally, the laxatives (e.g. lactulose 10–20mL tds) given with these agents may be more efficacious than the agent itself!
- Modest effect seen within 24–48h.
- May cause colonic ulceration and necrosis (recognized with SPS when given with sorbitol as a hyperosmotic laxative—previously a common practice in the USA. Post-op patients with an ileus are at highest risk).

Extracorporeal K⁺ wasting: dialysis

- Consider if K⁺ >6.0mmol/L, or rapidly rising, and renal function cannot be restored quickly.
- Lowers K⁺ within minutes.
- Haemodialysis (HD) can process 20–60L of blood against a dialysate K⁺ of 1–2mmol/L and is ∴ a potent means of removing K⁺.
- Haemofiltration (📖 p. 174), with returned infusate free of K⁺, can achieve much the same thing although much slower.
- Peritoneal dialysis is effective but rarely indicated acutely (📖 p. 188).
- Requires dialysis access and transfer to a dialysing facility (which potentially introduces delays).
- ⚠ Never transfer a dangerously hyperkalaemic patient—if they are not responding to emergency measures, speak to your ITU (📖 p. 123).

Further management

The aim is to prevent further dangerous rises.

- Restrict oral K⁺ intake to <2g per day. ► Speak to your dietetic staff (📖 p. 258). ⚠ K⁺ content of enteral and parenteral feeds may need modification.
- ⚠ No K⁺ in IV fluids.
- Avoid K⁺-sparing diuretics, ACE-I, ARB, spironolactone, and NSAIDs.
- ► Refractory ↑ K⁺ is an indication for dialysis.
- If ↑ K⁺ persists, despite dialysis, then:
 - Review dietary intake and compliance.
 - Triple-check the drug chart.
 - Check for GI or occult bleeding (reabsorbed red cells are rich in K⁺).
 - Exclude concealed tissue or muscle damage (e.g. compartment syndrome).
 - Review (and consider changing) dialysis access and dialysis adequacy (📖 p. 181). Check dialysate K⁺ concentration (📖 p. 179).

Blood transfusion

⚠ Caution is needed when administering a blood transfusion to a patient with AKI, particularly if oligo-anuric. The volume and K⁺ content of red cell transfusions can precipitate pulmonary oedema and hyperkalaemia, respectively. If the patient requires renal support, then transfusions are safest given during dialysis treatment (► seek expert advice).

AKI management: pulmonary oedema

Introduction

Oliguric or anuric patients rapidly accumulate salt and water unless (and even if) tightly fluid-restricted. Volume overload, often exacerbated iatrogenically, remains a relatively common presentation of AKI.

In AKI, the heart is often structurally normal, but salt and water overload push it inexorably along the Starling curve. Many patients may also have poor underlying cardiac reserve (\rightarrow Δ mortality is high).

Findings

Cool, clammy, agitated patient. Tachycardia, tachypnoea, \uparrow JVP, \uparrow BP (\downarrow BP in this context is worrying), gallop rhythm, respiratory crackles, and wheezes. Possibly: ascites, pleural effusions, and oedema.

Investigations

- Poor O_2 saturation.
- Hypoxaemia on ABGs ($PaO_2 < 8\text{kPa}$).
- Widespread alveolar shadowing on CXR.

Management

- Sit the patient up, and stop all IV infusions.
- *Oxygen*. Maintain $S_aO_2 > 95\%$. It should be possible to achieve an $FiO_2 > 60\%$ using a well-positioned high-flow (e.g. Venturi) mask with an O_2 flow rate of 6L/min. Combine with nasal prongs, if necessary. Masks with reservoir bags may allow $FiO_2 > 80\%$. Consider ward CPAP if available (e.g. Boussignac system).
- *Opiates*. Give IV diamorphine (1.25–2.5mg) or morphine (2.5–5mg) as an anxiolytic and a venodilator (+ 5mg metoclopramide as antiemetic). Can be repeated after 15min, but opiates will accumulate in AKI, so resist giving additional doses.
- *Nitrates*. If the systolic BP $\geq 90\text{mmHg}$, start intravenous GTN 2–10mg/h. Start low, and titrate every 10min, as tolerated. Give 2 puffs of sublingual GTN while the pump is being set up. If systolic BP is $< 90\text{mmHg}$ (\blacktriangleright ? cardiogenic shock), call your ITU and consider inotropic support.
- *Diuretics* (\square p. 144). Administer 80–120mg furosemide bolus IV. If this initiates a diuresis, then repeat or start a continuous infusion (10–40mg/h). \blacktriangleright If no increase in urine output, seek specialist help without delay.
- *Renal replacement therapy*. Oligo-anuric patients are likely to need renal support (\square p. 172). Δ If renal facilities are not on site, then ensure the patient is fit for transfer—discuss with your ITU (\square p. 123).

How to give loop diuretics in AKI

- A bolus of 80–120mg IV furosemide can be administered initially.
- If no response, then call for expert help. Consider 250mg (25mL ampoule) furosemide IV, made up to 50mL (syringe driver) or 100mL (infusion pump) at a rate not exceeding 4mg/min to avoid ototoxicity. Bumetanide 5mg is an alternative.
- If this initiates a diuresis, give a further 250mg.
- If no response, further doses are likely to be futile. (► Dialysis?)
- If there is a reasonable, but transient, response, then a continuous infusion 10–40mg/h over 24h may promote ongoing diuresis.

Consider respiratory support if:

- Continuing severe breathlessness.
- Falling respiratory rate (tiring patient).
- $\text{PaO}_2 < 8\text{KPa}$, rising PaCO_2 .
- Worsening acidosis ($\text{pH} < 7.2$).
- Inform your ITU team about the patient *before* these occur.

Continuous positive airways pressure (CPAP)

Provides a constant positive pressure support throughout the respiratory cycle (typically 5–10cmH₂O), allowing delivery of a higher FiO_2 (80–100%) and decreasing the work of breathing.

⚠ Patients must be conscious, able to protect their airway, and possess sufficient respiratory muscle strength.

Endotracheal intubation and mechanical ventilation

Requires critical care transfer. PEEP—a preset pressure is added to the end of expiration to prevent airway/alveolar collapse and open up atelectatic and fluid-filled lung.

Venesection

- Exceptional circumstances *and* $\text{Hb} \geq 100\text{g/L}$ *and* $\text{SBP} \geq 120\text{mmHg}$.
- 250mL blood removed from a large vein with venesection kit.
- Ideally, the blood should be saved to transfuse back when the patient is more stable.

AKI management: electrolytes and acidosis

Hyperphosphataemia

- ↓ urinary PO_4 excretion → ↑ serum PO_4 . (📖 p. 237).
- Likely to be a potential issue in more persistent AKI, such as established ATN.
- Particularly marked elevations occur (early) in rhabdomyolysis (📖 p. 152), tumour lysis syndrome (📖 p. 160), and haemolysis (tissue injury and cell death → release of intracellular PO_4).
- Acute ↑ PO_4 is important because it:
 - Contributes to ↓ Ca^{2+} (by a poorly understood mechanism).
 - Encourages 2° hyperparathyroidism.
 - Promotes soft tissue/vascular calcification.
 - Makes the patient feel itchy, uncomfortable, and anorexic.
 - May cause arrhythmias.

Treatment (see also 📖 p. 246)

- Dietary restriction of phosphate (<800mg/day, 📖 p. 258). This requires a careful balance against an adequate protein and calorie intake—speak to your dietitian.
- PO_4 removal through dialysis or haemofiltration.
- Oral phosphate binders (reduce intestinal absorption of phosphate):
 - If both ↓ Ca^{2+} and ↑ PO_4 , start calcium carbonate (usually 500mg calcium per tablet) or calcium acetate (250mg calcium).
 - If $\text{PO}_4 < 2.4\text{mmol/L}$, one tablet with each meal.
 - If $\text{PO}_4 > 2.4\text{mmol/L}$, two tablets with each meal.
- If serum $\text{Ca}^{2+} \geq 2.4\text{mmol/L}$, use a non-calcium-containing binder (e.g. sevelamer HCl (0.8–2.4g with meals) or Alu-cap® (1–2 capsules with meals)).
- Severe ↑ PO_4 is unlikely to correct until the patient dialyses or recovers independent renal function.
- If the patient is being NG or parenterally fed, liaise with your dietitian.

Hypocalcaemia

Relatively common in prolonged or severe AKI. Usually in the corrected range of 1.6–2.0mmol/L. Caused mainly by ↓ 1,25-dihydroxyvitamin D_3 synthesis but also by ↑ PO_4 . Clinical sequelae (e.g. paraesthesiae, tetany, and seizures) are rare, partly because concomitant acidosis protects by increasing the ratio of ionized to protein-bound Ca^{2+} . ⚠️ Rapid correction of acidosis with oral or IV HCO_3^- can precipitate symptomatic ↓ Ca^{2+} .

Calcium is supplemented orally (as ‘Hyperphosphataemia’ section)—the dual phosphate-binding role of calcium salts helps to make life simple. IV Ca^{2+} (e.g. calcium gluconate) is virtually never required. If $\text{Ca}^{2+} < 2.0\text{mmol/L}$ (and $\text{PO}_4 < 1.5\text{mmol/L}$), start alfacalcidol (or calcitriol) 0.25–0.5 micrograms PO_4 daily.

⚠ In rhabdomyolysis (📖 p. 152), Ca^{2+} can precipitate in injured muscle, causing necrosis and ischaemic contractures—resist the administration of Ca^{2+} unless symptomatic hypocalcaemia.

Other electrolyte abnormalities found with AKI

Hypokalaemia. Rare in AKI but can accompany non-oliguric ATN caused by tubular toxins (e.g. aminoglycosides, amphotericin, cisplatin). May also develop as GFR recovers, especially in the context of polyuria.

Hypomagnesaemia. ↓ Mg^{2+} occasionally complicates non-oliguric ATN. Usually asymptomatic but can → neuromuscular instability, cramps, arrhythmias, resistant ↓ K^+ , and resistant ↓ Ca^{2+} .

Metabolic acidosis

- AKI is usually associated with a raised anion gap metabolic acidosis:
 - As GFR falls, unmeasured anions (such as HSO_4^- and HPO_4^-) from dietary and metabolic sources accumulate.
 - As H^+ is buffered, HCO_3^- is consumed.
 - The struggling kidney is unable to reclaim filtered HCO_3^- from the urine (proximal tubule) or generate new HCO_3^- (through production and excretion of NH_4^+).
- The degree of acidosis is usually modest in uncomplicated AKI (serum $\text{HCO}_3^- > 10$, pH > 7.2) but more problematic in the critically ill where it may contribute to circulatory compromise. ⚠ If unexpectedly severe, consider 2° cause—especially lactic acidosis (sepsis, cardiogenic shock), ketoacidosis (diabetes and alcohol), and poisoning (salicylates, methanol, ethylene glycol).
- Acidosis per se may be an indication for dialysis, particularly if pH < 7.0 – 7.1 or evidence of cardiovascular compromise.

AKI management: other strategies

Anaemia

► Do not always assume anaemia is part of the uraemic syndrome. Beware bleeding—especially from the GI tract—and haemolysis.

An Hb of ~8–11g/dL is a frequent finding in AKI—it does not help to distinguish between AKI and CKD. Major contributing factors are impaired erythropoiesis (↓ renal EPO production), ↓ red cell lifespan, haemolysis (↑ red cell fragility), haemodilution (from fluid overload), and blood loss.

Treatment with an ESA is rarely effective in AKI (📖 p. 220), so transfusion may be necessary, particularly if ↓ cardiovascular reserve means ↓ Hb is poorly tolerated. See 📖 p. 133 for blood transfusion in oligo-anuric patients.

Bleeding

Acute renal insufficiency may be associated with a bleeding tendency 2° to platelet dysfunction. Uraemic toxins disrupt the interaction between platelet GPIIb/IIIa and adhesion molecules, such as von Willebrand factor (vWF) and fibrinogen. ↑ platelet nitric oxide synthesis may also inhibit aggregation.

Clinical manifestations are typically mild (e.g. spontaneous bruising, bleeding at venepuncture sites) though occasionally more troublesome (⚠ GI tract). Usually manifest if urea >25mmol/L for several days.

INR, APTT, and platelet count are usually normal (if abnormal → look for other causes). The bleeding time (if measured) is prolonged.

Correcting bleeding tendency

- The two situations that require specific intervention are:
 - Active bleeding or poorly controlled persistent oozing.
 - Prior to an invasive procedure (including renal biopsy).

Management

- Stop aspirin, clopidogrel, anticoagulants.
- Correct anaemia (transfusion of packed cells). A haematocrit (Hct) ≥25–30% will help to reduce bleeding time.
- DDAVP® (desmopressin): a synthetic analogue of ADH that probably acts by ↑ amount of available vWF. Easy to administer and often beneficial. Give 0.3 micrograms/kg IV in 100mL of 0.9% NaCl over 30min. Effective within 1h, lasts 4–24 h. Less effective on repetitive dosing. Can also be given subcutaneously (same dose) and intranasally (3 micrograms/kg). ⚠ Rarely causes coronary vasospasm—avoid if unstable angina.
- Cryoprecipitate: 10 units every 12–24h. Not usually required unless more severe bleeding.
- Dialysis: improves bleeding time, presumably through removal of uraemic toxins. ► Dialysis usually requires anticoagulation to prevent clotting of the extracorporeal circuit (📖 p. 182).

Infection

- ► Sepsis is an important cause of morbidity and mortality in AKI (~75% mortality if AKI + sepsis). It occurs in three contexts:
 - AKI is the consequence of a specific infection (e.g. post-infectious GN, endocarditis, malaria, leptospirosis, hantavirus).
 - Septicaemia → circulatory compromise → pre-renal AKI → ATN.
 - Localized or systemic infection arises in those with pre-existing AKI.

Approach

- Take signs of infection, such as fever, ↑ WCC, ↑ CRP, seriously—as a minimum, re-examine the patient thoroughly.
- Culture (and re-culture) blood, urine, sputum, and other secretions.
- Make use of imaging. Repeat CXRs frequently. If the source of sepsis remains obscure, consider abdominal/chest/pelvis CT.
- Attention to microbiological detail: chase up samples; review sensitivities; carefully consider antibiotic options, and speak to your microbiologist regularly about resistance patterns.
- ⚠ Many antimicrobials require dose adjustment in renal impairment (📖 p. 878).
- Strict aseptic technique for central venous line, dialysis catheter, and bladder catheter insertion. Consider prophylactic antibiotics when inserting a line or catheter into a febrile patient. Do not leave bladder catheters in place longer than necessary. In the majority of cases, accurate monitoring of UO does not require a catheter. Antibiotic cover for removal if the urine is a likely source of sepsis.
- Inspect IV cannula sites regularly, and look under dressings.
- Remove all lines as soon as feasible.
- ►► Treat proven infection aggressively.

AKI management: nutrition

Pre-existing and hospital-acquired malnutrition → ↑ morbidity and mortality in the critically ill. Preventing malnutrition preserves muscle function (including) respiratory, ↑ wound healing, and ↑ resistance to infection.

General rules

- If pre-existing nutritional status is normal and a normal diet is likely to be resumed in ≤5 days, support is not initially indicated.
- If the patient is malnourished, ignore this 5-day rule and start feeding.
- If hypercatabolic (sepsis, trauma, burns), initiate support early.
- Some protocols avoid feeding within first 24h: evidence that feeding during the 'insult phase' ↑ O_2 requirements and worsens tissue injury).
- Modify nutritional support as GFR changes and with dialysis initiation.
- Do not overprescribe—you can have too much of a good thing.
- Enteral feeding is always preferable to parenteral (although they are not mutually exclusive).

Step 1: determine the nutritional status of the patient

- Body weight: recent unintentional loss >10% body weight is a bad sign.
- Determine BMI (kg/height in m^2). Normal range 20–25 kg/m^2 .
- Beware fluid retention falsely ↑ weight.
- Serum albumin (<30g/L is worrying), though inflammation may be a confounder. Pre-albumin, transferrin, and cholesterol can also be used.
- Subjective global assessment (SGA): combines clinical parameters with albumin, anthropometry, clinical judgement, and other metrics (📖 p. 258).

Step 2: estimate energy requirements

- Standard formulae (>200 published), e.g. Schofield,³ revolve around gender-based, weight-adjusted formulae. Ask your dietitian.
- Energy expenditure in 'uncomplicated' AKI is usually within the normal range, and energy requirements for those with 'complicated' AKI are generally determined by associated disorders (e.g. sepsis). It is rare for energy requirements to exceed 130% basal.
- ► Broadly speaking: ♂ should receive 25–30 non-protein kcal/kg/day and ♀ 20–25kcal/kg/day.

Step 3: estimation of protein (and amino acid) requirements

- Depends on associated catabolic stress. Hypercatabolism → ↑ Ur, which can be used to estimate nitrogen balance. Rules of thumb:
 - For 'uncomplicated' AKI, daily protein or amino acid requirement is near the recommended allowance of 0.8g/kg/day for normal adults.
 - In 'complicated' AKI, the requirement is ~1.0–1.2g/kg/day.
 - If dialysis is necessary, add 0.2g/kg/day.
- Critically ill patients may need more (up to 1.5g/kg/day); ≥1.5g/kg/day may aggravate the situation by stimulating formation of urea and other nitrogenous waste products.

Step 4: decide on route of administration

See Table 2.5.

Step 5: ensure volume and electrolyte content appropriate for AKI

- Low volume and low electrolyte feeds are often necessary.
- Requirements may change as renal support is initiated (and will depend on whether intermittent dialysis or CRRT).
- Consider high dose vitamin administration (e.g. Pabrinex[®]) if pre-existing malnutrition.

Reference

3. Schofield WN (1985). Predicting basal metabolic rate, new standards and review of previous work. *Human Nutrition Clinical Nutrition*, **39**, 5–41.

Table 2.5 Administration routes

Route	What's in it?	Notes	Concerns in AKI	Complications
Oral: Nutrition-dense oral diet Supplementary sip feeding	Modest protein and energy content.	Many patients can tolerate an oral diet. Supplementation with nutrition drinks useful if appetite poor.	Observe restrictions: K ⁺ PO ₄ Volume	
Enteral	Enteral feeding formulae specifically for AKI are available; e.g. Nepro [®] (Ross), Nova source renal [®] (Novartis). Ensure correct position of NG tube (aspirate pH or CXR). Start at 30mL/h. Allow 4h bowel rest in every 24h.	Enteral feeding maintains the structural integrity of the gut and protects against translocation of GI bacteria.	A tailored regimen (i.e. non-standard feed) may be necessary if the above restrictions apply. To prevent refeeding syndrome in a malnourished patient, K ⁺ , PO ₄ , and Mg ²⁺ must be checked and corrected prior to commencement.	<i>Mechanical:</i> dislodged tube. <i>Gastrointestinal:</i> abdominal distension, nausea, cramps, and diarrhoea. <i>Infectious:</i> aspiration pneumonia. <i>Metabolic:</i> hyper/hypoglycaemia, electrolyte abnormalities.

Parenteral

Amino acids: combined essential and non-essential (the latter often become 'conditionally' essential in the context of AKI)

Energy: principally given as glucose, although $>5\text{g/kg/day}$ causes CO_2 production (increasing respiratory demands), lipogenesis (fatty liver), and hyperglycaemia. Lipids are used to provide the remainder (usually $\leq 1\text{g/kg/day}$ to avoid hyperlipidaemia).

Vitamins, trace elements, electrolytes (and sometimes insulin) are added, as necessary.

IV lipids have a low osmolality and can be given into peripheral veins.

They do not meet all energy requirements so are mainly a short-term measure.

Full TPN must usually be given centrally (via a dedicated line).

If possible, a small amount of enteral feed is run concurrently.

Start feed slowly.

Continuous renal replacement techniques (e.g. CVVHF) assist the delivery of feeding.

Catheter insertion: pneumothorax, etc.

Catheter infection.

Metabolic: requires close laboratory monitoring.

AKI management: myths

Loop diuretics

Theory. (i) ↑ urinary flow ‘washes out’ cellular debris, casts, and nephrotoxins from tubules; (ii) blockade of active transport processes → ↓ tubular O₂ consumption and protects against ATN; (iii) vasodilator action → ↑ RBF.

Evidence. None to suggest improved renal or patient outcome in any AKI setting. In particular, the natural history and prognosis of ATN remains unchanged. Some studies have suggested *harm*. May increase diuresis, however, assisting the management of fluid balance and preventing progressive volume overload. ► Given as part of the treatment of pulmonary oedema (📖 p. 134). ⚠ The only indication for diuretics is volume overload.

Mannitol

An osmotic diuretic, previously used for the prevention of ATN in high-risk CV surgery. A lack of evidence means the practice is in decline. Can paradoxically cause pulmonary oedema through volume expansion. Avoid.

Dopamine

Previously widely used for the prevention and treatment of AKI. A lack of evidence for efficacy and potential risk of harm have led most to abandon this practice. You should do the same.

Theory. Dopamine (DA) is synthesized in the proximal tubule from circulating L-dopa and helps regulate Na⁺ excretion and renal vasodilatation through specific DA1 and DA2 receptors. Exogenously administered ‘low-dose’ dopamine should → renal vasodilatation → ↑ RBF → ↑ natriuresis and mild ↑ GFR. All would be of potential benefit in AKI, although evidence suggests these mechanisms may not remain intact in renal insufficiency. (See Table 2.6.)

Table 2.6 Dopamine effects

Micrograms/kg/min	Effect
0.5–3	Selective DA (mainly DA1) receptor activation → ↑ renal (and mesenteric) blood flow
3–10	Both DA and B ₁ receptors are activated, the latter → ↑ cardiac output (mainly by ↑ SV).
10–20	B ₁ effect predominates. Starts to activate α adrenoreceptors.
>20	α adrenergic (vasoconstrictive) effect takes over with ↑ SVR.

Evidence. Largely anecdotal or from inadequate studies. Larger trials (e.g. ANZICS) have failed to show benefit.

⚠ It may cause *harm*: tachycardia, arrhythmias, myocardial ischaemia, blunted hypoxaemic drive, splanchnic vasoconstriction (→ bacterial translocation), digital ischaemia, impaired pituitary function, electrolyte disturbances (even at 'renal' dose), impaired T cell function. Dopamine accumulates in renal failure.

Other 'renoprotective' agents

Fenoldopam

- Dopaminergic agonist that acts through DA1 receptors (without significant α or β adrenergic activity) to produce afferent and efferent arteriolar vasodilatation.
- Preserves renal blood flow and tissue oxygenation in animal studies.
- Human studies (mainly small) have yielded variable results in several clinical contexts, including AKI prevention post-cardiac surgery.
- Larger randomized studies are awaited. In the meantime, fenoldopam use is not recommended in the KDIGO (2012) guideline.

Atrial natriuretic peptides

- ANP →↓ tubular Na^+ reabsorption, ↑ afferent arteriolar vasodilatation, and ↓ RAS activation.
- Tested in a post-surgical context in multiple studies, but overall quality of study evidence is variable and inconsistent.
- Can induce significant, and potentially harmful, hypotension.
- Other natriuretic peptides have been tried, e.g. brain natriuretic peptide (nesiritide) and urodilatin.
- Not recommended in KDIGO (2012) guideline.

N-acetylcysteine

- Most widely studied in the context of contrast-induced AKI (📖 p. 150).
- NAC is a modified form of the amino acid L-cysteine, a precursor of glutathione.
- NAC is a potent free radical scavenger and antioxidant that also possesses vasodilator properties (via nitric oxide availability).
- Shown to reduce ischaemic and nephrotoxic ATN in animal studies but clinical evidence lacking.
- Not recommended in KDIGO (2012) guideline.

AKI: hope for the future?

Phases of ATN (see also p. 108)

There are four pathophysiological/temporal phases of ATN that can help to conceptualize where pharmacological interventions might be targeted and applied.


Initiation phase

Characterized by aberrant vascular reactivity, diminished renal perfusion, and widespread oxidative injury.

Extension phase

A proinflammatory state, with macrophage activation, inflammatory mediator release, and stimulation of epithelial and endothelial cells.

Maintenance phase

Restoration of tubular cell integrity through the division of adjacent tubular cells and the differentiation of local (kidney) and systemic (haematopoietic—) stem cells.

Repair phase

Normal tubular cell function is restored.

Very broadly speaking, therapeutic interventions can, therefore, attempt to decrease vascular reactivity, moderate inflammation, preserve cell viability, and augment cell repair.

Putative agents are shown in Table 2.7.


Many of these are currently being studied in animal models of renal ischaemia-reperfusion injury, but benefit in human AKI is yet to be demonstrated. There are many potential reasons for this: AKI is a heterogeneous condition (both in terms of the type of patient affected and the underlying cause); study endpoints (such as mortality) are often confounded, and, until recently, there was no agreed consensus definition of AKI. Furthermore, late detection of AKI prevents timely administration. It is hoped that novel AKI biomarkers will facilitate earlier intervention ( p. 94).

Table 2.7 Putative therapeutic strategies in AKI

Pathogenic mechanism targeted	Interventions currently of unproven benefit in humans
Ameliorate renal vasoconstriction	Endothelin receptor antagonists (e.g. tezosentan) Leukotriene receptor antagonists PAF antagonists iNOS antisense oligonucleotides Phosphodiesterase inhibition (e.g. milrinone) Haem-oxygenases
Attenuate inflammation	Anti-ICAM-1 monoclonal Ab Anti-IL-18 monoclonal Ab N-acetylcysteine, desferrioxamine, and/or other free radical scavengers α -MSH Adenosine Minocycline Corticosteroids Fibroblast growth factor-inducible 14 (Fn14) blockade
Prevention of apoptosis and necrosis	Erythropoietin (initial trials disappointing) Protease (e.g. caspase) inhibitors Guanosine Pifithrin α (p53 inhibitor) PARP inhibition
Prevention of tubular obstruction	Diuretics RGD peptides
Promoting tubular regeneration	Insulin-like growth factor (IGF) Thyroxine Epidermal growth factor Hepatocyte growth factor Osteopontin Stem cell therapy (early studies with stem cells in high-risk patients undergoing cardiac bypass surgery have been promising)

PAF, platelet-activating factor; RGD peptides, peptides containing the arginine-glycine-aspartic acid motif (involved in adhesion); ICAM-1, intercellular adhesion molecule-1; α -MSH, α -melanocyte-stimulating hormone; PARP, poly ADP-ribose polymerase.

Contrast-induced AKI (CI-AKI)

Introduction

CI-AKI accounts for ~10% of in-hospital AKI and is associated with significant mortality ($\times 5.5$ odds adjusted risk of death), prolonged hospitalization, and future cardiovascular events. It may also irreversibly \downarrow GFR (esp. in those with pre-existing CKD). These adverse outcomes are worse in those who require dialysis treatment (2-year mortality rate $>80\%$ in one study!).

CI-AKI risk is low (~1–2%) in patients with normal renal function (even in the presence of diabetes) but much higher in patients with pre-existing renal impairment (~25%), particularly in the presence of additional risk factors (see Box 2.2—these factors are additive).



Why is contrast toxic?

- Direct toxicity: oxidant injury to proximal tubular cells.
- Vasomotor effects: contrast (perhaps through its osmolality) alters afferent/efferent tone and thus glomerular perfusion.
- ► AKI 2° to ATN results.

Box 2.2 Risk factors

- Pre-existing CKD.
- Diabetes mellitus.
- Hypertension.
- Cardiac failure.
- Volume depletion.
- Haemodynamic instability.
- \uparrow Age.
- Hyperuricaemia.
- Renal transplantation.
- Concurrent nephrotoxic drug administration.
- High contrast volumes.
- Intra-arterial contrast.

Precautions

- Specific measures are discussed on  p. 149.
- Recognize those at risk (see Box 2.2). For ambulatory patients in whom a recent measurement of renal function is not available, a simple questionnaire may identify those at increased risk.^{4,5}
- Dipstick proteinuria will also help identify individuals in whom measurement of renal function is desirable.
-  Many high-risk patients may not be suitable for 'day case' procedures.
- Is the procedure really necessary? Is there an alternative 'non-contrast' technique? Speak to your radiologist.
- Use iso-osmolar, non-ionic contrast.
- Minimize contrast volume ($<100\text{mL}$, if possible).
- ► Optimize volume status pre-study.

- Stop all other nephrotoxins prior to procedure (including high doses of loop diuretics).
- ☞ Although often undertaken, there is no evidence that cessation of ACE-I, ARBs, or metformin prior to contrast administration is protective.
- Space out multiple procedures whenever possible.
- Inform your renal team of high-risk cases (beforehand!).

Clinical features

- ↓ GFR begins immediately (although SCr may be unchanged initially).
- The earliest (and often only) sign may be oliguria (▶ so ensure UO is being measured in high-risk hospitalized patients).
- ↑ SCr at 12h is the best predictor of CI-AKI.
- Peak SCr usually occurs at 2–3d but can be delayed 5d in a minority of cases.
- In practice, CI-AKI often becomes apparent when renal function is rechecked the day after a procedure (so make sure it is checked and that you see the result).
- Although rarely (if ever) measured, fractional urinary excretion of Na⁺ often remains <1% (unlike other causes of ATN). This fact is useful for exam purposes only.

Treatment

- Once established, treat as for any other cause of ATN.
- Ensure adequate hydration, and avoid additional nephrotoxins.
- Standard indications for dialysis support apply (📖 p. 172).

Prognosis

- In the majority, renal dysfunction is mild and transient (although still associated with ↑ mortality).
- Recovery within a week is usual. Those with pre-existing advanced CKD are most susceptible to a permanent ↓ GFR.
- Dialysis support will be necessary in 3–4% of those with underlying CKD, and long-term renal replacement therapy will be required in the minority of these.

Strategies to prevent RCN

Hydration

- IV fluids correct volume depletion and ↑ RBF. They also minimize the pre-renal effects of a post-contrast diuresis.
- Evidence supporting their use is strong. Example regimens:
 - 1.26% NaHCO₃ 3mL/kg/h for 1h pre- and 1mL/kg/h for 6h during and post-procedure.
 - 0.9% NaCl 1mL/kg/h for 12h pre- and 12h post-procedure.
- NaHCO₃ may have theoretical advantages over other IV fluids through an antioxidant effect (peroxynitrate scavenging), but this remains poorly defined and clinically unproven.
- Examine the patient first—if overtly dehydrated, then larger volumes may be required and the procedure may need to be postponed. If already volume-overloaded, then further fluids are ill advised.
- Aim for a good urine output (>150mL/h).
- In diuretic dependent patients, withholding diuretics may be sufficient ‘hydration’.

📌 N-acetylcysteine (NAC)

- Used for its antioxidant properties, *always* in conjunction with hydration.
- The evidence underpinning NAC use from randomized trials and meta-analyses is inconsistent, with many actually suggesting no benefit.
- NAC may ↓ SCr independently of GFR through interference with tubular handling.
- Side effects are rare for the doses relevant to CI-AKI prevention (unlike those for paracetamol overdose); however, marginal effects on cardiac function and coagulation have been described.
- A typical regimen is 600–1200mg capsules PO 12h × 4 doses (generally two doses pre-contrast and two doses post).
- Despite the lack of compelling evidence, low cost and a favourable side effect profile have led to widespread use—as well as retention in several guidelines (although not KDIGO (2012)).

Others

- There has been interest in both theophylline (antagonizes adenosine-mediated ↓ RBF) and fenoldopam (specific dopamine 1 receptor agonist), but clinical studies have been disappointing and their use is not recommended (although a recent meta-analysis has suggested there may yet be a role for theophylline.⁶)
- Haemofiltration/haemodialysis: ‘prophylactic’ removal of circulating contrast, particularly in those with advanced CKD. No convincing evidence of benefit. Costly with significant potential adverse effects. (See Fig. 2.14.)

► All centres should have a locally agreed protocol, usually based on risk assessment and fluid ± NAC administration. An algorithm produced by LAKIN is shown in Fig. 2.14.

References

4. KDIGO. Available at: 🌐 <<http://kdigo.org/home/guidelines/acute-kidney-injury/>>.
5. Choyke PL, Cady J, DePollar SL, et al. (1998). Determination of serum creatinine prior to iodinated contrast media: is it necessary in all patients? *Techniques in Urology*, **4**, 65–9.
6. Dai B, Liu Y, Fu L, et al. (2012). Effect of theophylline on prevention of contrast-induced acute kidney injury: a meta-analysis of randomized controlled trials. *American Journal of Kidney Diseases*, **60**, 360–70.

Differential diagnosis

Many patients undergoing invasive endovascular studies have diffuse atherosclerotic disease and are at risk of renal atheroemboli. These may occur as a distinctive clinical syndrome (📖 p. 590) but can often go unrecognized until the anticipated recovery of renal function fails to materialize.

Contrast-induced nephropathy (CIN) prophylaxis

Assess risk

High volume (>100mL) iodinated contrast procedure and CKD with eGFR <60 (particularly diabetic nephropathy) or AKI

Other risk factors dehydration, heart failure, severe sepsis, cirrhosis, nephrotoxins (NSAIDs, aminoglycosides).
Risk factors are multiplicative.

Is contrast procedure necessary?

Yes

Resuscitate to euvolaemia

Give prophylaxis if high risk

Volume expansion (unless hypervolaemic) with normal saline or 1.26% bicarbonate
Sample regimens
IV Na bicarbonate 1.26% 3mL/kg/h for 1 hour pre-procedure and 6 hours post-procedure
or
IV 0.9% normal saline 1mL/kg/h pre- and 12 hours post-procedure

Minimize contrast, use low or iso-osmolar contrast

Monitor function to 72 hours in high-risk cases

If oliguria or rising creatinine, early referral to local renal team.
NB There is no proven role for N-acetylcysteine, post-contrast dialysis/CVVH or routine cessation of metformin or ACE inhibitors.

Fig. 2.14 The LAKIN contrast-induced nephropathy algorithm. Reproduced from London AKI network manual (2012), with permission. 🌐 <http://www.londonAKI.net/clinical>

Rhabdomyolysis

Introduction

First described as 'crush syndrome' during the London blitz of WWII. Rhabdomyolysis is a clinical syndrome caused by release of cellular contents after a significant injury to striated muscle.

Injury is caused by either energy depletion and cell death or, more commonly, during reperfusion of ischaemic muscle. Infiltrating leucocytes release oxidant species that cause myonecrosis. If cell death is widespread, intracellular elements and membrane products are released into the circulation: creatine kinase (mainly MM isoenzyme but also MB), LDH, myoglobin, purines (\rightarrow hyperuricaemia), electrolytes (esp. K^+ and PO_4), and aminotransferase enzymes. (See Table 2.8.)

Myoglobin (Mb)

The main nephrotoxin. A 19kDa weak O_2 carrier (similar to Hb but with a single haem moiety), Mb is usually bound to plasma proteins. When in excess, the ferric form (Fe^{3+}) is freely filtered and concentrated \rightarrow intraluminal cast formation. Tubular degradation generates highly toxic ferryl-Mb (Fe^{4+}), with direct oxidant tubular cell injury. A key feature of rhabdomyolysis is the large quantities of fluid retained in inflamed muscle, causing profound hypovolaemia, in addition to toxic renal injury.

► Not all rhabdomyolysis \rightarrow AKI (particularly if you act quickly).

Clinical presentation

Variable, but the classical myalgia, weakness, and dark urine are rare (~50% have no muscle pain at presentation). Maintain high index of suspicion in relevant clinical situation; initial clues: \uparrow ALT/AST, dipstick +ve haematuria, disproportionate \uparrow K^+ or PO_4 (see 'Investigations' section).

△ Examine the limbs carefully—do not miss a compartment syndrome. Recurrent rhabdomyolysis after mild exertion may suggest an underlying myopathy.

Investigations

- Dipstick cannot distinguish between myoglobin and haemoglobin. Classically, urine is dipstick +ve for blood but with no red cells on microscopy. ~20% of patients will have a -ve urinalysis.
- ► Urinary myoglobin (u-Mb) is +ve (not present in normal urine). \downarrow u-Mb can be used to monitor treatment.
- U&E (SCr:Ur ratio often very high), \uparrow Alb if volume-deplete, or hypoalbuminaemia if capillary leak.
- \uparrow CK (better indicator of amount of muscle damage than likelihood of AKI). \uparrow ALT, AST, LDH.
- \uparrow K^+ (△ often $\uparrow\uparrow$), $\uparrow\uparrow$ PO_4 , \uparrow urate, \uparrow lactate, and \uparrow anion gap acidosis (organic acids).
- $\downarrow\downarrow$ Ca^{2+} , often with avid calcium sequestration in injured muscle.
- Mild DIC frequent (\downarrow Plt, \uparrow D-dimers).
- Consider toxicology screen for drugs, viral screen, TSH if cause not apparent.

Table 2.8 Causes of rhabdomyolysis

Physical causes	Drugs and toxins
Trauma (crush injury)	Alcohol, heroin, amphetamines, cocaine, and ecstasy
Prolonged immobility	Statins and fibrates
Compartment syndrome	Antimalarials
Muscle vessel occlusion	Zidovudine
Sickle cell disease	Snake and insect venoms
Shock and sepsis	Infections
Excessive exertion	Pyomyositis and gas gangrene
Delirium tremens	Tetanus, <i>Legionella</i> , <i>Salmonella</i>
Electric shock	Malaria
Status epilepticus or asthmaticus	HIV, influenza, and Coxsackie
Neuroleptic malignant syndrome	Electrolyte abnormalities:
Malignant hyperthermia	↓ K ⁺ , ↓ Ca ²⁺ , ↓ PO ₄ ⁻ , ↓ Na ⁺ , ↑ Na ⁺
Myopathies:	Endocrine disorders:
Polymyositis/dermatomyositis	Hypothyroidism
McArdle's disease and other inherited myopathies	Hyperglycaemic emergencies

Rhabdomyolysis: management

Prevention of AKI

In the early phase of the disorder, vigorous resuscitation may protect patients from many of the subsequent complications.

- Aim to resuscitate to euvolaemia:
 - As much as 12L may be required/day (and more if severe injury).
 - Alternate 1L 0.9% NaCl (or balanced crystalloid) with 1L 1.26–1.4% NaHCO_3 .
 - If the Na^+ load $\rightarrow \uparrow \text{Na}^+$, use 1L 5% dextrose or 1L 0.45% NaCl containing 50mL 8.4% NaHCO_3 to \downarrow total Na^+ load.
- Aim to maintain a UO $\geq 150\text{mL/h}$ or $\geq 300\text{mL/h}$ with traumatic injuries.
- Continue therapy until disappearance of urinary myoglobin.

Urinary alkalinization and mannitol

⚠ The role of urinary alkalinization (stabilizes oxidizing form of myoglobin) and forced diuresis (\uparrow urine flow $\rightarrow \downarrow$ tubular precipitation) remains controversial. ► The priority is to volume-resuscitate the patient.

- Aim for a target u-pH > 6.5 by using alternating NaCl and NaHCO_3 , as described in previous section, but increasing the frequency of NaHCO_3 as necessary. Evidence for a meaningful clinical impact is weak, and volume overload is a risk unless good UO. In addition, urinary alkalinization can cause a significant systemic alkalosis and \therefore symptomatic $\downarrow \text{Ca}^{2+}$.
- Loop diuretics acidify the urine and should be avoided. Mannitol, an osmotic diuretic, is preferred: give as a bolus (e.g. 12.5–25g as a bolus (= 62.5–125mL of 20% (200mg/mL) mannitol solution)) or as an infusion (10mL/h of 15–20% mannitol). ⚠ Mannitol $\rightarrow \uparrow$ osmolar gap and may potentially worsen AKI.

Supportive care

- Standard indications for dialysis apply (📖 p. 172), although $\uparrow \text{K}^+$ may occur early.
- Physiotherapy to debilitated muscles is essential.

Prognosis

- The prognosis is good if the causative insult is removed, and renal function will return to normal in the majority—even in those who require an extended period of dialysis support.

Compartment syndrome in rhabdomyolysis

- May occur in two circumstances:
 - If the blood supply to particular limb has been compromised (immobility after drug overdose, seizures, etc.).
 - Generalized muscle injury and inflammation (toxic, viral).
- Inflammation and oedema within a closed muscle compartment → ↑ intracompartment pressure → ↓ O₂ delivery → myonecrosis.
- ► Always examine the major muscle groups for the characteristic 'woody' consistency of an evolving/established compartment syndrome. Timely fasciotomy in these circumstances may save limb function.
- If in doubt, compartmental pressure can be measured via the insertion of a needle with an attached tonometer. An intracompartment pressure >50mmHg with a normal BP, or 30–50mmHg in hypotensive patients, is suggestive. If necessary, recheck every 6h.

Hypocalcaemia

Do not attempt to correct ↓ Ca²⁺, unless it is symptomatic (tetany, arrhythmias)—there is a risk the administered calcium will precipitate in injured muscle. Rebound hypercalcaemia is common during the recovery phase.

▲ Symptomatic ↓ Ca²⁺ may complicate NaHCO₃ administration.

Haemoglobinuric AKI

- Occurs in the context of massive intravascular haemolysis:
 - Transfusion reactions (ABO incompatibility).
 - Falciparum malaria (blackwater fever, [p. 702](#)).
 - Haemolytic anaemias (glucose-6-phosphate deficiency (G6PD), drug-induced, autoimmune).
 - Mycoplasma infection.
 - Snake, insect, and spider venoms.
- Free Hb does not enter the urine as freely as myoglobin, so AKI is relatively rare.

Investigations

↓ Hb, ↓ haptoglobins, ↑ bilirubin, ↑ LDH, ↑ K⁺; urine is dipstick +ve for blood; plasma appears dark.

Management

Treat underlying disorder; volume resuscitation to establish a diuresis.

AKI in cirrhosis

Introduction

AKI is common in cirrhosis. ~25% patients presenting with cirrhosis-associated ascites will develop AKI within 1 year. The presence of AKI at the time of an admission increases mortality ~8-fold, and >50% of patients will develop AKI during an inpatient episode.

►► Not all concomitant hepatic and renal impairment is due to the hepatorenal syndrome (HRS); it is not even top of the list. Alternative diagnoses may imply a better prognosis. Always consider:

- Sepsis → ATN (40% of AKI in cirrhotic patients).
- Hypovolaemia (e.g. GI haemorrhage, diuretics) → ATN (30% AKI in cirrhotic patients).
- Nephrotoxins (drugs and ↑ bilirubin → ATN).
- Glomerulonephritis (e.g. MCGN 2° to hepatitis C).

Hepatorenal syndrome

HRS occurs in advanced liver dysfunction, usually cirrhosis, in conjunction with ascites and portal hypertension. Often split into two types, based on: (i) rapidity of onset, (ii) severity of AKI, and (iii) prognosis (see Table 2.9).

Table 2.9 Classification of HRS

Type I	AKI is the dominant clinical feature Rapid ↓ GFR (SCr >221 μmol/L (2.5mg/dL)) or CrCl falling to <20mL/min in less than 2 weeks Progressive oligo-anuria (often profound) Median survival 2 weeks
Type II	Ascites (often refractory) the dominant clinical feature Prolonged clinical course Renal impairment less acute and severe Can convert to type I Median survival 6 months

Pathophysiology of HRS

Liver disease is associated with marked splanchnic (and systemic) vasodilatation (→ arterial underfilling and ↓ SVR), in part 2° to local excess NO and other vasodilator (e.g. adrenomedullin) production (caused by ↑ shear stress in portal hypertension). Also ↑ bacterial translocation (→ peritoneal inflammatory response) and ↑ vasoactive gut peptides (e.g. glucagons, prostacyclin).

As a result, the effective arterial blood volume is sensed to have fallen, leading to intense α adrenergic activity, 2° hyperaldosteronism, ANP synthesis, and non-osmotic ADH release (hence salt and water overload). Tubular V2 receptor activation causes a dilutional hyponatraemia. An increase in cardiac output attempts to compensate, but LV dysfunction eventually results. Excess catecholamine, angiotensin II, adenosine, thromboxane A2, and endothelin → profound and intense renal vasoconstriction (→ ↓ RBF).

The kidneys remain structurally normal, and the renal impairment is entirely pre-renal in nature—tubular integrity and function are preserved. Renal biopsies are normal (in practice, unnecessary and hazardous), and kidneys from HRS patients have been used successfully for transplantation.

Clinical features

- ► The diagnosis of HRS depends on exclusion of other causes of AKI.
- Recognition can be difficult, as cirrhotic patients are usually malnourished, with significantly ↓ muscle mass (∴ SCr may overestimate GFR). Urea may also be unhelpful (GI bleeding, low hepatic production ± variable dietary protein intake). Cystatin C (📖 p. 36) has ∴ been used as an alternative. Other biomarkers (📖 p. 94) are awaited.
- Signs of advanced liver disease: ascites (practically universal in HRS), stigmata of chronic liver disease, portal hypertension (beware GI bleeding!), encephalopathy, jaundice (degree variable), and coagulopathy.
- Cardiovascular: oedema (Na^+ and water retention) and ↓ BP (↓ SVR and effective circulating volume).
- ►► Infection: look carefully and regularly for evidence of sepsis (⚠ pneumonia, line infections, and spontaneous bacterial peritonitis).
- Electrolyte disorders: dilutional ↓ Na^+ is almost universal.
- Nutritional state: usually poor and deteriorating.
- Urine output: oligo-anuria the norm in type I HRS, with urine volumes decreasing as the condition progresses. Anuria is an ominous sign.
- Urinalysis bland, with no proteinuria/haematuria.
- Tubular function is preserved, so the kidneys excrete concentrated urine that is low in Na^+ (<10mmol/L) (i.e. indistinguishable from other pre-renal AKI). Heavily emphasized in the past but no longer included in diagnostic criteria.
- Normal renal ultrasound/imaging. Renal Doppler can detect ↑ vascular resistance (elevations predict HRS in cirrhotic patients).

Box 2.3 HRS: diagnostic criteria

- Acute or chronic liver disease with advanced hepatic failure and portal hypertension.
- Renal impairment: serum SCr $\geq 133 \mu\text{mol/L}$ (1.5mg/dL).
- Absence of hypovolaemia: no improvement in renal function after diuretic withdrawal and appropriate volume expansion with IV albumin (1g/kg/d).
- Absence of other alternative explanations for ↓ GFR, particularly nephrotoxic drugs and sepsis (► spontaneous bacterial peritonitis).
- Absence of intrinsic renal disease: proteinuria <500mg/d, urine RBCs <50 cells per hpf (with no urinary catheter), normal renal USS.

After Arroyo V, et al. (1996). Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology*, 23, 164; and Salerno F, et al (2007). Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*, 56, 1310.

Management of HRS

Risk factors

- Cirrhosis + ascites = 40% 5-year probability of HRS.
- Large volume (>5L) paracentesis without concurrent plasma expansion. (☛ Give 100mL 20% human albumin per 1.5L ascites removed.)
- GI bleeding (variceal bleeding is a common precipitant).
- Overdiuresis (possibly—see Box 2.3).
- Sepsis: especially spontaneous bacterial peritonitis (SBP) (~20% will develop HRS). ► Any cirrhotic patient with ascites should be assumed to have SBP until proven otherwise. The administration of IV albumin 1.5g/kg at diagnosis of SBP and 1g/kg 48h later, in addition to antibiotics, appears to decrease HRS risk.
- Surgery.

Managing established HRS

- Seek expert help early.
- Volume assessment:
 - IV 20% albumin (salt-poor) for volume expansion (e.g. 0.5–1g/kg/day or aiming for CVP of 5–10cmH₂O).
 - Na⁺ restrict (80mmol/24h) and fluid restrict (<1L/24h) if overloaded.
- Culture blood, urine, and ascites. Empirical IVI cefotaxime 2g tds for suspected SBP (Δ adjusted for renal function). Discuss with microbiology.
- Consider therapeutic paracentesis if tense ascites with intravesical pressure >30cmH₂O (↑ intra-abdominal pressure transmitted to kidneys (↑ renin release, ↓ GFR) and ureters (relative obstruction)) (📖 p. 162).

Specific rescue therapies

- Vasoconstrictors → constrict the splanchnic bed → improve circulatory (and ∴ renal) function. Given in combination with IV albumin. Aim for MAP >75mmHg.
 - Vasopressin analogues (act via splanchnic V1 receptors), e.g. terlipressin (initially 0.5–1mg/4–6h IVI). Benefits: ↓ SCr, ↑ UO, ↑ MAP, and improved early survival. Physiological benefits seen early and often persist. Repeat courses can be effective. Δ Side effects: ischaemia, e.g. digital, cardiac, mesentery. Terlipressin is not available in the USA.
 - Noradrenaline (0.5–3mg/kg/h) is an alternative.
 - Midodrine (7.5–12.5mg PO tds), a selective α₁ agonist, may be given in combination with the somatostatin analogue octreotide (100–200 micrograms SC tds). Aim to ↑ MAP by 15mmHg. Benefits include improved survival although probably less effective than vasopressin analogues.

- Transjugular intrahepatic portosystemic shunts (TIPS) may improve SCr in selected patients (esp. those with refractory ascites and variceal bleeding). However, there is a 5% incidence of *de novo* AKI post-TIPS.
- N-acetylcysteine may have additional benefits and remains under study.

Renal replacement therapy

- ⚠ RRT does not improve outcome in HRS and should be viewed as a bridge to liver transplantation in this context.
- ► However, AKI in a cirrhotic patient is not always 2° to HRS and may ∴ be reversible. Dialysis treatment should not be withheld in these circumstances.
- Standard indications apply (📖 p. 172), although volume overload is the usual precipitant in this group.
- Continuous RRT techniques (📖 p. 174) may be better tolerated (less haemodynamic instability, slower correction of ↓ Na⁺, and less fluctuation in intracranial pressure) than intermittent HD.

It has been hoped that artificial hepatic assist devices can be developed, following the same general principles as dialysis for renal failure; for example, the molecular adsorbent recirculating system (MARS) is an extracorporeal technique in which dialysate is circulated through charcoal and anion exchanger columns (removing potential HRS mediators, e.g. TNF, IL-6, and NO). Unfortunately, the diverse metabolic functions of the liver have proved difficult to replicate, and results have been disappointing. Technologies under current development are based on the use of various hepatocyte cell lines to deliver synthetic liver capacity.

Liver transplantation

The most (only?) effective therapy of HRS, although many patients die before transplantation is possible. Organ allocation differs between countries, but, in many scoring systems (e.g. MELD), HRS patients are afforded high priority.

~40% patients admitted for liver transplantation have AKI by RIFLE criteria, and ~70% develop AKI post-operatively (the majority of these will require renal replacement therapy).

Treatment of HRS pre-transplantation improves outcomes post-transplantation, although patients with pre-transplant renal impairment have ↓ long-term survival, compared with those with a normal GFR.

Most patients will have improved renal function after they have recovered from surgery, although the majority do not regain a normal GFR (~10% incidence of ESRD at 11 years).

Combined liver kidney transplantation is an option in selected patients.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) usually occurs at initiation of treatment (chemo- or radiotherapy, or even corticosteroids) of lymphoproliferative (and, less commonly, solid) malignancies but may occur spontaneously, with a large tumour burden, or at later stages of treatment. Classically, it is a complication after chemotherapy for high-blast count acute lymphocytic leukaemias, lymphoma, myeloma, or germ cell tumours.

It results from treatment-induced necrosis of large numbers of purine-rich (actively proliferating) malignant cells, with intracellular and membrane products released abruptly into the circulation. Uric acid, in particular, causes AKI. (See Table 2.10.)

Table 2.10 Criteria for laboratory and clinical diagnosis

The Cairo–Bishop definition (2004)

Uric acid	≥476µmol/L (8mg/dL) or 25% increase
Potassium	≥6.0mmol/L or 25% increase
Phosphate	≥1.45mmol/L or 25% increase
Calcium	<1.75mmol/L or 25% decrease

≥2 of these features between 3 days pre- and 7 days post-tumour treatment encompasses the *laboratory* definition.

A *clinical* diagnosis of TLS can be made if AKI, arrhythmias, or seizures occur in conjunction with the laboratory features.

Cairo MS, Bishop M (2004). *British Journal of Haematology*, 127(1), 3–11.

Acute uric acid nephropathy

Uric acid is freely filtered and, in excess, precipitates in the tubular lumen to form obstructing crystalline casts. This is more likely in volume-deplete patients with low urinary flow rates or if u-pH ↓.

Clinical findings

In the context of recent cancer therapy, symptoms and signs are due to electrolyte abnormalities (▶▶↑ K⁺ and dysrhythmias) and AKI. TLS usually occurs within 24–48h of treatment. Nausea, vomiting, anorexia, muscle cramps, and flank pain may also be present.

Investigations

Measure the following pre- and 4–6h post-therapy and serially 6–12h.

- ↑ K⁺: often rapid ↑ to >7mmol/L.
- ↑ PO₄ and ↓ Ca²⁺: phosphate avidly binds calcium, precipitating hypocalcaemia and calcium phosphate deposition in the vasculature, myocardium, and kidney.
- ↓ Mg²⁺.
- ↑ uric acid: purine nucleotides are metabolized to hypoxanthine, xanthine, and then uric acid, often rising to >1000µmol/L (~18mg/dL).
- ↑ SCr.
- ↑ LDH.
- Urinary urate measurement and microscopy for crystals rarely needed.

Prevention

- Identify at-risk patients. Algorithms to assist this risk assessment have been developed. These are based on tumour type, disease burden, and presence or absence of renal impairment. They stratify patients to low, intermediate, or high risk. Local protocols may vary.
- Pre-hydration: 0.9% NaCl or glucose saline 2–3L/m² (~4–5L/d) for 48h pre- and post-therapy. Aim for UO >3L/d (preferably >2mL/kg/h).
 ▲ Beware volume overload if renal or cardiac impairment. Diuretics may be used cautiously to maintain urine flow unless persistent hypovolaemia.
- Prevent uric acid formation:
 - If risk low to moderate: allopurinol PO 100mg/m² 8-hourly (max 800mg/d) from 2 days prior to therapy (▲ reduce dose by 50% if renal impairment). Inhibits xanthine oxidase and prevents the metabolism of hypoxanthine to xanthine (and then uric acid and its salt urate). IV allopurinol is available if oral medication not possible (200–400mg/m²/day in 1–3 divided doses—maximum 600mg/day).
 - If high-risk for TLS, pre-emptive rasburicase (see below).

Treatment of established tumour lysis

- Laboratory tests every 4–6h. Cardiac monitor. Consider ITU transfer.
- ► Beware ↑ K⁺.
- ► Beware ↓ Ca²⁺ induced by ↑ PO₄. Correct ↑ PO₄ first to avoid systemic calcium phosphate precipitation. Parenteral calcium should only be administered if evidence of neuromuscular instability and then with extreme caution.
- Continue volume expansion with 0.9% NaCl, and maintain high UO.
- Continue allopurinol.
- ● Alkalinise the urine: 50mL 8.4% NaHCO₃ in 1L 0.45% NaCl or 5% glucose (depending on sodium load and serum Na⁺), aiming for u-pH >7.0. ↑ u-pH converts uric acid → more soluble urate salt, although simply maintaining adequate UO may be as effective. ▲ In addition, alkalosis may promote systemic calcium phosphate deposition (shifts ionized calcium to non-ionized form), so many have abandoned this practice (unless severe concomitant metabolic acidosis).
- Rasburicase:
 - A recombinant form of the enzyme urate oxidase that occurs in most species but not higher primates.
 - Oxidizes uric acid to soluble allantoin.
 - Rapidly ↓ uric acid levels (within 4h; often to undetectable).
 - Effective at preventing tumour lysis syndrome.
 - Usually given as 200 micrograms/kg IVI over 30min daily for 5–7 days, although shorter protocols (including single dose) have been developed (it is expensive). ▲ Avoid if G6PDH-deficient.
 - No adjustment required in renal impairment.
 - SE: rashes, GI upset, headache.
- Institute intermittent haemodialysis early if oliguric or uncontrolled electrolyte abnormalities. Aim for high dialysis clearances with daily treatments. Continuous techniques may be preferred (📖 p. 174).

Abdominal compartment syndrome (ACS)

Introduction

An important cause of AKI in a critical care setting.

Intra-abdominal pressure (IAP) is the pressure enclosed within the abdomen and usually correlates with BMI. Intra-abdominal hypertension (IAH) is defined as a persistent IAP of ≥ 12 mmHg (with various grades of severity as IAP rises).

Increased IAP \rightarrow \downarrow blood flow to abdominal viscera \rightarrow organ dysfunction. It strongly predicts adverse outcomes in critically ill patients.

Abdominal compartment syndrome (ACS) describes the syndrome of organ (including renal) dysfunction 2° to IAH. It is most often seen in an HDU/ICU setting where it may be difficult to diagnose amongst the complications of a primary disease.

Causes

- 1° ACS: disease/injury within the abdomen (e.g. trauma, surgery, ascites, bowel distension, intraperitoneal bleeding, liver transplantation, retroperitoneal disease—including AAA, pancreatitis).
- 2° ACS: disease/injury outside the abdomen (e.g. sepsis, burns, aggressive fluid resuscitation).

Estimates of prevalence vary widely, e.g. 1–15% in the context of traumatic injury.

Consequences

- ACS can affect virtually organ system:
 - CV: \downarrow venous return \rightarrow reduced cardiac output.
 - Respiratory: \downarrow chest compliance \rightarrow respiratory compromise and \uparrow infection.
 - GI: \downarrow mesenteric blood flow \rightarrow bowel ischaemia. Venous congestion \rightarrow gut oedema. Bacterial translocation \rightarrow sepsis.
 - Liver dysfunction \rightarrow lactic acidosis.

Renal

- Renal vein compression \rightarrow venous congestion.
- \downarrow cardiac output \rightarrow SNS and RAS activation \rightarrow renal vasoconstriction.
- Both of these \rightarrow \downarrow RBF \rightarrow glomerular perfusion \rightarrow oliguria \rightarrow AKI.

Clinical presentation

Abdominal pain, tenderness, bloating and distension, breathlessness (or \uparrow ventilatory requirements), \uparrow pulse, \downarrow BP, \uparrow JVP, \downarrow UO, peripheral oedema, lactic acidosis.

Diagnosis

Diagnosis requires recognition of at-risk patients and situations with appropriate measurement of the IAP.

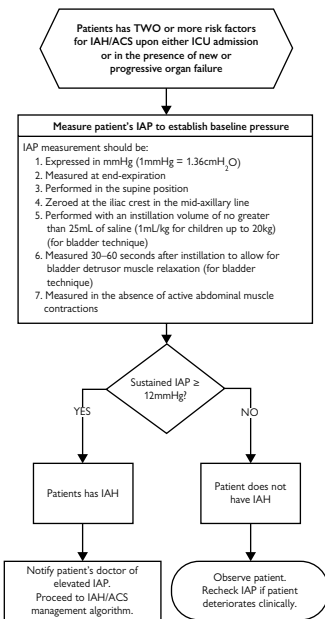
IAP can be measured indirectly, using intra-gastric, intra-colonic, IVC, or intra-vesical (most common) catheters. The World Society of the Abdominal Compartment Syndrome recommends the latter (see Fig. 2.15). Commercial devices are available, although a pressure transducer connected to a standard Foley catheter is often used.

Imaging is non-diagnostic.

Management

- Supportive care ± surgical decompression:
 - Supportive care: adequate analgesia, sedation, and muscle paralysis (with ventilatory support); consider NG and rectal decompression; accurate fluid management; nurse in supine position.
 - Surgical decompression: early intervention as IAP rises (and prior to development of ACS) is increasingly advocated. The most common technique is midline decompression, leaving an open abdomen.

• Patients should be screened for IAH/ACS risk factors upon ICU admission and with new or progressive organ failure.
 • If two or more risk factors are present, a baseline IAP measurement should be obtained
 • If IAH is present, serial IAP measurements should be performed throughout the patient's critical illness.



- Risk factors for IAH/ACS**
1. Diminished abdominal wall compliance
 - Acute respiratory failure, especially with elevated intrathoracic pressure
 - Abdominal surgery with primary fascial or tight closure
 - Major trauma/burns
 - Prone positioning, head of bed >30 degrees
 - High body mass index (BMI), central obesity
 2. Increased intra-luminal contents
 - Gastroparesis
 - Ileus
 - Colonic pseudo-obstruction
 3. Increased abdominal contents
 - Haemoperitoneum/pneumoperitoneum
 - Ascites/liver dysfunction
 4. Capillary leak/fluid resuscitation
 - Acidosis (pH <7.2)
 - Hypotension
 - Hypothermia (core temperature <33°C)
 - Polytransfusion (>10 units of blood/24 hours)
 - Coagulopathy (platelets <55,000/mm³ OR Prothrombin time (PT) >15 seconds OR partial thromboplastin time (PTT) >2 times normal OR international standardised ratio (INR) >1.5)
 - Massive fluid resuscitation (>5L/24 hours)
 - Pancreatitis
 - Oliguria
 - Sepsis
 - Major trauma/burns
 - Damage control laparotomy

IAH grading

Grade I	IAP 12–15mmHg
Grade II	IAP 16–20mmHg
Grade III	IAP 21–25mmHg
Grade IV	IAP ≥25mmHg

Abbreviations

IAH - intra-abdominal hypertension
 ACS - abdominal compartment syndrome
 IAP - intra-abdominal pressure.

Fig. 2.15 IAH assessment algorithm. Used with the kind permission of the World Society of the Abdominal Compartment Syndrome. <http://www.wsacs.org>

AKI in the developing world

Introduction

The aetiology (and \therefore presentation) of AKI may be different from that seen in developed countries, particularly in more rural areas. This may vary down to a regional level, depending on socio-economic and environmental factors. However, basic pathophysiological and management principles still apply.

Epidemiology

Cases are underreported, so accurate epidemiological data are scarce. However, community-acquired AKI is more common (estimate ~150 pmp) and affects a younger age group (mean age 37 in one study from southern India). Mortality rates are also higher and more dependent on local resources. There may be less access to RRT in some areas, with peritoneal dialysis more commonly employed for this purpose (📖 p. 188).

Overall, 'medical' causes of AKI, such as sepsis, predominate; however, cases related to surgery are rising, as increasing numbers of procedures are undertaken in older, more comorbid patients. Fortunately, obstetric-associated AKI is in fairly rapid decline in most areas.

Causes

Infective causes of AKI

- Diarrhoeal disease:
 - Common cause of pre-renal AKI and ATN (and HUS—see further in list).
 - Children with diarrhoea are much more susceptible to AKI (diarrhoea causes ~50% of dialysis-requiring AKI in Indian children).
 - Viral causes: rotavirus and Norwalk agent.
 - Bacterial causes: *E. coli*, *Shigella* spp., *Salmonella enteritides*, *Vibrio cholera*, *Campylobacter jejuni*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*.
 - Treatment is supportive (\rightarrow directed at fluid and electrolyte imbalances) \pm antimicrobials for specific infections.
 - Diarrhoea-associated (D+) haemolytic uraemic syndrome (📖 p. 578) is common in paediatric practice internationally. It is most commonly associated with *Shigella dysenteriae* serotype 1 but has many other precipitants.
- Malaria (📖 p. 702).
- Leptospirosis:
 - *Leptospira interrogans* is a spirochaete that infects many mammalian species and is shed in urine.
 - Illness classically follows a biphasic course, with an initial febrile illness, followed by more fulminant disease with liver involvement.
 - AKI occurs in ~50% of severe cases.
 - Associated AKI may be pre-renal/ATN, but an interstitial nephritis (with marked urinary K^+ wasting) is also common.
 - Diagnose with serology (late) or antigen detection via PCR (early).
 - Treatment is supportive, plus penicillin, doxycycline, or 3rd-generation cephalosporin (e.g. ceftriaxone).

- HIV (📖 p. 676):
 - AKI usually 2° to HIV-associated infection or HAART-related nephrotoxicity, but many other renal lesions are recognized.
- Melioidosis:
 - Organism: *Burkholderia pseudomallei*.
 - Area: South East Asia and Northern Australia.
 - Illness: pneumonia, visceral and cutaneous micro-abscesses, septicaemia.
 - AKI in >50%. Renal micro-abscesses are common.
- Viral haemorrhagic fevers:
 - Severe multisystem illnesses (including Dengue, Yellow, Ebola, Marburg, and Lassa fever) caused by 12 RNA viruses from four families (flavi-, arena-, bunya-, and filovirus).
 - Haemodynamic instability and increased vascular permeability → ATN. Also rhabdomyolysis. Proteinuria is common.
 - Hantavirus is discussed on 📖 p. 73.

Non-infective causes

- Herbal or traditional medicines are a common part of healthcare in many developing countries (📖 p. 901).
- Surgical AKI:
 - Incidence steadily increasing with the growth of surgical specialties and facilities across the globe.
 - Includes perioperative AKI and post-operative complications.
- Trauma.
- Obstructive uropathy is increasing (ageing population, particularly ♂).
- Pregnancy-related AKI is declining, with fewer illegal abortions and better access to good antenatal care.
- Glucose-6-phosphate deficiency (G6PD):
 - Affects several hundred million people worldwide, mainly in the Mediterranean, Africa, Middle and Far East.
 - Intravascular haemolysis occurs, following significant oxidative stress (e.g. infections, drugs).
 - Haemoglobinuric AKI results (📖 p. 155).
- Toxins:
 - Snake bites (e.g. from Elapidae, Viperidae, Colubridae, and Hydrophidae species) cause an astonishing 70% of AKI in Myanmar although much less in India (3%) and Thailand (1.2%). Venom → haemoglobinuric and myoglobinuric AKI (📖 pp. 152–155), as well as ATN 2° to circulatory compromise and DIC (and occasional direct nephrotoxicity). Early administration of anti-venom (monovalent preferable to polyvalent) may prevent renal injury.
 - Scorpion, spider, centipede, and jellyfish bites or stings.
 - Mushroom ingestion (of *Amanita*, *Galerina*, and *Cortinarius* genera), associated with liver and renal failure in severe cases.
- Chemicals:
 - The incidences of AKI 2° to poisoning with copper sulphate (leather industry), formic acid (rubber industry), and paraquat (agriculture) are now falling.

AKI in sepsis

What is the sepsis syndrome?

Sepsis accounts for 2% of all hospital admissions but 25% of admissions to ITU. AKI is a frequent complication of the sepsis syndrome, increasing in incidence as the severity of sepsis increases. Patients whose renal failure is sepsis-related have a mortality of up to 75%. With sepsis, there is evidence of (usually local) infection, with systemic signs of inflammation (\uparrow temp, \uparrow HR). This progresses to the sepsis syndrome if organ dysfunction ensues—typically, confusion, oliguria, hypoxia, and acidosis. Full-blown septic shock implies hypotension, despite adequate volume resuscitation, with signs of organ dysfunction.

Causes of significant sepsis

- Gram +ve organisms:
 - Staphylococci (incl. *S. aureus*, MRSA, and *S. epidermidis*) 20–35%.
 - *Streptococcus pneumoniae* 10%.
 - Other Gram +ve 10–20%.
- Gram –ve organisms:
 - *E. coli* 10–25%.
 - Other Gram –ve (commonly *Pseudomonas*) 5–20%.
- Others:
 - Fungi (*Candida*) 3%, viruses 3%, parasites (malaria) 1–2%.

How sepsis becomes shock

Engulfed pathogens are lysed, liberating membrane products (including lipopolysaccharide (LPS) and exotoxin), proteins, and DNA. These fragments are recognized by specific cellular receptors (Toll-like receptors) which \rightarrow NF κ -B-dependent cell activation.

Activated cells then release proinflammatory mediators (e.g. IL-1, TNF, IFN), stimulating local and systemic host defence networks.

Systemically activated leucocytes now orchestrate the immune response, with local leucocyte recruitment into inflamed tissue encouraged.

At the same time, anti-inflammatory and resolution pathways (negative feedback) are induced; inappropriate regulation of these pathways often leads to a deleterious prolongation of systemic inflammation.

Within inflamed tissue, and eventually systemically, the endothelium upregulates cellular adhesion molecules and tissue factors to encourage recruitment of effector cells. Inducible nitric oxide synthase generates large quantities of NO, and the integrity of intracellular tight junctions is compromised.

The consequences are reduced microvascular flow and mitochondrial dysfunction, leading to organ failure.

Clinically, this translates into

- ↓ systemic vascular resistance (NO is a potent vasodilator and renders angiotensin II and adrenaline less efficacious).
- ↑ capillary leakiness (tight junctions impaired).
- Local tissue injury (neutrophil recruitment with elastase release and oxidant burst).
- ↑ sympathetic activity.
- RAS activation:
 - A2 → vasoconstriction.
 - Aldosterone → Na⁺ retention (📖 pp. 456–7).
- Non-osmotic ADH (vasopressin) release → vasoconstriction.
- Vascular smooth muscle becomes less sensitive to vasoconstrictors, so, despite high circulating levels of adrenaline, angiotensin, and endothelin, the circulation remains (maximally) vasodilated.

The kidney in sepsis

- Noradrenaline → afferent arteriolar vasoconstriction → ↓ transglomerular perfusion pressure → ↓ GFR and Na⁺ retention.
- ↑ systemic NO → downregulation of intrarenal NO production → further ↓ RBF (particularly in the metabolically vulnerable outer medulla).
- Inflammatory cells produce oxidants and proteases that injure renal endothelium (remember 20% of cardiac output is to the kidney) → local coagulopathy with intra-glomerular thrombus formation → ↓ capillary blood flow.
- The end result is ↓ O₂ delivery and ATN (📖 p. 108).

Vasopressor therapy

- Treatment with noradrenaline (NADR) acts to counteract the generalized vasodilation and sepsis associated ↓ SVR.
- However, NADR may ↓ RBF through the mechanism just described, thus potentiating AKI.
- In fact, available studies suggest that NADR affects renal outcome differently, depending on whether ↓ RBF is 2° to sepsis-induced vasodilation or hypovolaemia.
 - In sepsis, NADR has a greater effect on arteriolar resistance and can normalize renal vascular resistance, maintaining transglomerular perfusion pressure.
 - NADR → ↑ SVR → ↓ renal sympathetic tone → ↑ renal perfusion.
 - The key point is that 'adequate' fluid resuscitation must take place before (or at least simultaneously with) vasopressor administration.

Managing septic shock and AKI

Definitions

Systemic inflammatory response syndrome (SIRS)

- Temperature $>38.5^{\circ}$ or $<36.0^{\circ}$.
- HR >90 .
- RR >20 , $p\text{CO}_2 <4.2\text{kPa}$, or the need for ventilation.
- WCC >12 or <4 (or blasts $>10\%$).

Sepsis—SIRS and:

- Positive cultures or focus of infection identified (e.g. cellulitis/pneumonic changes on CXR).

Severe sepsis—sepsis + one of:

- Skin mottling.
- Capillary refill $\geq 3\text{s}$.
- UO $<0.5\text{mL/kg/h}$ or the need for dialysis.
- Lactate $>2\text{mmol/L}$.
- Altered mental status (or abnormal EEG).
- Plt <100 or DIC.
- Acute lung injury (ARDS).
- Impaired cardiac function.

Shock—severe sepsis + one of:

- MAP <60 (80 if known hypertensive) after 40–60mL/kg 0.9% NaCl or 20–30mL/kg colloid, i.e. does not respond to volume resuscitation.

Calculating MAP

Mean arterial pressure is expressed as: $\text{DBP} + (\text{SBP} - \text{DBP})/3$.

Septic shock bundle





▶▶ Start immediately, and complete within 6h. Resuscitation of these patients should be subject to a locally agreed protocol that can be initiated as soon as these patients are identified.

- Antimicrobial therapy:
 - ▶▶ Culture blood and other sites, and institute broad-spectrum antibiotics within 1h.
 - Antiviral and antifungal cover may be necessary, depending on the clinical scenario.
 - Reassess antimicrobial regimen daily.
 - Further diagnostic measures should not delay resuscitation. Image possible sites of infection as early as possible. Consider surgical treatment of localized source.
- In the event of \downarrow BP and/or lactate $>4\text{mmol/L}$, administer a minimum bolus of 30mL/kg of crystalloid within 1h.
- Apply vasopressors for \downarrow BP unresponsive to initial fluid resuscitation. Aim to maintain MAP $\geq 65\text{mmHg}$.

- If persistent ↓ BP, despite volume resuscitation (septic shock), and/or initial lactate >4mmol/L, consider invasive monitoring (📖 p. 13).
 - Aim for CVP >8mmHg and central venous oxygen saturation (ScvO₂) of >70%.
 - If ScvO₂ 70% (or SvO₂ equivalent of 65%) persists, despite adequate fluid resuscitation, then consider transfusion of packed red blood cells to achieve a haematocrit of 30% ± dobutamine infusion (to a maximum of 20 micrograms/kg/min).
- During the first 6h of resuscitation, the goals include all of the following:
 - CVP >8mmHg.
 - MAP ≥65mmHg.
 - UO ≥0.5mL/kg/h.
 - Central venous (superior vena cava) oxygen saturation ≥70% (or mixed venous oxygen saturation ≥65%).
- Aim to normalize serum lactate (a marker of tissue hypoperfusion) as quickly as possible.
- Fluid therapy:
 - Give an initial fluid challenge of ≥1000mL crystalloids (to achieve a minimum of 30mL/kg in the first 4–6h).
 - More rapid administration and larger amounts of fluid may be necessary in some patients.
 - Continue incremental fluid boluses as long as there is haemodynamic improvement, as evidenced by either dynamic (e.g. stroke volume variation) or static (e.g. CO, BP, heart rate) variables.
 - Consider adding albumin to the initial fluid resuscitation regimen if serum albumin is low.
 - Avoid sodium bicarbonate therapy for the correction of hypoperfusion-induced lactic acidaemia with pH ≥7.15.
- Vasopressor therapy:
 - Use vasopressor therapy to target an initial MAP of ≥65mmHg.
 - Noradrenaline is first-line.
 - Adrenaline can be added or substituted if an additional agent is required to maintain BP.
 - Vasopressin (0.03 units/min) can also be added to, or substituted for, noradrenaline.
 - Dopamine is an alternative to noradrenaline in selected patients at low risk of arrhythmias who have low CO ± low heart rate. Do not use low-dose dopamine for ‘renal protection’.
 - Consider early placement of an arterial catheter in all patients receiving vasopressor therapy.
- Inotropic therapy:
 - Add dobutamine to vasopressor therapy (if administered) in the presence of: (i) myocardial dysfunction (as suggested by elevated cardiac filling pressures and low CO); or (ii) ongoing signs of hypoperfusion despite adequate intravascular volume and MAP.
- Corticosteroids:
 - If patients require persistent high doses of vasopressors for maintenance of adequate BP despite adequate fluid resuscitation.

- Consider a continuous infusion of IV hydrocortisone (200–300mg daily—no higher) for a minimum of 5 days.
- Do not base the need for corticosteroid therapy on ACTH stimulation testing.
- Hydrocortisone is now recommended alone, rather than in combination with fludrocortisone.
- Blood product administration:
 - Transfuse to maintain Hb >7.0g/dL.
 - Do not administer FFP to correct laboratory clotting abnormalities unless bleeding or planned invasive procedures.
 - Antithrombin administration is no longer recommended in the treatment of severe sepsis.
 - Consider platelet administration if:
 - Counts are <5000/mm³ ($5 \times 10^9/L$), regardless of bleeding.
 - Counts are 5000–30,000/mm³ ($5\text{--}30 \times 10^9/L$) and bleeding risk.
 - Surgery or invasive procedures is required: counts $\geq 50,000/mm^3$ ($50 \times 10^9/L$) are recommended.
- Glucose control:
 - Hyperglycaemia impairs leucocyte function \pm less well-understood effects.
 - Commence insulin when two consecutive blood glucose levels are $\geq 10\text{mmol/L}$ (180mg/dL), and aim to keep blood glucose levels $\leq 10\text{mmol/L}$.
 - All patients receiving IV insulin should receive a glucose calorie source.
 - Blood glucose values should be monitored every 1–2h until glucose values and infusion rates have stabilized and then at least every 4h (Δ point-of-care testing of capillary blood should be interpreted with caution, as they may overestimate plasma glucose concentration).

Renal priorities in the ITU

- Maintain independent renal function, if possible.
- No convincing data to suggest any particular volume expander or vasopressor is better or worse for the kidneys, although balanced crystalloid solutions are increasingly recommended (hydroxyethylstarch has also previously been implicated in \uparrow AKI).
- Avoid renoprotective strategies that lack an evidence base, e.g. low-dose dopamine is NOT recommended ( p. 144).
-  There is no measurable superiority of either intermittent HD (IHD) or CVVHDF, including outcomes for renal recovery, in critically ill AKI patients, although management of fluid balance is often easier with continuous therapies.
-  'High-dose' CVVHF (aiming for an UF rate of 45mL/kg/min over 25mL/kg/min) does not demonstrably improve outcomes.
-  A larger delivered IHD dose (e.g. daily treatment) may not improve outcomes but may have benefits over thrice weekly HD in terms of fluid and electrolyte management.

Renal replacement therapy in AKI

Introduction

☞ Opinions differ regarding indications, timing, what technique to use, what 'dose' to give, and when to stop.

Indications

Since evidence is currently lacking, it is principally a matter for clinical judgement, based on the patient's clinical condition, trends in laboratory tests, and the potential for swift recovery of renal function.

The indications are distinct from those applied to CKD. In general, the clinician must carefully consider what goals they want to achieve with RRT in an individual patient with AKI.

Absolute indications

- ►► Hyperkalaemia:
 - There is no universally agreed K^+ concentration. A helpful rule: consider urgent dialysis if $K^+ \geq 6.5$ mmol/L or rapidly rising, regardless of ECG changes (particularly if not responding to other interventions, such as insulin and glucose).
- ►► Volume overload:
 - Pulmonary oedema in an oligo-anuric patient with an inadequate response to diuretics.
 - Volume status is an important determinant of outcome in AKI and should be afforded a high priority in this setting.

The remaining indications for dialysis are *urgent*, rather than *emergent*. This can be an important distinction—depending on local resources, it may be preferable to delay dialysis and perform it as a planned daytime procedure under adequate supervision and with multidisciplinary support.

When to start RRT

- There is limited evidence to support an earlier start to RRT in AKI, e.g. at lower values of urea (<25–30 mmol/L or 70–85 mg/dL), the onset of oliguria, and certainly well before 'classical' indications supervene.
- However, the benefits of this practice (in terms of survival, duration of AKI, and renal recovery) are not clear-cut.
- Clinicians have a general tendency, perhaps extrapolated from their CKD care, to wait as long as possible before dialysis initiation.
- The recent KDIGO guidelines sensibly recommend a pragmatic approach and to 'consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single Ur or SCr thresholds alone'.

Relative indications

- Acidosis (pH <7.2), especially if haemodynamically unstable, or where volume overload precludes IV bicarbonate administration.
 - There is evidence that myocardial enzymes are dysfunctional with pH <7.2 → higher risk of arrhythmia.
- Critically unwell patients (usually in an HDU/ITU setting):
 - To maintain fluid balance and allow safer administration of fluid, feeding, blood and blood products, antimicrobials, and drugs.
- Uraemic complications:
 - Rare for these to be a significant factor in AKI. If you are waiting for these before initiating dialysis, then you are waiting too long!
 - Uraemic pericarditis or encephalopathy.
 - Uraemic symptoms, especially once Ur >40mmol/L (112mg/dL) (⚠ there is no absolute figure that equates with 'uraemia', and there is considerable interpatient variation in 'biochemical tolerability').
- Diuretic-resistant cardiac failure.
- Poison or toxin removal (lithium, ethylene glycol, etc.) (📖 p. 906).
- Hyperthermia.

Why delay RRT—the potential complications

- Complications of dialysis access insertion (📖 p. 180).
- Haemodynamic strain or overt hypotension in an already sick patient (☹ which may then perpetuate AKI).
- Electrolyte imbalances, e.g. rapid reduction of K⁺ (⚠ → arrhythmias).
- Complications of anticoagulation (📖 p. 182).
- Dialysis disequilibrium (📖 p. 177).

When to stop RRT

- Requires regular (at least daily) assessment.
- Average duration of RRT in AKI is ~12 days.
- Assessment of underlying renal function during RRT can be difficult. It is often particularly uncertain for intermittent haemodialysis (IHD) where variable rebound in Ur, SCr, and electrolytes may occur between treatments.
- An increase in urine output is particularly helpful, although the use of diuretics will need to be factored in (routine administration of diuretics to ↑ UO and facilitate earlier cessation of RRT is not recommended).
- Trends in SCr, Ur, and electrolytes need to be carefully considered (and allowance made for non-renal confounding factors, such as the patient's catabolic state and volume status).
- Theoretically, serial measurements of urinary Cr excretion might be helpful but are very rarely undertaken in practice.
- Cessation of RRT does not have to be an absolute. It might be prudent to initially adjust the duration and frequency of treatment or to consider a modality change (e.g. step down from CRRT on ITU to IHD on a renal unit).
- On occasion, particularly in a critical care setting, more fundamental issues concerning the futility of further treatment will need to be included in the decision-making.

RRT in AKI: modalities

Introduction

The ideal modality of RRT in AKI is unknown. In practice, the choice will be based primarily upon: (i) the availability of different treatments and (ii) a patient's haemodynamic status and overall clinical condition. PD use in AKI is infrequent, except in paediatric practice and in areas where resources are constrained (📖 p. 188). The treatments are not mutually exclusive, with changes between them dictated by clinical circumstances.

Modalities

Generally, intermittent haemodialysis (IHD) is preferred on renal units whilst continuous techniques (CRRT), such as continuous veno-veno haemofiltration (CVVHF), continuous veno-venous haemodialysis (CVVHD), continuous veno-veno haemodiafiltration (CVVHDF), and sustained low-efficiency dialysis (SLED), are more often encountered in high dependency and critical care environments.

Intermittent haemodialysis (IHD) (see Fig. 2.16)

- Solute clearance mainly by diffusion across semi-permeable membrane.
- Pores in the membrane allow small molecules (e.g. Ur (MW = 60Da), Cr (113Da)) and electrolytes but not larger ones (e.g. plasma proteins (albumin 60,000Da, IgG 140,000Da) or blood cells) to pass through.
- Dialysate (physiological solution of electrolytes) is required.
- Concentration differences across the membrane allow molecules to diffuse down a gradient. This allows waste products to be removed and desirable molecules or ions (e.g. HCO_3^-) to be replaced.
- Diffusion is maximized by maintaining high-flow rates of blood and dialysate and by pumping the two through the dialyser in countercurrent or opposite directions.
- Usually administered intermittently (e.g. 4h, 3x/week), although the delivery in AKI may differ from this (📖 see chapter 4).
- Water can be driven through the membrane by hydrostatic force (ultrafiltration or UF). The pressure gradient across the membrane (transmembrane pressure or TMP) can be controlled to vary the amount of water removed (but usually <3–4L in a 4h treatment).

Haemofiltration (HF) (see Fig. 2.16)

- Solute clearance by convection (mainly), i.e. fluid shifts across the dialysis membrane also allow solutes to cross ('solute drag').
- Achieved by generating a TMP across the membrane.
- Large volumes need to be filtered to achieve adequate solute clearance. This would cause hypovolaemia, unless replacement fluid is administered—usually pre-prepared 5–10L bags (during IHD, HF is used to remove fluid that has accumulated between treatments ∴ no fluid replacement is necessary). No dialysate is required.
- Removes larger MW (30–50kDa) molecules (e.g. vitamin B12 and β_2 microglobulin) more efficiently than dialysis. ⚡ May also remove pro- (and anti-) inflammatory cytokines.
- Delivered as a continuous, rather than intermittent, technique.

IHD modifications (e.g. SLED)

- This essentially refers to treatments using standard dialysis equipment but for a longer treatment than the ‘traditional’ 4h.
- Both IHD and CRRT machines can be adapted easily for this purpose.
- Sustained low-efficiency dialysis (SLED) uses extended (e.g. 6–12h) treatments with blood and dialysate flows of between 100–300mL/min.
- The aim of SLED is to improve tolerability over IHD.
- The ‘low-efficiency’ tag is misleading—it is often commendably efficient.

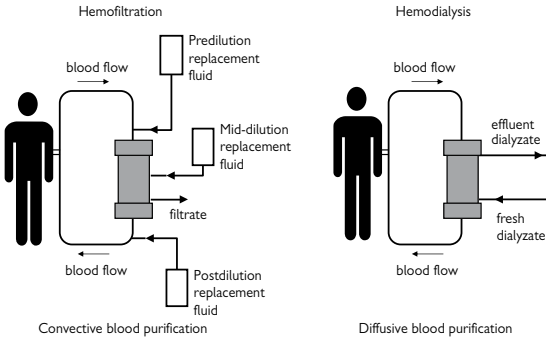


Fig. 2.16 Principles of HD and HF. For HF, replacement fluids can be given before, into, or after the haemofilter (pre- or post-dilution). Reproduced from *Oxford Desk Reference: Nephrology*, Jonathan Barratt, Kevin Harris, and Peter Topham (2008), with kind permission of Oxford University Press.

Haemodiafiltration

- Combines HD and HF to get the best of both modalities (see Fig. 2.17).
- Set up as for HD, but with a higher TMP, to produce a significant filtration.
- Both dialysate and replacement fluid are required.

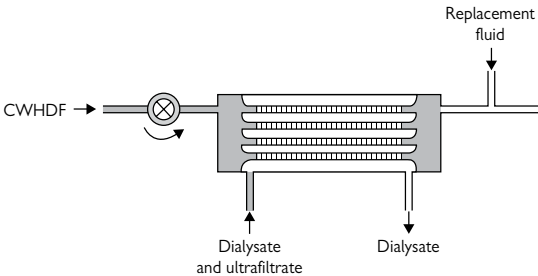


Fig. 2.17 Haemodiafiltration. Reproduced with permission from Levy J, Morgan J, and Brown E (2004). *Oxford Handbook of Dialysis*, 3rd edn.(2009), with permission from Oxford University Press.

RRT in AKI: choosing modality?

Introduction

One size does not fit all. No single modality of RRT is ideal for all patients in all situations. It is ∴ important to be aware of the advantages and disadvantages of available techniques and to tailor treatment to a particular clinical context. The treatments should not be considered competitive but complementary. It should also be acknowledged that availability may influence choice to a greater or lesser extent.

Advantages and disadvantages

CRRT

- Advantages: slower fluid removal (→ haemodynamic stability); continuous (∴ improved) fluid balance (including greater overall capacity for fluid removal); gentler solute control (→ slower fluid shifts and ↓ risk of cerebral oedema); adjustable as clinical circumstances evolve; relatively simple equipment.
- Disadvantages: continuous anticoagulation (📖 p. 182); immobilized patient; risk of hypothermia; potential higher cost.

IHD

- Advantages: faster correction of electrolyte abnormalities and toxin removal (∴ potential advantage for ↑↑ K⁺, poisoning, tumour lysis, rhabdomyolysis); rapid fluid removal; allows mobilization (→ less muscle wasting and respiratory infection) and time for other investigations and interventions to take place; fewer bleeding complications; transfer to a high dependency environment is usually unnecessary; several patients can be treated with the same equipment each day; possible reduced cost.
- Disadvantages: haemodynamic instability; dialysis disequilibrium (📖 p. 177); less overall control of fluid balance and less adaptability; technically more complicated.

Hybrid treatments

The aim of treatments, such as SLED, is to share the advantages whilst minimizing disadvantages of both CRRT and IHD.

Evidence

Several RCTs have compared CRRT to IHD in the context of AKI. However, a clear demonstration of the superiority of either technique has proved elusive, e.g. a Cochrane collaboration meta-analysis analyzed 15 studies involving ~1500 patients and concluded that outcomes were similar in terms of mortality, length of hospital stay, and renal recovery.

🔍 An often debated benefit of CRRT is a favourable effect on renal recovery (as a by-product of improved haemodynamic stability). However, whilst reduced progression to ESRD has been suggested by a few observational studies, all controlled trials and meta-analyses to date have failed to demonstrate a consistent benefit of CRRT.

Comparative studies between SLED and CRRT demonstrate similar outcomes, particularly with respect to haemodynamic tolerability.

General guidance

- In the patient with haemodynamic instability, CRRT is preferred to standard IHD. CRRT is also preferred in patients with AKI who cannot tolerate fluctuations in fluid status (e.g. cardiogenic shock).
- In a critically ill patient with multi-organ involvement, particularly in an HDU/ITU setting, the adaptability of CRRT means that it is generally preferred to IHD.
- CRRT is preferred for a patient with acute brain injury where IHD may worsen neurological status (\downarrow BP + cerebral oedema \rightarrow \downarrow cerebral perfusion pressure).
- CRRT is preferred in combined liver-kidney failure (possible advantage for prevention of \uparrow intracranial pressure).
- SLED may be better tolerated than IHD, particularly if other forms of CRRT are unavailable.

Dialysis disequilibrium

- A syndrome thought to be 2° to cerebral oedema: blood Ur drops rapidly during dialysis but slower both in the intracellular compartment and within the blood–brain barrier. This results in water influx into the brain and cerebral oedema (\pm cerebral acidosis).
- Usually occurs in the context of AKI on a background of CKD.
- ►► Rare if first dialysis prescription/precautions observed (📖 p. 178).
- Those with Ur >60 mmol/L (168mg/dL) at particular risk.
- Symptoms (during or shortly after dialysis): nausea, dizziness, headache, visual disturbance, agitation, confusion, \downarrow GCS, and seizures.
- ► Exclude hypoglycaemia, \downarrow Na⁺, drug toxicity (has a renally excreted drug stayed at the same dose despite a dramatic reduction in kidney function, e.g. antibiotics?), and intracerebral bleeding.
- Prophylaxis: observation of first dialysis prescription/precautions is mandatory. Phenytoin 15mg/kg loading dose, then 200–300mg/d, is no substitute for applying these but has been used.
- Treatment: stop dialysis, and supportive care (improvement should occur within 24h). Seizures: mannitol 10–15g IV (raises plasma osmolality) and diazepam \pm phenytoin.

RRT in AKI: prescription

► Remember: the dialysis staff have considerable expertise and are likely to know a great deal more than you can possibly learn from this book.

Intermittent HD

- *Time:*
 - ⚠ Rapid overcorrection of uraemia may cause the syndrome of dialysis disequilibrium (📖 p. 177), so initial treatment aims for partial correction of uraemia only (\downarrow Ur \leq 30%).
 - A guide: 1st session \rightarrow 2h, 2nd \rightarrow 3h, and subsequent \rightarrow 3–4h.
- *Blood flow:*
 - Relatively slow, ~150–200mL/min (\uparrow by 50mL/min/session to 300–400mL/min).
- *Frequency:*
 - Ur rebound is common, so aim to dialyse daily against symptoms and chemistry (⚠ beware \uparrow K⁺) for the first 2–4d.
 - Catabolic patients (e.g. sepsis) may need to remain on a daily regimen for longer.
- *Dialyser:*
 - Small dialyser (\leq 1.2m²) preferable (📖 p. 284).
- *Fluid removal or ultrafiltration (UF):*
 - ► Assessment of volume status is crucial.
 - Hypovolaemia: administer saline (e.g. 1–2L) prior to, and during, dialysis—no UF.
 - Euvolaemia: no UF.
 - Overload: up to 2–3L can be removed over 2h, depending on haemodynamic status, progress and stability of the patient. If further fluid removal is desirable (patient remains in pulmonary oedema with satisfactory BP), then it can be removed through ‘isolated UF’ (\rightarrow dialysate flow is turned off, leaving fluid removal, rather than biochemical control, as the 1^o treatment goal). ⚠ Note: UF without dialysis can still cause hypotension and CV instability.
- *Anticoagulation* (📖 p. 182):
 - Use minimal or no heparin, as necessary, to prevent clotting in the extracorporeal circuit.
 - AKI patients are at high risk of bleeding (📖 p. 138) e.g. GI haemorrhage, unintentional arterial puncture during line insertion, \uparrow BP, pericarditis (which may \rightarrow haemorrhagic tamponade).
- *Dialysate* (📖 p. 282):
 - Bicarbonate buffer is preferred to lactate.
 - Lactate \rightarrow liver metabolism \rightarrow HCO₃⁻. However, lactate may accumulate in multi-organ failure, esp. in patients with liver failure (\downarrow clearance) or shock (\uparrow production) \rightarrow worsening acidosis.
 - Dialysate Na⁺ of 145mmol/L is typical. If serum Na⁺ <125mmol/L, use a dialysate Na⁺ \leq 20mmol/L higher to avoid rapid correction.
 - Serum K⁺ decides dialysate K⁺. ⚠ Overcorrection \rightarrow arrhythmias. (See Table 2.11.)

- *Haemodynamic tolerability of IHD:*
 - Measures to help improve this: (i) prime circuit with saline; (ii) stop vasodilator therapy (if possible); (iii) dialysate $\text{Na}^+ \leq 10 \text{ mmol/L}$ above plasma Na^+ (up to 150 mmol/L); (iv) dialysate Ca^{2+} $1.35\text{--}1.5 \text{ mmol/L}$; (v) dialysate K^+ as in Table 2.11 (use highest possible); (vi) cooled dialysate ($35\text{--}37^\circ\text{C}$); (vii) minimum UF clinical status allows.

Table 2.11 Serum decides dialysate

Serum (mmol/L)	Dialysate (mmol/L)
>5.5	2.0
3.5–4.5	4.0
<3.0	4.5

K^+ -free dialysate can be used if $\uparrow\uparrow \text{K}^+$.



CRRT

- *Time:*
 - Continuous.
- *Blood flow:*
 - Usually $150\text{--}200 \text{ mL/min}$.
- *Filter:*
 - High-flux (synthetic) membrane.
- *Fluid removal:*
 - UF rates of $10\text{--}45 \text{ mL/kg/h}$ are typical. Fluid removal is achieved by the UF rate exceeding replacement fluid administration per hour (e.g. net 100 or 200 mL UF/h).
 - Replacement fluid (usually supplied in 5 L bags) contains:
 - Buffer: bicarbonate is preferred to lactate.
 - K^+ : generally $0\text{--}4 \text{ mmol/L}$ and adjusted to serum K^+ .
 - Also Na^+ ($132\text{--}140 \text{ mmol/L}$), Ca^{2+} , Mg^{2+} , and Cl^- .
 - Note: replacement fluid is not the same as dialysate.
- *Anticoagulation:*
 - Heparin, citrate, or epoprostenol (📖 pp. 182–7).

SLED

- *Time:*
 - Usually $5\text{--}12 \text{ h}$.
- *Blood flow:*
 - Blood and dialysate flows of between 100 and 300 mL/min .
- *Dialyser:*
 - Standard IHD dialyser.
- *Fluid removal:*
 - Prolonged treatment time allows more UF than IHD.
- *Anticoagulation:*
 - Heparin. Circuits potentially more prone to clotting than IHD.
- ⚠ *Drugs:*
 - Guidelines for appropriate drug-dosing in RRT are usually for IHD or CRRT. As SLED will potentially provide more effective clearance than IHD, caution is necessary before extrapolating such recommendations. Speak to your pharmacist.

Vascular access

- **Type:**
 - An uncuffed, double-lumen dialysis catheter ('temporary line' or vascular catheter) is acceptable for periods of <7 days.
 - If >7 days, consider a cuffed (and tunnelled) double-lumen catheter (not in ICU).
- **Route:**
 - Δ Avoid the subclavian veins (\rightarrow more difficult insertion and \uparrow incidence of central venous stenosis).
 - Jugular: often the route of choice, although a volume-overloaded patient may find it difficult to lie flat during insertion. Left-sided jugular lines are technically more difficult to insert.
 - Femoral: no need to wait for a CXR post-insertion in emergent situations. However, \uparrow infection risks, reduced mobility, increased risk of DVT.
- **Insertion:**
 - For insertion technique, see  p. 936.
 - \blacktriangleright The benefits of insertion under ultrasound guidance have been clearly demonstrated (fewer attempts necessary, quicker procedure, better catheter position, fewer complications).
- **Precautions:**
 - Strict adherence to infection control policies. This includes, but goes significantly beyond, a sterile technique at insertion—catheter aftercare is just as important.
 - CXR prior to the use of jugular (or subclavian) lines.
 - Review ongoing need for, and function of, access regularly—remove or replace, as necessary.
 - Beware recirculation ( p. 297) with temporary lines, particularly short catheters in the femoral vein. Optimal lengths:
 - 12–15cm right internal jugular.
 - 15–20cm left internal jugular.
 - 19–25cm femoral.
- $\blacktriangleright\blacktriangleright$ Complications of central venous catheterization. These should be explained to the patient (and audited regularly):
 - Unsuccessful insertion (10–20%).
 - Arterial puncture (<6%).
 - Haematoma (<5%).
 - Haemothorax (<1%).
 - Pneumothorax (<3%).

Adequacy ('dose')

The optimal 'dose' of RRT in AKI (and how best to measure it) is unknown. In addition, the actual *delivered* dose of RRT often falls short of that intended or prescribed (reasons: haemodynamic instability, variations in BMI, access malfunction, technical difficulties, filter or dialyser clotting, and patient disconnection, e.g. for other interventions or investigations).

Measurement

Although routinely used for the assessment of dialysis adequacy in CKD (📖 p. 286), Kt/V for urea has less utility in AKI where patients are more metabolically unpredictable, particularly with respect to urea production.

Many clinicians aim for a consistent blood Ur (post-dialysis Ur for IHD), e.g. <25mmol/L or even <15mmol/L.

Overall, the goals of RRT prescription in AKI should ∴ be more holistic, aiming to achieve the optimum electrolyte, acid–base, and fluid balance that are appropriate for a particular clinical circumstance. This may require continuous reassessment and adjustment.

Guidelines

There is currently no evidence that increased RRT dose in AKI improves outcomes with respect to either mortality or renal recovery. However, KDIGO recommended the following:

IHD: a cumulative weekly Kt/V of 3.9, e.g. Kt/V 1.3 for each treatment on a 3×/week dialysis prescription.

CRRT: filtration volume of 20–25mL/kg/h. For the reasons given earlier, this is likely to require a prescribed dose in the range of 25–30mL/kg/h.

High-dose RRT in sepsis

- There has been interest in high-dose RRT in the context of AKI and septic shock.
- It is postulated that removal of proinflammatory cytokine removal might be important.
- Limited data suggest potential benefit, particularly in terms of the vasopressor doses required to maintain MAP in these patients.
- In the IVOIRE trial, there was no evidence that high volume HF at 70mL/kg/h, compared with contemporary standard volume HF at 35mL/kg/h, leads to a reduction in 28-day mortality, or contributes to early improvements in haemodynamic profile or organ function.
- Cytokine removal may not only be through UF, but also via adsorption on the filter membrane (potentially increasing costs, as the filter becomes cytokine-saturated and requires regularly changing).
- It seems likely that anti-inflammatory cytokines are just as likely to be removed as their proinflammatory counterparts.
- High-dose CRRT means filtration volumes in the range of 65mL/kg/h.
- Cytokine removal can also be achieved with IHD and SLED, using special high-flux (i.e. large pore size) membranes.

RRT in AKI: anticoagulation

Introduction

Contact between blood and the dialysis circuit → coagulation pathway and platelet activation → clotting. This reduces treatment efficiency and causes blood loss. Prevention requires concomitant anticoagulant therapy, which introduces a bleeding risk and increases technical complexity. (See Fig. 2.18)


Patient factors

- Anticoagulant therapy can be individualized to the patient.
- Patients with pre-existing coagulation issues (e.g. thrombocytopenia, liver disease) will be at higher risk from therapeutic anticoagulation.
- AKI patients may already be anticoagulated for an underlying condition (e.g. ACS, AF) and ∴ not require additional treatment.


If anticoagulation is not possible, other measures (and nursing skill) can prevent or delay thrombosis, e.g. satisfactory vascular access, pre-filter fluid replacement for CRRT, regular saline flushes, ↑ blood flow, and immediate attention to equipment alarms.

Intermittent haemodialysis

Unfractionated heparin

- Remains the most widely used anticoagulant for IHD (see also  p. 290).
- Dose and target ACT/APTT can/should be patient-specific.
- Advantages: vast experience with use; widely available; short half-life; reversible with protamine; tests required for monitoring (APTT, ACT) are usually readily accessible; relatively low cost.
- Disadvantages: narrow therapeutic index; drug kinetics often unpredictable; HIT; heparin resistance (2° to ↓ antithrombin levels in the critically ill), (page 184).

LMW heparin

- Use in AKI has increased, as experience has grown in chronic IHD.
- ⚠ LMWH relies on renal elimination, so AKI patients are at ↑ risk of accumulation and bleeding ( p. 138).
- Doses lower than those familiar from therapeutic anticoagulation, e.g. enoxaparin (0.5mg/kg) single bolus at start of IHD.
- ⚠ Caution if patient also receiving LMWH for thromboprophylaxis (consider combining at the start of dialysis to achieve two goals).
- Intermittent measurement of anti-factor Xa activity desirable with prolonged, or daily, use.
- Advantages: simple regimen; more predictable drug kinetics; consistent anticoagulant effect; less monitoring usually necessary; ↓ risk of HIT.
- Disadvantages: accumulation; measurement of anti-factor Xa activity may not be available; incomplete reversal by protamine; higher cost.

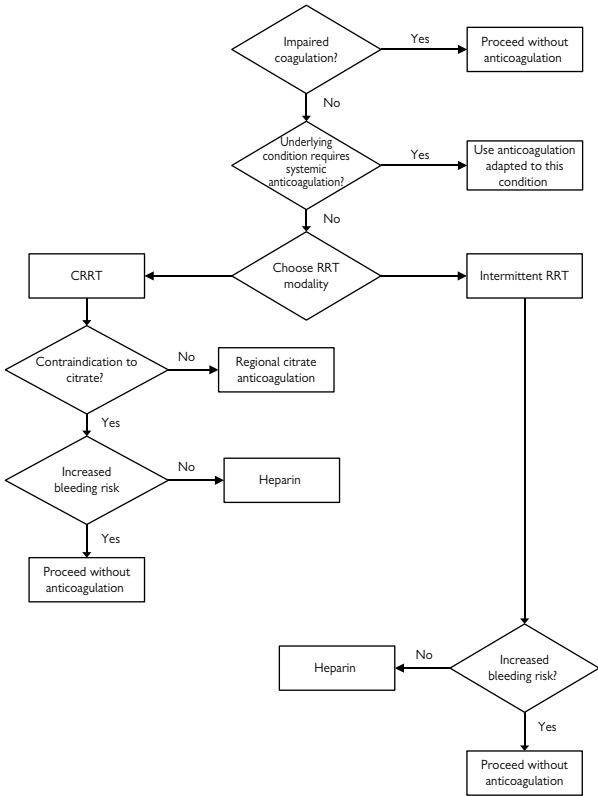


Fig. 2.18 Flow chart summary of KDIGO recommendations for anticoagulation during RRT for AKI. Reproduced from *Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Inter.*, Suppl. 2012; 2: 1–138.* with permission from Nature Publishing Group.

CRRT**Heparin**

- Unfractionated heparin widely used. Usually a pre-filter infusion, e.g. 15–30IU/kg, followed by maintenance 5–15IU/kg/h (Δ the relationship between dose, APTT, circuit longevity, and bleeding is complicated).
- LMWH is less popular for CRRT and requires factor Xa monitoring.

Heparin-induced thrombocytopenia (HIT)

- HIT is an immune phenomenon. Antibodies react against the heparin: platelet factor 4 complex on platelets (\rightarrow clumping, activation, and thrombosis).
- Incidence: <3% of heparin-treated patients.
- Consequences: severe thrombocytopenia \pm thrombosis (usually within 5–10d of heparin use).
- Treatment: stop *all* heparin (LMWHs are not safe in this context). Usually resolves within 1–2 weeks.
- In patients undergoing RRT with heparin, monitor the platelet count and suspect the diagnosis if repeated circuit clotting occurs.
- If ongoing anticoagulation for RRT is required, alternatives include:
 - Citrate (📖 p. 186).
 - Argatroban (direct thrombin inhibitor, hepatic elimination, short half-life, continuous infusion, monitored with APTT).
 - Factor Xa inhibitors (e.g. danaparoid, fondaparinux).
 - Epoprostenol.

RRT in AKI: citrate regional anticoagulation

- Citrate regional anticoagulation is an increasingly popular means of anticoagulation for CRRT. (See Fig. 2.19)
- Citrate forms a complex with ionized calcium (iCa^{2+}), thereby eliminating a crucial constituent of the coagulation cascade.
- Citrate reaching the systemic circulation is metabolized (liver, muscle, kidney), releasing calcium and generating bicarbonate.
- Low or zero calcium dialysate/replacement solutions are required, and separate calcium infusions prevent $\downarrow Ca^{2+}$.
- Advantages: \downarrow bleeding; \downarrow transfusion requirement; longer circuit patency; generation of HCO_3^- .
- Disadvantages: citrate accumulation \rightarrow acidosis; $\downarrow Ca^{2+}$ (esp. liver impairment or shock); $\downarrow Mg$ (citrate binds to Mg); risk of metabolic alkalosis; $\uparrow Na^+$ (trisodium citrate); technically much more complicated.

Procedure

- Citrate (e.g. 4% trisodium citrate) is infused into the 'arterial' side of the haemofilter circuit, for example:
 - 90mL of stock 46.7% trisodium citrate in 1L 5% dextrose.
 - Infused at 175–350mL/h, depending on blood flow.
- Different protocols use different concentrations of calcium, e.g. 0.75% calcium chloride infused concomitantly into central vein:
 - 80mL of 10% calcium chloride in 1L normal saline.
 - Infuse at \sim 60mL/h.
- Circuit and systemic total and iCa^{2+} are measured hourly until stable and then 4–6h.
- Aim to maintain circuit iCa^{2+} 0.25–0.35mmol/L and systemic iCa^{2+} 0.9–1.23 mmol/L. Titrate citrate infusion to circuit iCa^{2+} and calcium infusion to systemic iCa^{2+} .
- Total systemic Ca^{2+} (and total to ionized ratio) will rise if citrate accumulates.

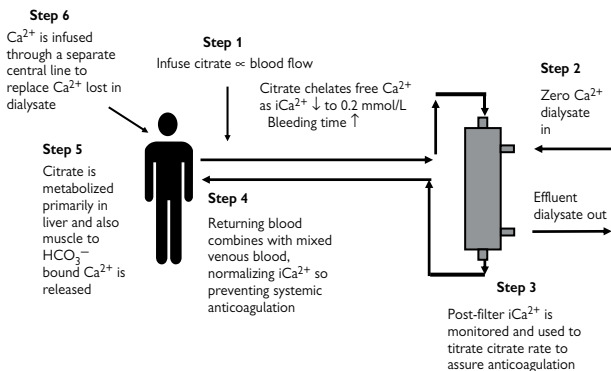


Fig. 2.19 Principles of citrate anticoagulation for CRRT. $i\text{Ca}^{2+}$, ionized calcium. Reproduced from *Oxford Desk Reference: Nephrology*, Jonathan Barratt, Kevin Harris, and Peter Topham (2008), with permission of Oxford University Press.

Peritoneal dialysis (PD) in AKI

Rarely used for AKI in Europe and North America but an important treatment worldwide. Until recently, it was also the most popular technique for the treatment of AKI in children.

Potential advantages

- No need for a specialist renal set-up.
- Technical aspects and apparatus are relatively straightforward.
- Minimizes haemodynamic instability (making fluid removal easier).
- Gentle correction of biochemical abnormalities.
- No need for vascular access or systemic anticoagulation.
- Glucose in PD fluid increases caloric intake.
- Low cost.

Potential disadvantages

- Bowel perforation during catheter insertion (esp. if previous surgery → adhesions).
- Δ Infection: peritonitis and catheter exit site.
- Poor clearance: relatively slow correction of uraemia and $\uparrow K^+$, particularly in catabolic patients.
- Unpredictable UF rate (interpatient variability).
- Protein and amino acids lost in dialysate.
- Catheter problems: migration, poor inflow/outflow, leakage.
- Abdominal distension → diaphragmatic splinting → respiratory compromise.
- Hyperglycaemia (PD fluid uses glucose to generate hypertonicity).
- Contraindicated by recent abdominal surgery.
- Diaphragmatic splinting with respiratory compromise.

Catheter placement

Semi-rigid ('stab PD')

Pros: inserted at the bedside under LA (usually via a Seldinger technique).
Cons: non-cuffed, therefore, high infection rates. Uncomfortable and easy to dislodge. Higher incidence of bowel perforation. Usually requires removal after 48–72h (→ repeated insertions often necessary).

Cuffed catheter (similar to those used in chronic PD)

Pros: cuff prevents bacterial migration \therefore \downarrow infection rates. Softer catheter so more comfortable with less risk of bowel perforation. More compatible with automated cyclers.

Cons: insertion requires more expertise (although LA still possible).

PD vs IHD or CRRT for AKI?

Studies are limited. Comparisons have suggested a worse outcome for PD than for CVVHF—though second-rate PD equipment (rigid catheters, home-made fluids, acetate buffer, no automated cyclers) are often judged against first-rate CVVHF technology in highly catabolic patients. However, PD cannot be considered a front-line treatment for AKI in most settings but may be lifesaving if HD/CRRT unavailable.

Prescribing acute PD

- Commercially available dialysate solutions preferable. Warm to body temperature prior to infusion.
- A correctly positioned catheter should allow inflow and outflow times of <10–15min. Both proceed under gravity. Ensure complete drainage (remember: more drains out than in if UF has occurred).
- Dwell times of 1h are typical (<30min a waste of time and effort).
- With non-cuffed rigid catheters, peritonitis risk ↑ dramatically after 72h. Cuffed catheters offer uninterrupted treatment.
- Aim for 20–24 exchanges/day (although often logistically difficult).
- Record the number of exchanges and fluid input:output.
- Continuous equilibrium PD (CEPD), which is similar to standard CAPD, is an alternative. Dwell times are 4–6h, allowing more time for solute equilibration between blood and dialysate. Less time 'hands on' the catheter → ↓ risk of infection.
- Dialysate volume: most patients tolerate 2L exchanges. Larger volumes (up to 3L) can → catheter leaks, hernias, and diaphragmatic splinting.
- Dialysis dose is increased by ↑ dialysate volume ± ↑ exchange frequency.
- Fluid balance. If the patient is euvoelaemic, mildly fluid-overloaded, or haemodynamically unstable, a 1.5% dextrose concentration ('light bag') is appropriate. Check the subsequent drainage volume to assess UF. Use this figure, in combination with repeated clinical assessment, to direct the need for higher dextrose concentrations (usually 2.5% or 4.25%).
- Heparin (200–500U/L) can be added to the dialysate to prevent plugging of the catheter with fibrin clots. It is not absorbed systemically.
- Commercial PD solutions do not usually contain K⁺, so if the patient is hypokalaemic or the serum K⁺ is rapidly falling, potassium chloride may be added (usually 2–4mmol/L).

Chronic kidney disease (CKD)

- What is chronic kidney disease (CKD)? 192
- Prevalence of CKD 194
- Diagnosis of CKD 196
- Cardiovascular disease in CKD 198
- Pathogenesis of CKD 200
- Progression of CKD: general 202
- Progression of CKD: antihypertensives in CKD 204
- Progression of CKD: miscellaneous 208
- Advanced CKD: the uraemic syndrome 212
- Complications of advanced CKD 214
- Anaemia and CKD 216
- EPO and the kidney 218
- Erythropoiesis-stimulating agents (ESAs) 220
- Prescribing ESAs 222
- ESAs: additional benefits 224
- ESAs: target haemoglobin 226
- Iron 1: metabolism and markers 228
- Iron 2: therapy and targets 230
- CKD-mineral and bone disorder (CKD-MBD) 232
- CKD-MBD: bone disease 234
- CKD-MBD: physiology 236
- CKD-MBD: clinical features 240
- CKD-MBD: vascular calcification 242
- CKD-MBD: treatment 244
- CKD-MBD: hyperphosphataemia 246
- CKD-MBD: vitamin D treatment 250
- CKD-MBD: calcimimetics 252
- CKD-MBD: parathyroidectomy 254
- Calcific uraemic arteriopathy (calciphylaxis) 256
- Diet and nutrition in CKD 258
- Malnutrition in CKD 260
- Endocrine problems in CKD 262
- CKD management overview 264
- Advanced CKD care 266
- Conservative treatment of CKD: symptomatic management of ESRD 268
- Conservative treatment of CKD: general 270

What is chronic kidney disease (CKD)?

Definition

The NKF KDOQI (National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative) classification of chronic kidney disease (CKD) has been rapidly adopted internationally.¹ It is simple and useful and has helped to raise awareness of kidney disease. CKD is divided into five stages, according to estimated GFR. (See Table 3.1.)

Table 3.1 NKF KDOQI classification of CKD

CKD stage	GFR (mL/min/1.73m ²)		Description
1	>90 [†]		Normal or increased GFR but other evidence of kidney damage
2	60–89 [†]		Mild reduction in GFR, with other evidence of kidney damage
3	3A*	45–59*	Moderately reduced GFR, with or without other evidence of kidney damage
	3B*	30–44*	
4	15–29		Severely reduced GFR
5	<15		End-stage, or approaching end-stage, kidney failure
5D	<15		On dialysis

[†] Early CKD is not diagnosed on eGFR alone. There must also be evidence of kidney damage (see rest of table). Patients with an eGFR of 60–89 mL/min without kidney damage do not have CKD.

* The subdivision of stage 3 into 3A and 3B is not part of the original KDOQI classification but has been advocated by other organizations (e.g. NICE in the UK). It reflects the higher incidence of cardiovascular disease and complications (e.g. anaemia) that are more prevalent, as eGFR falls below 45 mL/min.

- Patients with a GFR >60 mL/min should not be considered to have CKD, unless there is concomitant evidence of kidney damage:
 - Urinary abnormalities (proteinuria, haematuria).
 - Structural abnormalities (e.g. abnormal renal imaging).
 - Genetic disease (e.g. APKD).
 - Histologically established disease.
- The reduced eGFR and/or urinary abnormalities should ideally be present on at least two occasions ≥3 months apart.
- It has been suggested that the suffix (p) is added to the CKD stage to indicate the presence of proteinuria (uACR ≥30 mg/mmol or uPCR ≥45 mg/mmol). This helps to highlight the ↑ risk of both progression and CV disease (e.g. stage 3p).
- Chronic renal failure (CRF) is now an outmoded term that indicates an irreversible decline in GFR.

- ►► The majority of patients with CKD stages 1–3 do not progress to kidney failure. The risk of death from CV disease is far higher than the risk of progression (📖 p. 198).

Causes of CKD

Accurate data on the causes of early CKD are scarce. Registry data focuses on causes of end-stage renal disease (ESRD). As only a relatively small number progress (and live long enough) to reach dialysis or transplantation, it is difficult to extrapolate back to early CKD. Recent UK and US causes are shown in Table 3.2, but there is considerable variation worldwide.

Table 3.2 Causes of CKD—the US and UK

Renal disease	UK Renal Registry	US Renal Data System (USRDS)
Cystic or congenital disorder	7	7
Diabetes mellitus	13	37
Glomerulonephritis ^a	15	18
Hypertension/atherosclerotic	9	24
Infective or obstructive (including reflux)	12	3
Miscellaneous ^b	18	7
Unknown	26	4

^a May not be histologically proven.

^b Includes analgesic nephropathy, TB, HIV-related, sickle cell disease, sarcoidosis, acute interstitial nephritis, trauma.

Reference

1. National Kidney Foundation (2002). KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *American Journal of Kidney Diseases*, 1, S1–S266.

Prevalence of CKD

- The exact prevalence of CKD in the general population remains unknown.
 - A large UK study in primary care suggested an age-standardized prevalence of stages 3–5 CKD of 8.5% (10.6% in ♀ and 5.8% in ♂).
 - Over 19 million of the US adult population are thought to have some form of CKD.
- The most common associations are ↑ BP, diabetes, and vascular disease.
 - In the UK study just mentioned, the age- and gender-adjusted odds ratios were 2.1 for ↑ BP, 1.33 for diabetes, and 1.69 for CV disease.
- CKD prevalence rises dramatically with age—from 78 pmp age <40 to 5,900 pmp age >80.
- Early stages appear common, so the base of the pyramid in Fig. 3.1 should actually be drawn much wider, with a much narrower peak.
- These colossal estimates of prevalence have led to CKD being proposed as an important public health issue.
- CKD is more common in many ethnic minorities, e.g. in association with diabetes in South Asian and hypertension in black people. Additional genetic factors are also likely to play a role in the relative over-representation of certain ethnic groups in ESRD programmes.
- Many cases of early CKD are unrecognized.
- Many cases of advanced CKD are unknown to specialist renal services.

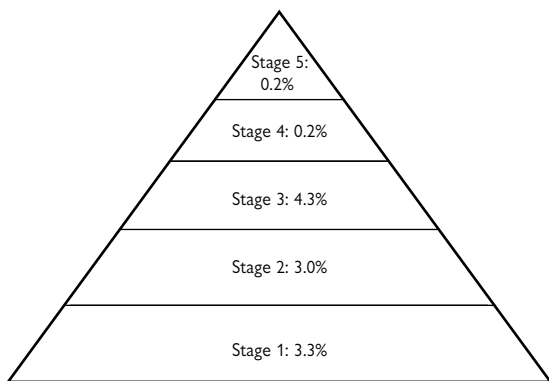


Fig. 3.1 The burden of chronic kidney disease. Data taken from NHANES study in US population.² ESRD represents just the tip of the iceberg—note the large numbers in stages 1–3, compared to 4 and 5. All stages have significantly increased CV risk.

Reference

2. Coresh J, Astor BC, Greene T, et al. (2003). Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Study. *American Journal of Kidney Diseases*, **41**, 1–12.

Criticisms of the KDOQI classification

Although the 2002 classification is now ubiquitous, it is not without its problems. Criticisms include the following:

- The classification sets out to identify risk yet labels as a disease.
- It defines disease on a laboratory variable alone, with no clinical assessment or correlation.
- Many patients will be caused unnecessary anxiety.
- Many live kidney donors have an eGFR <60mL/min post-nephrectomy. Do they have a disease?
- The MDRD eGFR equation was validated in subjects with renal disease and yet is being used to evaluate subjects without it.
- The equation is not sufficiently validated for differences in age, race, and body habitus.
- MDRD tends to underestimate true GFR (yet the values are generally unconditionally accepted).
- The vast estimates of CKD prevalence offered by the classification are unrealistic and should be viewed as distribution values for eGFR in a particular population, rather than true disease prevalence.
- The classification does not take account of the age-related change in GFR. Many view this as natural senescence, not pathology (~25% age >70 have an eGFR <60mL/min and ∴ kidney 'disease').
- The eGFR bands used to define stages are arbitrary:
 - Stage 3: a 25-year-old proteinuric ♂ whose renal function has rapidly deteriorated to an eGFR of 30–35mL/min.
 - Stage 3: a 75-year-old ♀ with no other evidence of kidney disease and a stable eGFR of 55–59mL/min.
 - Identical stage notwithstanding, the implications for these individuals are very, very different.
- Is it a useful CV risk assessment tool? Although there is an association between ↓ eGFR, proteinuria, and CV risk, a causal link is unproven. Also, this relationship mainly operates at eGFR <45mL/min.
- The classification implies progression from one stage to the next. In reality, this does not occur. Stage 3 seldom progresses to 4 or 5.
- It defines normal function as >90mL/min and disease as <60mL/min. Neither is particularly satisfactory nor evidence-based.
- It does not give enough weight to microalbuminuria or overt proteinuria, which may be better markers of CV risk (especially in early stages).
- Many laboratories do not report a value for eGFR when >60mL/min, removing any justification for separating stages 1 and 2.
- Large numbers have been diagnosed with early CKD—this has diverted specialist time away from kidney failure and its treatment.
- The term CKD should be reserved for persistent, irreversible renal pathology, not just reductions in eGFR—unless there are pathophysiological consequences, such as anaemia or altered salt and water homeostasis (often not present until eGFR <30mL/min).
- It has been suggested that percentile charts of eGFR in healthy individuals of both sexes, across all ages, and in different populations should be used to define an abnormal eGFR.

Diagnosis of CKD

► Always assume a ↓ eGFR represents acute kidney injury until proven otherwise. Is there a historical eGFR for comparison? Has there been a recent illness or change in medication? If uncertain, repeat within 5 days, and seek specialist help, as necessary.

Why is it important to identify patients with CKD?

- CKD is associated with ↑ CV risk. Modifying CV risk factors (► ↑ BP) would be expected to ↓ morbidity and mortality.
- Some patients will benefit from further investigation (e.g. renal biopsy) to identify a potentially treatable intrinsic renal disease (e.g. glomerulonephritis) or renal involvement in a systemic illness (e.g. myeloma).
- Whatever the underlying cause, it may be possible to slow or prevent progression to kidney failure.
- Complications (e.g. anaemia) can be identified and treated early.
- Those (relatively few) patients who will go on to kidney failure and potentially need dialysis or transplantation can be adequately prepared.
- Patients with CKD are at higher risk of acute kidney injury. This is often preventable (e.g. after IV contrast administration).

eGFR for diagnosis and management of CKD

- Serum creatinine (SCr) has a non-linear relationship with GFR. In early CKD, SCr may remain within the 'normal' range and be misleading.
- eGFR is calculated from formulae that adjust SCr for age, sex, and race.
- The most widely used (and foundation of the KDOQI classification) is the Modification of Diet in Renal Disease (MDRD) equation since it appeared the most reliable and reproducible in individual patients.
- More recently, the CKD Epidemiology Collaboration pooled study data to produce the CKD-EPI equation. This provides a more accurate assessment of GFR in individuals with normal or only slightly ↓ GFR. This results in lower estimates of CKD prevalence and more accurate prediction of adverse outcomes.
- Most laboratories will routinely report an MDRD eGFR, although the use of CKD-EPI is likely to increase. Formulae are available at: <http://www.renal.org/eGFRcalc> or <http://www.kidney.org/professionals/tools>. Several useful free Apps are also available, e.g. MedCalc, QxMD, MedMath, Epocrates (fee-requiring).
- Normal GFR is ~100mL/min/1.73m², so eGFR gives a (very) rough percentage of kidney function.

Cautions

- It is only an estimate (confidence intervals are wide; 90% of patients will have a GFR within 30% of their eGFR).
- eGFR is likely to be inaccurate at extremes of body habitus (malnourished, obese) as well as in amputees and during pregnancy.
- It is not fully validated in age <18.
- Race: only validated in Caucasians and black people though probably acceptable utility in South Asians (⚠ check whether your lab corrects for race, otherwise use a correction factor of × 1.21 for black patients).
- It is not validated if the GFR is rapidly changing (e.g. AKI).

- The MDRD equation tends to underestimate normal renal function. CKD-EPI is more reliable in this situation.
- It is less accurate in individuals with very poor kidney function.

Screening for CKD?

There is no evidence that screening of the general population for CKD saves lives or money. Screening can be targeted at those at highest risk.

Who

- ↑ BP.
- Diabetes mellitus.
- CCF.
- Atherosclerotic disease (coronary, cerebral, peripheral).
- Possible renal involvement in multisystem disease (e.g. SLE, myeloma).
- Urological problems: bladder outflow obstruction, neurogenic bladder or diversion surgery; renal stone disease.
- Chronic nephrotoxin use (e.g. NSAIDs, lithium, ciclosporin, ACE-I).
- Urologically unexplained haematuria.
- Unexplained oedema.

How

- eGFR, BP, urinalysis for blood ± protein, uACR, or uPCR (annually).

Proteinuria

Why is proteinuria so important?

- It is a marker of chronic kidney damage.
- It has prognostic value in the progression of CKD.
- It may itself cause progression of CKD (☹).
- It is a helpful surrogate treatment target.
- It is an independent CV risk factor.

Detection and quantification of proteinuria

- Dipstick: if ≥1+, send MSU to exclude UTI, and repeat after 2 weeks.
- All with an eGFR <60mL/min (and high-risk patients in stages 1 and 2) should have their urinary protein excretion quantified. (See Table 3.3.)
- 24h collection unnecessary. Send spot sample (preferably early morning).
- The relationship between uACR and uPCR is non-linear.

Table 3.3 Approximate equivalent values for proteinuria quantification

uACR (mg/mmol)	uPCR (mg/mmol)	Urinary protein excretion (g/24h)
30	50	0.5
70	100	1

- uACR is more sensitive for early disease and favoured in many guidelines, esp. as an initial test. uPCR is adequate for monitoring.
- uACR ≥2.5mg/mmol (♂) or ≥3.5mg/mmol (♀) represents microalbuminuria (still a marker of early renal disease and associated with an ↑ CV risk, particularly in diabetes and ↑ BP).

► Cardiovascular disease in CKD

CKD patients are at higher risk of CV events, including coronary disease, CCF, stroke, and peripheral vascular disease (see Table 3.4). Both ↓ eGFR and proteinuria (itself a marker of generalized endothelial dysfunction) are independently (and additively) associated with adverse CV outcomes. Even those with early CKD are at increased risk—most will die a CV death before progressing to kidney failure. (See Table 3.4.)

Table 3.4 Percentage of 5-year clinical outcomes in patients with CKD^a

Endpoint	Stage 2	Stage 3	Stage 4
Progression to RRT	1.1%	1.3%	19.9%
Death	19.5%	24.3%	45.7%

^a Keith DS, Nichols GA, Guillion CM, et al. (2004). Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med*, **164**, 659–63.

Take 100 patients with an eGFR <60mL/min. ~1% will progress to kidney failure each year. However, there is a 10% death rate (mainly CV disease), so, after 10 years, 8 patients will require RRT, 27 will have ‘smouldering’ CKD, and 65 will be dead!

- An estimated 8 million people in the USA have an eGFR <60mL/min. Those that survive to start RRT do so with a high CV disease burden.
- Dialysis patients are ~20× more likely to die a CV death than the general population.
- A cardiac cause is implicated in >40% of all deaths at ESRD.
 - ESRD 5-year survival (UK data): age 18–34 is >90%; age 45–54 is 70%; age 65–74 is 30%; age >75 is <20%.

Managing risk factors

- Good evidence for the benefit of many interventions in CKD patients is lacking—it is often inferred by extrapolation from the non-CKD population.
- Lifestyle advice:
 - Encourage exercise.
 - Offer smoking cessation help and advice.
 - Healthy diet; adequate nutrition.
 - Meticulous BP control (<130/80): use ACE-I and ARB to ↓ proteinuria.
- Management of lipids, usually with a statin:
 - Evidence of benefit for lipid-lowering therapy in CKD is limited.
 - For example, the *Die Deutsche Diabetes Dialyse* (4D) study showed no benefit from cholesterol reduction by atorvastatin in dialysis patients with T2DM. Explanation: competing CV risk may ‘drown out’ the benefit of statins in this very high-risk group.
 - Similarly, AURORA, a RCT of 2,776 HD patients comparing rosuvastatin vs placebo, showed no benefit of LDL reduction against a composite endpoint of CV death, non-fatal MI- and non-fatal stroke.

- However, SHARP, an RCT of 9,438 CKD (dialysis or CKD) with no history of MI or CV revascularization, compared simvastatin + ezetimibe against placebo, finding a 17% reduction in major vascular events after mean 4.7 years' follow-up.
- Recent guidelines, including those for non-CKD populations (e.g. those produced by the American Heart Association/American College of Cardiology), have moved away from traditional numeric targets for primary and secondary prevention towards the estimation of risk as the basis for treatment (usually a statin). This is also the case in KDIGO lipid management guidelines for CKD (2013). See [\[1\]](#) p. 205.
- Glycaemic control; HbA1c <7.0% (if diabetic—but see [\[1\]](#) p. 612).
- Aspirin 75mg daily for 2° prevention unless contraindicated.
- Appropriate CKD-MBD management (↓ vascular calcification).
- Appropriate anaemia management (↓ LVH).
- Adequate dialysis.
- No current evidence for homocysteine reduction using folic acid.
- Ongoing interest in antioxidant therapy (e.g. vitamin E and acetylcysteine) but no compelling evidence to date.

Cardiovascular risk factors

Traditional cardiovascular risk factors more common in CKD

- Hypertension (almost always present).
- Diabetes (common cause of CKD).
- Dyslipidaemia: CKD → ↓ HDL, ↑ IDL, ↑ pro-atherogenic lipid particles, and ↑ oxidation of LDL (all promote atherogenesis).
- Obesity and reduced physical activity.

Risk factors common in (or unique to) advanced CKD

- Arteriosclerosis.
- Diastolic dysfunction.
- Vascular calcification (and cardiac valvular calcification).
- Proteinuria.
- Volume overload.
- Anaemia ([\[1\]](#) p. 216).
- Higher Hb targets on ESA therapy ([\[1\]](#) p. 226).
- Oxidant stress:
 - ↑ Reactive oxygen species.
 - ↓ Antioxidants (e.g. vitamin E).
- Inflammation ([\[1\]](#) p. 261).
- Malnutrition ([\[1\]](#) p. 260).
- Vitamin D deficiency ([\[1\]](#) p. 251).
- Accumulation of advanced glycation end-products.
- LVH (a strong predictor of mortality in ESRD).
- Hyperparathyroidism.
- Myocardial fibrosis and abnormal myocyte function.
- Carnitine deficiency.
- Hyperhomocysteinaemia.
- Asymmetric dimethyl arginine (ADMA) retention.
- Reduced nitric oxide bioavailability.
- Insulin resistance.
- Renin–angiotensin system activation.

Pathogenesis of CKD

Progression of CKD

Once CKD is established, it tends to progress, regardless of the underlying cause. Decline in GFR tends to be linear over time, unless clinical circumstances change. Progression of CKD is more often due to 2° maladaptive haemodynamic and metabolic factors than underlying disease activity (see Fig. 3.2). A series of interacting processes eventually results in:

- Glomerulosclerosis (glomerular scarring and obsolescence).
- Proteinuria.
- Tubulointerstitial fibrosis.

Mechanisms

Raised intra-glomerular pressure

- As nephrons scar and 'drop out', remaining nephrons undergo compensatory adaptation, with ↑ blood flow per nephron and hyperfiltration attempting to 'normalize' GFR (the Brenner hypothesis).
- Changes in glomerular capillary wall permeability are a feature of glomerular diseases.
- Renal vasodilatation may be an initiating event, with the glomerulus exposed to a higher capillary pressure.

Glomerular damage

- ↑ intra-glomerular pressure → ↑ wall stress and endothelial injury.
- ↑ strain on mesangial cells → ↑ matrix deposition mediated (in part) by angiotensin II and cytokine release (TGF-β, PDGF).

Proteinuria may be due to an underlying glomerular lesion or result from raised intra-glomerular pressure. Protein or factors bound to filtered albumin (such as fatty acids, growth factors, or metabolic end-products) may lead to:

- Direct proximal tubular cell injury.
- Local cytokine synthesis (→ recruitment of interstitial inflammatory cells).
- Pro-fibrotic factors → interstitial scarring.
- Myofibroblast activation and tubular epithelial to mesenchymal transition (EMT) occur, further fuelling the fibrogenic process.

Tubulointerstitial scarring

- The degree of tubulointerstitial damage correlates better with long-term prognosis than glomerular damage.
- Proteinuria may itself be harmful to the tubulointerstitium, but chronic ischaemic damage is also important: tissue O₂ tension is relatively low in the renal medulla, making tubules sensitive to hypoxic injury. Chronic ischaemia ∴ occurs with:
 - Damage to glomerular capillaries (glomerulosclerosis → altered peritubular perfusion).
 - RAS activation → intrarenal vasoconstriction.
 - Intratubular capillary loss and ↑ diffusion distance between capillaries and tubular cells (→ a vicious cycle of hypoxic damage).

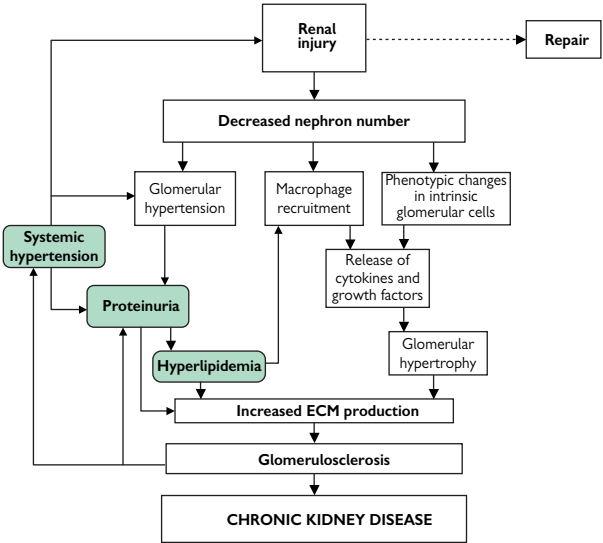


Fig. 3.2 Potential 'maladaptive' responses which contribute to progression in CKD. Reproduced from *Oxford Desk Reference: Nephrology*, Jonathan Barratt, Kevin Harris, and Peter Topham (2008), with permission of Oxford University Press.

Progression of CKD: general

Defining progression

Arbitrary, but progression may be defined as a decline in eGFR of $>5\text{mL}/\text{min}$ in 1 year or $>10\text{mL}/\text{min}$ in 5 years (in the absence of other causes of an acute deterioration).

Factors influencing CKD progression

Non-modifiable

- Underlying cause of kidney disease (tubulointerstitial disease tends to progress more slowly than glomerular disease).
- Race (progression faster in black patients).

Modifiable

- BP.
- Level of proteinuria.
- Plus:
 - Exposure to nephrotoxic agents.
 - Underlying disease activity (e.g. SLE, vasculitis).
 - Further renal insults (superimposed obstruction, UTI).
 - Hypovolaemia or intercurrent illness.
 - Dyslipidaemia.
 - Hyperphosphataemia.
 - Metabolic acidosis.
 - Anaemia.
 - Smoking.
 - Glycaemic control (if diabetic).

What can be done to prevent or slow progression?




Identify any potentially modifiable underlying cause

- Helps determine prognosis.
- Is specific intervention/treatment possible, e.g. immune suppression in immunologically mediated renal disease, relief of obstruction?
- History: systemic disease (e.g. SLE, myeloma), lower urinary tract symptoms, stone disease, review all medications.
- Examination: BP, hypovolaemia, atherosclerosis, palpable bladder, stigmata of inflammatory disease.
- Investigation: urinalysis (haematuria and/or proteinuria may suggest a renal or systemic disease that could benefit from specific intervention), USS renal tract, renal biopsy.

Influence mediators of progression

- There is considerable overlap in the measures employed to prevent progression and those used to modify CV risk (📖 p. 202).
- In addition, these often dovetail with a patient's existing treatments for CV disease, diabetes, or hypertension.
- This enables an integrated management programme to be developed that is easy for the patient (and physician) to understand and administer.

Preventing progression: blood pressure

- ↑ BP is almost universal in CKD and may be both cause or effect.
- ↑ BP → glomerular filtration pressure and ↑ proteinuria → ↑ renal injury.
- BP control unequivocally slows progression of CKD and is the main renoprotective strategy.
- A large body of evidence supports the use of ACE-I and ARBs as first-line antihypertensives in both diabetic and non-diabetic CKD, particularly if concomitant proteinuria. These agents:
 - ↓ efferent arteriolar tone → ↓ intra-glomerular pressure and ↓ proteinuria.
 - ↓ A2 activity → A2-induced inflammation → ↓ fibrosis and scarring.
 - ACE-Is affect both angiotensin type 1 (A1) and type 2 (A2) receptors but may not completely inhibit A2 formation.
 - ARBs block A1, but not A2, receptors.
- BP targets are more stringent in CKD (and lower still for patients with proteinuria). (See  p. 204.)
- The stringent application of current evidence would result in:
 - ACE-I for renoprotection in: (i) T1DM and microalbuminuria or overt diabetic nephropathy; (ii) T2DM with ↑ BP or microalbuminuria; (iii) non-diabetic CKD with proteinuria 0.5g/day.
 - ARBs for renoprotection in T2DM and microalbuminuria or overt nephropathy.
- Few studies have directly compared ACE-I and ARB treatment in CKD.
- Combination ACE-I and ARB therapy ('dual blockade') reduces BP and proteinuria to a greater extent than monotherapy but has not been shown to ↓ CKD progression (see also  p. 614).
- There is often reluctance to use ACE-I in more advanced CKD because of fears of ↑ K⁺ or a rapid fall in GFR. However, evidence suggests that the benefit of ACE-I therapy is present, regardless of the initial level of renal function.
-  There is evidence that dihydropyridine calcium channel blockers (e.g. nifedipine and amlodipine) may adversely effect the progression of CKD through effects on the renal microcirculation. They should ∴ be avoided as first-line treatment but are frequently used as part of combination therapy (particularly in patients taking beta blockers where non-dihydropyridine CCBs are best avoided).

Starting an ACE-I or ARB in CKD

- Clinical trials show a good safety profile, even in higher CKD stages.
- Ensure patient is well hydrated.
- Avoid NSAIDs:
 - If on diuretic therapy, consider reducing diuretic dose for 48h, and request first dose is taken at bedtime.
- Check eGFR and K⁺ before and 3–5 days after.
- Expect (and allow) a rise in SCr or ↓ eGFR of up to 20%, but recheck within 2–4 weeks.
- If K⁺ >5.5mmol/L, assess diet and other medications.
- Stop if K⁺ >6.0mmol/L.
- Measure K⁺ and eGFR during intercurrent illnesses.

Progression of CKD: antihypertensives in CKD

Antihypertensives in CKD: a suggested batting order

Expect to need ≥ 2 agents (warn the patient this is likely to be the case).

- First, limit Na^+ intake ($<100\text{mmol/day}$), and recommend other lifestyle measures (▢ p. 259).
- ACE-I (especially if $\text{uPCR} >100\text{mg/mmol}$ or $\text{uACR} >70\text{mg/mmol}$).
- Loop diuretic (e.g. furosemide) if evidence of salt and water overload.
 - Thiazide diuretics may be effective in early CKD.
- Add ARB if uPCR remains $>100\text{mg/mmol}$ or $\text{uACR} >70\text{mg/mmol}$.
- Calcium channel blocker:
 - If a beta blocker is likely to be necessary, then use dihydropyridine CCB (e.g. nifedipine, amlodipine); if not, then a non-dihydropyridine (e.g. diltiazem) is preferred.
- Beta blocker (e.g. atenolol, bisoprolol).
- Alpha blocker (e.g. doxazosin).
- Centrally acting agent (e.g. moxonidine).
- Vascular smooth muscle relaxant (e.g. minoxidil).

Blood pressure targets in CKD

KDIGO

- Recommend a BP target $<140/90\text{mmHg}$ for non-diabetic, nonproteinuric CKD patients.
- Target $<130/80\text{mmHg}$ if proteinuria ($>30\text{mg/24h}$) whether diabetic or not.
- Tailor treatment regimes for individual elderly patients by carefully considering age, co-morbidities and other therapies. Escalate treatment carefully under appropriate supervision.

UK Renal Association and NICE recommend:

- Without proteinuria ($\text{uPCR} <100\text{mg/mmol}$ or $\text{uACR} <70\text{mg/mmol}$):
 - Target $140/90\text{mmHg}$ (NICE suggest target range for SBP $120\text{--}139\text{mmHg}$ and DBP $<90\text{mmHg}$).
- With proteinuria ($\text{uPCR} >100\text{mg/mmol}$ or $\text{uACR} >70\text{mg/mmol}$):
 - Target $130/80\text{mmHg}$ (NICE suggest target range for SBP $120\text{--}129\text{mmHg}$ and DBP $<80\text{mmHg}$).
- Diabetes mellitus:
 - Target $130/80\text{mmHg}$.
- ↓ Reduction of proteinuria should also be seen as an important
 - Therapeutic goal (target $\text{uPCR} <50\text{mg/mmol}$ or $\text{uACR} <30\text{mg/mmol}$).

Others

Recent international guidelines for hypertension from nonnephrological bodies, such as ESH-ESC (and JNC 8 – in preparation), have, or are expected to, suggest that the evidence for lower treatment targets, such as $<130/80\text{mmHg}$, in the presence of comorbidities such as diabetes and CKD is not currently robust (see ▢ pp. 464–8).

For example ESH-ESC (2013) suggests all patients (apart from the elderly) should be treated to a SBP of $<140\text{mmHg}$.

Dyslipidaemia

- In addition to placing CKD patients at ↑ risk of CV disease (📖 p. 198), lipid abnormalities may also accelerate progression.
- Potential mechanisms: mesangial cell proliferation, cytokine expression, LDL oxidation to reactive O₂ species.
- Treatment has attenuated renal injury in animal models.
- Patchy evidence from clinical trials (⚠️ statins only—not fibrates).
- Recent guidelines, including those for non-CKD population (such as those produced by the American Heart Association/American College of Cardiology) have moved away from numeric targets for 1° and 2° prevention and towards the estimation of CV risk.
- The KDIGO lipid management guidelines for CKD (2013) suggest:
 - Adults aged ≥50 years with eGFR <60 mL/min (not on RRT) are treated with a statin (or statin/ezetimibe combination) (evidence graded 1A).
 - Adults aged ≥50 years with CKD and eGFR ≥60 mL/min are treated with a statin (graded 1B).
 - Adults aged 18–49 years with CKD (not on RRT) are statin treated if one or more of the following is present (graded 2A).
 - Known coronary disease (MI or revascularization).
 - Diabetes mellitus.
 - Prior stroke.
 - Estimated 10-yr incidence of coronary death or MI >10%.
 - Initiation of statin treatment is not recommended for adults on dialysis (2A).
 - Patients receiving statins (or statin/ezetimibe) at the time of dialysis initiation should continue treatment (2C).
 - Statin treatment is suggested for transplant recipients (2B).
- ⚠️ Statin side effects are more common in CKD. Myalgia and a small rise in creatine kinase common. ▶ More rhabdomyolysis reported. Liver function abnormalities also more common.

Hyperphosphataemia (📖 p. 246)

Calcium phosphate deposition in the renal interstitium may contribute to progression of CKD, strengthening the argument for good control of mineral homeostasis in these patients.

Anaemia

ESA treatment may ↓ progression. Robust evidence is lacking.

Acidosis

- Experimentally, acid in the nephron → complement activation and interstitial damage.
- A recent RCT has shown that administration of oral sodium bicarbonate significantly slows CKD progression vs placebo.³
 - 134 patients, CrCl 15–30 mL/min, baseline bicarbonate 16–20 mmol/L
 - Dose: 600 mg tds, increased to achieve a bicarbonate of 23 mmol/L (500 mg capsules are also widely available).
 - 2-year follow-up (exclusions: CCF, uncontrolled ↑ BP).

Drugs, toxins, and infections

Once CKD is established, remaining kidney function is highly susceptible to further (often irreversible) damage. ► Avoid:

- Hypovolaemia, obstruction, recurrent UTIs.
- Nephrotoxins: drugs (e.g. NSAIDs), radiocontrast.

Smoking

Smoking → ↑ proteinuria and CKD progression in both diabetic and non-diabetic CKD, adding to the already overwhelming benefits of smoking cessation. Patients should be offered practical help and support to quit.

Diabetes

Poor glycaemic control is a major determinant of the progression of diabetic nephropathy. The evidence is stronger for T1DM.


- T1DM: in the DCCT trial, intensive treatment was associated with less microalbuminuria and ↓ progression to macroalbuminuria. In addition, the EDIC/DCCT follow-up study cohort has suggested lowering HbA1c preserves GFR in the long term.
- T2DM: in the UKPDS study, intensive treatment led to a ↓ incidence of microalbuminuria, and other studies have shown reduced progression to macroalbuminuria. UKPDS also demonstrated a reduced decline in GFR.
- However the ADVANCE and ACCORD studies suggested that intensive treatment of hyperglycemia in T2DM does not always lead to an acceptable risk/benefit ratio. These studies involved large populations and used aggressive tactics for glycaemic control. Participants had strong CV risk profiles (including prior events) and were at high risk of future events. Microvascular end points, including renal outcomes, were improved in both studies. However, primary CV outcomes were not improved by intensive glycaemic therapy and, in ACCORD, intensive treatment was associated with a 22% increase in all-cause mortality; i.e. intensive glucose lowering in high-risk populations, later in the course of T2DM, delivered only a weakly protective effect on CV outcomes.
- KDOQI practice guidelines recommend maintaining HbA1c at <7%. However, some authorities suggest a target between 7–8% in higher risk patients later in the course of their disease.

Reference


3. de Brito-Ashurst I, Varaganam M, Raftery MJ, Yaqoob MM (2008). Bicarbonate supplementation slows progression of CKD and improves nutritional status. *Journal of the American Society of Nephrology*, **20**, 1869–70.

Progression of CKD: miscellaneous

Vitamin D

- Vitamin D has many important paracrine functions, with roles in immunity, inflammation, vascular and cardiac function, and insulin resistance.
- In the kidney, it influences mesangial cell and podocyte proliferation, downregulates RAS (via renin inhibition), prevents glomerular hypertrophy, decreases cytokine production, reduces inflammation, and blocks epithelial to mesenchymal transition.
- There is experimental (and limited clinical) evidence that it may ameliorate proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis.
- Optimum replacement strategies, however, remain unclear (see  p. 250).

Dietary protein restriction

- ↓ Protein intake in animal models protects against glomerulosclerosis.
- Appears to ↓ intra-glomerular pressure and ↓ glomerular hypertrophy.
- Non-haemodynamic effects, such as ↓ TGF- β and ↓ matrix accumulation, may also be important.
- In humans, the benefit of protein restriction is controversial.
- Although progression may be slowed, a huge investment is required by both patients and dietetic staff. Long-term compliance is often poor.
- At present, optimal dietary protein intake in CKD is uncertain.
-  A reasonable regimen is an intake of ~0.8–1.0g/kg of protein/day. Lower levels may risk malnutrition (particularly in advanced CKD or with nephrotic range proteinuria).
- Diabetic nephropathy may be more responsive.

Preventing progression—what's on the horizon?

- *Endothelin receptor blockade* → ↓ BP, ↓ renal vasoconstriction, ↓ proteinuria, and ↓ tissue damage in experimental diabetic nephropathy.
- *Vasopeptide inhibitors* → ↓ vasoconstrictors (A2) + ↑ vasodilators (natriuretic peptides and bradykinin).
- *Renin inhibitors*. Available as antihypertensives. Theoretical benefit would be through aggressive RAS blockade. However, the ALTITUDE study, designed to determine if a renin inhibitor could reduce CV and renal morbidity and mortality in T2DM when added to conventional treatment (including ACE-I or ARB), was stopped early after more frequent adverse events were reported in the treatment arm.
- Mineralocorticoid receptor activation → interstitial fibrosis + vascular damage. Antagonism (*eplerenone/spironolactone*) may \therefore be beneficial.
- *Sulodexide*, an orally active glycosaminoglycan, reduces proteinuria and is under evaluation in clinical trials.
- *Pirfenidone* and *hepatocyte growth factor* are antifibrotic and show experimental promise.
- *BMP-7* antagonizes TGF- β and inhibits the pro-fibrotic epithelial to mesenchymal cell transition.

- The anti-inflammatory, antioxidant, and possibly antifibrotic molecule *bardoxolone methyl* was associated with an early improvement in eGFR in advanced diabetic nephropathy. Unfortunately, the subsequent international BEACON trial was terminated, following the reporting of excess of adverse events in the treatment arm.

The cardiorenal syndrome (CRS)

- A newly described syndrome of interdependency. Each dysfunctional organ can initiate and maintain disease in the other through common haemodynamic, neurohormonal, and immunological pathways.
- Five subtypes have been suggested, describing the scenarios in which CRS can occur (and defining the 1° and 2° organ in each case) (see Table 3.5).
- Significant controversy and debate around this topic remains.
- Cardiac + renal failure = magnification of poor outcomes:
 - Renal failure is as powerful a prognostic marker in CCF as ejection fraction (EF) or NYHA status.
 - ↑ SCr on admission with CCF predicts longer hospital stay, ↑ risk of ITU admission, and ↑ mortality.
 - In parallel, patients with CKD are much more likely to manifest CV disease than the non-CKD population (📖 p. 198).

Pathophysiology

- The traditional view that ↓ GFR in CCF is simply a consequence of impaired renal blood flow (RBF) 2° to impaired LV function is correct, in part, although a gross oversimplification.
- ↓ RBF → RAS stimulation → Na⁺ and water retention.
- A2 → ↑ cardiac pre- and afterload and ↑ myocardial O₂ demand.
- A2 also promotes NADH and NADPH oxidase activation → oxidative stress, ↓ NO (→ endothelial dysfunction), vascular inflammation, and fibrosis (both cardiac and renal).
- Chronic sympathetic nervous system (SNS) activation → ↓ adrenoceptor sensitivity, ↑ LVH, and ↑ myocyte apoptosis.
- Elevated venous pressures → intra-abdominal hypertension → further ↓ renal perfusion.
- Anaemia is common and integral to a progressive vicious cycle of organ dysfunction. EPO itself may exert anti-apoptotic effects (📖 p. 219).

Management

- A heterogeneous group, often excluded from major trials.
- Diuretics and ACE-I are key components of management but may further ↓ GFR. Physician anxiety means they are often not prescribed—further influencing outcomes. Close monitoring is essential.
- The role of IV iron and ESAs remains contentious (📖 p. 226).
- Future: inotropes, ultrafiltration for diuretic resistance, AVP antagonists, adenosine A₁ antagonists, and BNP analogues have variably been shown to improve symptoms, if not overall outcomes.

Table 3.5 Subtypes of CRS

Name	Description
1. Acute cardiorenal	Acute cardiac dysfunction → AKI
2. Chronic cardiorenal	CCF → ↓ GFR (very common)
3. Acute renocardiac	AKI → acute cardiac dysfunction (e.g. fluid overload)
4. Chronic renocardiac	CKD → cardiac dysfunction (e.g. LVH and diastolic dysfunction)
5. Secondary	CRS 2° systemic condition, e.g. septic shock

Advanced CKD: the uraemic syndrome

Uraemia is the metabolic and clinical syndrome caused by a substantial fall in GFR—it is *not* a result of \uparrow blood urea concentration, but rather of failure to eliminate many potentially toxic small and middle molecules. This leads to chronic inflammation and oxidative stress, with accumulation of metabolic end-products, accelerated atherogenesis, disruption of the immune system, and anaemia. The retained compounds or toxins have multiple effects:

- Many remain unidentified.
- They are divided into ‘low’ and ‘middle’ molecular weight molecules by size (<500Da = low; >500Da = middle).
- Ur and SCr are routinely measured but are not directly toxic. They act as markers for other LMW substances, including guanidines, such as asymmetric dimethyl arginine (ADMA)—a potent inhibitor of NO synthase.
- Retained middle molecules include:
 - β 2 microglobulin (12,000Da)—a component of MHC (the cause of dialysis-related amyloid).
 - Advanced glycation end-products (AGEs)—products of non-enzymatic breakdown of sugars. Also retained in normal ageing and diabetes. Linked to atherogenesis and susceptibility to infection.
 - Complement factor D—may activate the complement system and contribute to chronic inflammation.
 - Cytokines—may maintain uraemic chronic inflammation and malnutrition (although a short half-life suggests overproduction is more important).
 - Many, many others.
- \uparrow oxidant stress \rightarrow \uparrow oxidation products with \downarrow antioxidant levels (in part due to impaired polyamine balance).
- Phosphate is retained, contributing to hyperparathyroidism, arteriosclerosis, and vascular calcification (\rightarrow \downarrow arterial compliance, wide pulse pressure, and diastolic dysfunction) (📖 p. 242).

Uraemic cardiomyopathy

Not the result of one specific uraemic toxin but of a combination of factors:

- \uparrow Arterial stiffness. \uparrow phosphate \rightarrow vascular smooth muscle cell transdifferentiation into osteoblast-like cells, causing vascular medial calcification. This leads to arteriosclerosis, \downarrow arterial compliance, and \uparrow pulse pressure. This is analogous to the arterial changes seen in the elderly but premature. The result is \uparrow cardiac workload and worsening LVH and diastolic dysfunction.
- Cardiac fibrosis. Local and systemic angiotensin II and PTH \rightarrow \uparrow cardiac stiffness, myocyte injury, and diastolic and systolic dysfunction.
- Anaemia. \rightarrow \uparrow LVH and \uparrow cardiac work.
- Myocyte dysfunction. Myocyte contractility is reduced, possibly as a result of changes in intracellular bioenergetics.

The uraemic syndrome

Water, electrolyte, and acid–base balance

- Breathlessness 2° to volume overload, and Kussmaul breathing 2° to acidosis.
- Postural hypotension caused by volume depletion.
- Effects of ↑ or ↓ K⁺.

Haematological system

- Symptomatic anaemia and bleeding tendency.

Cardiorespiratory

- Cardiac failure associated with fluid overload, ↑ BP, anaemia, and impaired LV function.
- Accelerated atherosclerosis (angina, stroke, PVD) and vascular calcification.
- Pleuropericarditis.
- Cardiac arrhythmias 2° electrolyte disturbances.

Musculoskeletal

- Weakness, bone pain, and deformity 2° to osteodystrophy.
- Gout.

Nervous system

- Hypertensive stroke and encephalopathy.
- Anxiety, depression, and other psychological disturbances.
- Impaired cognitive function.
- Peripheral and autonomic neuropathy.
- Involuntary movements (including restless legs).
- Decreased conscious level and seizures (late).

Gastrointestinal

- Nausea, anorexia, and malnutrition.
- GI bleeding (peptic ulceration and angiodysplasia).
- Fetor, constipation, and diarrhoea.

Skin

- Dry skin, nail changes, and pruritus.
- Bullous eruptions.
- Pallor, pigmentation, and uraemic frost (late).

Eyes

- Conjunctival calcium deposits and retinal vascular disease.

Immunity

- Impaired cellular and humoral immunity (→ infection and malignancy).

Endocrine

- Aberrant vitamin D and PTH metabolism.
- Impaired IGF-1 production (growth retardation in children).
- Hyperprolactinaemia (gynaecomastia).
- Multiple other subclinical abnormalities.

Sexual function

- Sexual dysfunction.
- Decreased fertility.

Complications of advanced CKD

Fluid overload

Salt and water overload is usual in advanced CKD. However, as tubulointerstitial scarring progresses, loss of concentrating ability may → fixed (and often large) urine volumes and a relative salt-losing state. Such patients may be chronically *hypo-*, rather than *hypervolaemic*, and require salt and water supplementation (e.g. NaHCO_3 0.5–1.5g PO tds and increased fluid intake).

Treating salt and water retention in CKD

- ▶ Careful clinical assessment of volume status.
 - Restrict dietary salt (📖 p. 259).
 - Restrict fluid intake.
 - Start furosemide 40mg PO od, and titrate as necessary (max. 250mg daily).
 - Loop diuretics do not have a particularly smooth dose-response curve—a diuresis/natriuresis will not occur until a threshold is reached. This means a patient not responding to 40mg furosemide should have the dose, rather than frequency dosing, increased, i.e. ↑ to 80mg once daily, rather than 40mg twice daily.
 - If poor response, consider thiazide diuretic (metolazone 2.5–10mg od) for synergistic effect. ⚠ Diuresis may be brisk. Beware ↓ Na^+ , ↓ K^+ , and volume depletion (consider admission).
 - Monitor:
 - Daily weight—the best day-to-day guide of salt and water status. Ask the patient to keep a diary of their weight at home. Weight loss should generally be ≤0.5–1kg/day.
 - BP (esp. postural ↓ BP if overdiuresed).
 - A rise in $\text{Ur} \pm \text{SCr}$ may restrict dose escalation. If $\text{Ur} > 25\text{mmol/L}$, consider dose reduction (or cessation), depending on clinical need.
 - ⚠ Refractory volume overload may signal the need for renal replacement therapy.

Hyperkalaemia

↓ Na^+ delivery to the distal convoluted tubule → ↓ aldosterone-mediated Na^+/K^+ exchange and ↓ K^+ excretion. ▶ ↑ K^+ is a common, and potentially life-threatening, problem in advanced CKD. Rapid rises in K^+ are generally more dangerous than gradual ones, as cell membrane stability is more vulnerable to acute changes. The widespread use of ACE-I, ARBs, and, more recently, mineralocorticoid antagonists, such as spironolactone, is changing the natural history of CKD-related hyperkalaemia. It is increasingly common, with awareness more important than ever.

When to worry about the K^+ level...?

Depends on context and chronicity.

- 5.5–6.0mmol/L: recheck routinely. Review medications. Arrange dietary advice.
- 6.1–6.5mmol/L: recheck urgently. Review medications (withhold ACE-I, ARB, spironolactone). Arrange dietary advice.
- >6.5mmol/L: ► consider admission. Treat as an emergency.

Measures to prevent $\uparrow K^+$

- Dietary restriction (📖 p. 259).
- Diuretics: a loop diuretic (e.g. furosemide 40–160mg PO od) may promote urinary K^+ loss (thiazides may be less effective).
- Drug withdrawal or dose reduction if taking an ACE-I or ARB. Review other contributory drugs (e.g. spironolactone, beta blockers, NSAIDs).
- Correct acidosis (see Box 3.1).
- ⚠ Refractory $\uparrow K^+$ may indicate the need for dialysis.

Acidosis (📖 p. 820–823)

Systemic effects of acidosis

- *Bone.* \uparrow bone resorption and impaired mineralization, contributing to renal osteodystrophy (📖 p. 234).
- *Metabolism.* Muscle weakness, fatigue, sense of ill-health.
- *Effects of respiratory compensation* (📖 p. 820). Overventilation; may \rightarrow symptoms of dyspnoea \pm exhaustion.
- *Hyperkalaemia.* Aldosterone-mediated exchange of H^+ for K^+ is enhanced in the collecting duct $\rightarrow \uparrow K^+$. Acidosis also lessens K^+ ingress via cell membrane Na^+/K^+ pumps.
- *Ionized calcium.* \uparrow ionized (free) calcium (acidosis $\rightarrow \downarrow$ albumin-bound fraction). ⚠ Correction of acidosis may $\rightarrow \downarrow Ca^{2+}$ and provoke tetany.
- *Nutrition.* Acidosis promotes catabolism by induction of proteolysis and resistance to growth hormone (\rightarrow malnutrition).

Box 3.1 How to correct acidosis?

- Treat when venous HCO_3^- is <21 mmol/L.
- Give $NaHCO_3$ 0.5–1.5g/tds as capsules, or 0.6–1.8g tds as tablets (start at low dose, and titrate).
- ⚠ Na^+ load may cause or worsen fluid overload. Consider concomitant loop diuretic.
- ⚠ Refractory acidosis is an indication for dialysis.

Anaemia and CKD

Key facts

- Common; prevalence and severity increase as GFR falls (see Table 3.6).
- Typically normochromic, normocytic, with normal WCC and platelets.
- Associated with reduced quality of life and poorer prognosis.
- Erythropoietin (EPO) deficiency is the dominant, but by no means the only, cause (see Box 3.2).
- The introduction of human recombinant erythropoietin (hrEPO or epoetin) ~20 years ago completely transformed management. Prior to this, recurrent transfusion was the norm (→ iron overload, risk of blood-borne viruses, and sensitization to foreign antigens—with implications for transplantation).
- Newer therapeutic agents still aim to stimulate red cell production via the EPO receptor but may not be based on recombinant EPO. The term erythropoiesis-stimulating agent (ESA) has been introduced to reflect this.
- Increasing numbers of early CKD patients—and virtually all dialysis patients—receive an ESA.
- Black and diabetic patients tend to have higher rates of anaemia for each CKD stage.
- The target range for Hb is lower than the normal physiological range, e.g. 10–12g/dL (UK Renal Association).
- 🔄 Randomized trials have found ↑ CV complication rate with higher Hb targets—so optimal treatment strategies remain uncertain (📖 p. 226).
- Patients receiving ESAs invariably need concomitant iron therapy—and iron alone may be sufficient to correct anaemia in some (📖 p. 230).
- CKD patients require different targets for iron parameters from non-CKD individuals to facilitate optimal red cell production (📖 p. 230).
- The success of ESAs in CKD has led to their use to treat anaemia in other contexts, particularly chemotherapy-associated anaemia (🔄 ESAs have been associated with ↑ thromboembolic events and ↓ survival in cancer patients and could theoretically stimulate tumour growth).
- The cost of anaemia management is substantial.

Table 3.6 Prevalence of anaemia from NHANES III (📖 p. 228)

CKD stage	Median Hb in men (g/dL)	Median Hb in women (g/dL)	Prevalence of anaemia ^a
2	14.9	13.5	1%
3	13.8	12.2	9%
4	12.0	10.3	33%

^a Hb <12g/dL in ♂; <11g/dL in ♀.

Reprinted from *American Journal of Kidney Diseases*, 41, Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey, 1–12, Copyright (2003), with permission from Elsevier.

Box 3.2 Differential diagnosis of anaemia in CKD patients

► EPO deficiency is not the only cause of ↓ Hb in CKD.

Think of the following before commencing ESA therapy and particularly if disproportionate anaemia or ESA resistance (📖 p. 223):

- Blood loss:
 - Peptic ulcer disease, GI vascular ectasia.
- ↓ red cell survival:
 - Inflammation + oxidative stress + uraemic toxins → RBC membrane and cytoskeletal damage.
 - Haemolysis
- Related to dialysis:
 - Blood loss during treatment ('lost lines').
 - Haemolysis: contaminated dialysate, hypo-osmolar or overheated dialysate, residual sterilizing agents, trauma in blood pump, high flow through narrow gauge needles.
- Haematinic deficiency:
 - Iron deficiency.
 - B12 or folate deficiency.
- Impaired bone marrow response:
 - Chronic infection or inflammation.
 - Uraemic toxins (? underdialysis).
 - Hyperparathyroidism (→ marrow fibrosis).
 - Carnitine deficiency.
 - Aluminium overload; now rare (📖 p. 247).
- Malnutrition.
- Relating to underlying or unrelated disease:
 - Myeloma.
 - Myelodysplasia.
 - Sickle cell disease or other haemoglobinopathy.
 - SLE.
 - Autoimmune haemolysis.
 - Coeliac disease.
 - Occult malignancy.
 - Hypothyroidism.
- Relating to treatment:
 - Poor compliance with ESA therapy or incorrect dosing.
 - Immune suppression.
 - ACE-I (several mechanisms, including: ↓ endogenous EPO production and ↓ angiotensin II stimulation of erythroid precursors). Rarely mandates cessation of treatment.
 - Pure red cell aplasia (PRCA) (📖 p. 225).

EPO and the kidney

- RBC production is tightly regulated by a number of growth factors, including EPO—a 165 amino acid-secreted glycoprotein (with four complex carbohydrate side chains) that is required for terminal erythrocyte maturation.
- EPO differs importantly from other hematopoietic growth factors because it is produced in the kidney—specifically by the peritubular interstitial fibroblasts in the outer medulla and deep cortex.
- Hepatic EPO production is also important in fetal, but not adult, life.
- The kidney is ideally placed to regulate RBC production, as it is uniquely able to sense and control both O_2 tension and circulating volume (and to differentiate between the two):
 - Control of red cell mass is mediated by EPO.
 - Circulating volume is regulated by renal salt and water excretion.
- CKD and renal scarring \rightarrow \downarrow functioning renal tissue \rightarrow \downarrow EPO synthesis \rightarrow \downarrow RBC production \rightarrow anaemia.
- Exceptions (where EPO may be overproduced) are: APKD, benign renal cysts, renal cell carcinoma, and chronic hypoxia.

EPO production

(See Fig. 3.3)

- If GFR is normal, plasma EPO levels are inversely proportional to Hb concentration. This relationship breaks down in CKD (where EPO levels are usually inappropriately in the normal range).
- Anaemia or \downarrow environmental O_2 \rightarrow \downarrow blood O_2 content \rightarrow O_2 -dependent gene expression \rightarrow \uparrow EPO secretion.
- Central to this are the hypoxia inducible transcription factors HIF-1 and HIF-2.
- HIF-1 and 2 have an O_2 -regulated α subunit and constitutively expressed β subunit.
- In states of normal O_2 tension, intracellular HIF-1 and 2 are continuously inactivated by (iron-dependent) proline hydroxylation of their α subunit.
- Once hydroxylated, they are targeted by the von Hippel–Lindau protein (pVHL) for ubiquitination and proteasomal degradation.
- In hypoxic conditions, α subunit hydroxylation and degradation do not occur, and HIF α remains free to enter the nucleus and form a heterodimer with HIF β .
- The HIF α + HIF β heterodimer binds the hypoxia response element (HRE) and initiates EPO transcription.
- Several mechanisms exist to regulate EPO production, including the GATA family of transcription factors hepatocyte nuclear factor 4 (HNF-4) and haematopoietic cell phosphatase (HCP-1). All are potential therapeutic targets (📖 p. 221).
- During hypoxia, HIF activity is induced in multiple cell types where it activates a panoply of target genes (>100), including those involved in angiogenesis and glycolysis. Genetic mutations in the HIF pathway are responsible for certain congenital polycythaemias.
- Activation of the EPO receptor (EPO-R) prevents erythroid cell apoptosis through downstream JAK2/STAT5 signalling pathways.

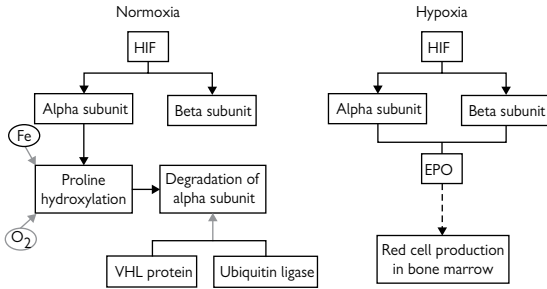


Fig. 3.3 Regulation of EPO production.

EPO beyond anaemia: cytoprotection

- In addition to the role of EPO in the regulation of erythropoiesis, there is increasing interest in its potential anti-apoptotic and cytoprotective effect.
- The EPO-R is widely distributed (e.g. neurons, cardiac myocytes, endothelial cells, hepatocytes, and mesangial cells), and expression is increased in response to hypoxic injury.
- It is hoped this might be therapeutically exploited and that exogenous ESA administration might offer protection from injury in various clinical scenarios.
- This concept has been successfully explored in numerous animal models of tissue injury, particularly ischaemia reperfusion (including nervous system, cardiac, and renal).
- There are currently a number of trials in progress in a variety of clinical settings, including traumatic brain injury, subarachnoid haemorrhage, myocardial infarction, cardiopulmonary bypass, renal transplantation, sepsis, and many others.
- However, a recent randomized, placebo-controlled trial of an IV ESA in early acute ischaemic stroke reported more deaths in the group receiving the ESA.
- Short-acting ESAs with retained cytoprotective, but reduced erythropoietic, effects are under development.

Erythropoiesis-stimulating agents (ESAs)

At present, no evidence distinguishes ESAs in terms of clinical efficacy. All have similar issues around cost, complexity of manufacture, routes of administration, storage requirements and potential immunogenicity. See Table 3.7 for dosing information.

Short-acting

Epoetin α and β . EPO- α (Eprex[®], Epogen[®], or Procrit[®]) and EPO- β (NeoRecormon[®]) have been in use for ~20 years and are clinically indistinguishable. Both are synthesized in transformed Chinese hamster ovary cells and have identical amino acid sequences (if different glycosylation patterns). Other recombinant epoetins have emerged, sharing the 165-amino acid structure, e.g. epoetins omega and delta.

Biosimilar agents. The term biosimilar is used to describe a generic product that is deliberately similar to molecules already in clinical use. Manufacturers submit data suggesting their agent is chemically and pharmacokinetically identical to a reference drug (usually EPO- α or - β). Clinical data generated with the original is then extrapolated to the new product. The reduced R&D and marketing costs ensure products are commercially competitive, e.g. epoetin-zeta (Retacrit[®]).

Long-acting

Darbepoetin α (Aranesp[®]). Recombinant EPO with a twist: five amino acids are substituted away from the EPO-R binding site to allow the insertion of two carbohydrate side chains. This significantly increases circulating half-life.

Table 3.7 ESA dosing

Generic name	Trade name	Half-life	Initial dosing	Example starting dose
Epoetin α	Eprex [®] , Epogen [®] , Procrit [®]	4–8h	80–120IU/kg in 3 divided doses ^a	2,000IU 3 \times week
Epoetin β	NeoRecormon [®]	4–12h	80–120IU/kg in 3 divided doses ^a	2,000IU 3 \times week
Darbepoetin α	Aranesp [®]	21–25h	0.45 micrograms/kg 1 \times week ^b	30 micrograms 1 \times week
Methoxy polyethylene glycol epoetin β	Mircera [®]	130h	0.6 micrograms/kg fortnightly, then monthly (usually at twice the fortnightly dose)	50 micrograms fortnightly

^a Increase by 25% for IV dosing.

^b 1 microgram is equivalent to 200IU of epoetin α or β , though there is considerable variability. No dose adjustment SC to IV for darbepoetin.

Continuous EPO receptor activator (CERA). Methoxy polyethylene glycol epoetin β (Mircera[®]) incorporates a large polymer chain to increase its MW to 760kDa (EPO: 30.4kDa). Half-life is increased (considerably) to 130h, and it can rapidly dissociate from the EPO-R after binding.

ESAs: future developments

Alternative methods of ESA administration: aerosol, mucosal, transdermal, and oral are currently drawing much attention.

New ESAs

- EPO fusion proteins:
 - Contain additional C-terminal peptides to \uparrow half-life.
 - EPO-EPO: two EPO molecules joined via a polypeptide bridge.
 - GM-CSF-EPO: provides two haematopoietic growth factors at once.
 - Fc-EPO: incorporates the Fc region of human IgG to promote cellular recycling and \uparrow half-life.
 - CTNO 528 is an EPO-mimetic antibody fusion protein, with no structural similarity to EPO but erythropoietic effects.
- Synthetic erythropoiesis protein (SEP):
 - 51kDa protein-polymer construct that activates the EPO-R. Long half-life.
- Peptide-based ESAs:
 - Unrelated in sequence to EPO but able to bind the EPO-R and induce intracellular signalling.
 - Peginesatide (formerly hematide) is a pegylated dimeric peptide ESA currently in phase III clinical trials. It has been successfully used to treat patients with PRCA (📖 p. 225).
 - Manufactured by a relatively simple process, less immunogenic, and stable at room temperature.
 - Administered IV/SC $\times 1$ /month.
 - Currently awaiting FDA approval.
- Non-peptide ESAs:
 - Offer potential for oral administration.
- Prolyl hydroxylase inhibitors (HIF stabilizers).
 - Prevent the hydroxylation and inactivation of HIF α (📖 p. 218).
 - Problem: many other genes are regulated by prolyl hydroxylation.
 - HIF stabilizer FG-4592 currently in clinical trials.
- GATA inhibition:
 - GATA are a family of transcription factors. GATA-2 is a negative regulator of EPO gene expression, so its inhibition is of interest.
- Haemopoietic cell phosphatase (HCP) inhibitors:
 - HCP is a tyrosine phosphatase that dephosphorylates JAK-2 and functions as a negative regulator of intracellular EPO signalling.
- Gene therapy:
 - Various delivery systems, such as adenovirus transfection, are under investigation. EPO could be released into the circulation at any site and by any cell type. Regulation of expression is likely to be the greatest obstacle to this approach.

Prescribing ESAs

When to start?

Consider an ESA when Hb <11g/dL (local protocols may vary).

◆ There is uncertainty as to the optimum time to commence ESA therapy. Does a numerical Hb threshold decide the best time, or would an earlier start prevent CV complications? ESAs have previously been thought of as safe and effective—but recent evidence suggests you *can* have too much of a good thing (📖 p. 226). UK Renal Association guidelines ∴ recommend that treatment should be reserved for patients who are likely to benefit from improved quality of life or physical function and to avoid transfusions. They remain relatively underprescribed in CKD (only 1/3 of patients starting dialysis are receiving an ESA). Economic considerations will inevitably apply.

Preparation for ESA therapy

- ► Have other causes of anaemia been considered (📖 p. 217), especially iron deficiency?
- Is the patient likely to respond? Cytokine release associated with infection (or chronic inflammation) impairs ESA response. Identify and treat these first. ↑ CRP usually predicts poor response.
- Is BP controlled? ESAs tend to ↑ BP. Severe ↑ BP was not uncommon in the early days of ESA use (mechanism: vasoconstriction and enhanced adrenergic responsiveness) but has ↓ in incidence with the refinement of treatment algorithms (which generally aim for a slower rise in Hb).

Investigations

- FBC with red cell indices.
- Determine iron status:
 - Serum ferritin; recommended range 200–500 micrograms/L.
 - Serum iron and total iron-binding capacity (TIBC).
 - Transferrin saturation (TSAT); recommended range 20–40%.
 - % hypochromic RBCs (% HRBC); recommended target <6%.
- CRP.
- Serum B12 and folate.
- Consider faecal occult blood testing.
- ► Measurement of EPO levels is expensive, misleading, and unnecessary.

Choice of ESA

There is no evidence to distinguish between ESAs on the basis of clinical efficacy. Choice will depend on local protocols, availability, and patient/physician preference.

Route of administration

- Either SC or IV (IV often used in haemodialysis patients—given at the end of a dialysis treatment to reduce dialyser absorption). This can also assist compliance.

- Pre-dialysis CKD and peritoneal dialysis patients can be taught to self-administer an ESA at home, using a range of user-friendly devices.
- There is a dose adjustment between SC and IV administration for some ESAs (📖 p. 220), but there is much interpatient variability.
- Rare reports of pure red cell aplasia (PRCA) in patients treated with SC epoetin α have been resolved.

Starting ESAs

- ► Ensure iron-replete; iron stores may rapidly deplete once an ESA is commenced so will require monitoring.
- See Table 3.7 (📖 p. 220) for typical starting doses.
- The initial dose can be \uparrow if there is clinical urgency and/or ESA resistance is likely.
 - Measure Hb and BP 2–4-weekly at first (and after a dose change).
 - If deterioration in BP, intensify antihypertensive medications (it is rarely necessary to withhold ESA).
 - Aim for \uparrow Hb of 1–2g/dL/month until target achieved.
 - \uparrow dose monthly (~25% increments) if slow Hb rise.
 - \downarrow dose by 25–50% if Hb rises >2 g/dL in a month.
 - Changing dose intervals can be a convenient way of dose increases/reductions—avoiding the need to dispense a substitute dose and waste existing supplies.
 - Once in ‘steady state’, monitor Hb 1–2-monthly in pre-dialysis patients and monthly in dialysis patients.
 - An intercurrent illness may reduce Hb. There is no consensus on the best approach, but consider temporary \uparrow dose.

ESA resistance or hyporesponsiveness

- True ESA resistance is variously defined as:
 - Failure to reach target Hb, or
 - The need to administer above a threshold ESA dose (e.g. ≥ 300 IU/kg/wk of epoetin α or β) or 1.5 micrograms/kg/wk of darbepoetin α to maintain target Hb.
- Relative resistance is common.
- Run through, and proactively exclude, the alternative causes of CKD-associated anaemia (see 📖 p. 217).
- ► Always exclude iron deficiency.
- If iron stores prove refractory to iron administration, check for faecal occult blood, and consider further GI investigation.
- Assess compliance.
- Check reticulocyte count in non-responders.
 - High: suggests an appropriate marrow response (i.e. there is probably bleeding or compromised RBC survival).
 - Low: RBC production problem (e.g. inflammation) or poor compliance.
- If haemolysis suspected, check LDH, haptoglobins, direct Coombs’ test.

ESAs: additional benefits

Non-haematological effects of ESAs


- Enhanced quality of life scores.
- Improved exercise capacity.
- Reduced fatigue.
- Improved cardiac functional status.
- Regression of LVH and improved LV architecture.
- ↓ symptomatic angina.
- Improved survival in ESA-treated patients after starting dialysis.
- ↓ hospitalization.
- Improved cognitive function.
- Improved sexual function.
- Improved sleep quality.
- Partial normalization of cortisol and carbohydrate metabolism.
- Avoidance of transfusion.
- Improved immune responses.
- 🦋 Slowed progression of CKD (conflicting evidence: suggested mechanisms include ↓ oxidative stress, ↓ tubular hypoxia, ↑ angiogenesis, and ↓ apoptosis).
- 🦋 Cytoprotection (📖 p. 219).

🦋 Adjuncts to ESA therapy

In addition to iron, there has been interest in several other agents as possible adjuncts to ESA therapy.

- Ascorbic acid:
 - Increases iron release from ferritin and the reticuloendothelial system.
 - Enhances iron utilization during Hb synthesis.
 - Needs to be given IV as orally ineffective.
 - 2° oxalosis is a safety concern.
 - Insufficient evidence for routine use.
- L-carnitine:
 - Required for long chain fatty acid transport into mitochondria.
 - Membrane-stabilizing effect → ↑ RBC survival (+ ↑ formation of bone marrow erythroid colonies).
 - IV administration may ↑ Hb and ↓ ESA requirement.
 - Inadequate and unconvincing body of evidence.
- Androgens:
 - Patchy evidence to support nandrolone (given IM).
 - Side effects, including acne, virilization, and abnormal LFTs, make it an unattractive option.

Pure red cell aplasia (PRCA): a detective story

- Presents as an abrupt decline in Hb, with normal platelets, normal WCC, and reticulocyte count <1%.
- Bone marrow examination reveals absent erythroid precursors.
- Anti-EPO antibodies can be measured.
- There has always been a low background incidence of PRCA due to viral infections (parvovirus), lymphoma, and certain drugs.
- Acquired PRCA was first reported in the late 1990s, with ~250 patients worldwide developing anti-EPO antibodies.
- These antibodies cross-react with endogenous EPO, rendering patients profoundly anaemic and transfusion-dependent.
- Almost all these cases occurred in dialysis patients on SC (but not IV) epoetin α (a handful of cases have been described with other ESAs).
- Extensive (and expensive) investigation suggested that polysorbate (in the drug vehicle) was able to react with compounds leaching from uncoated rubber stoppers in prefilled syringes. This had an adjuvant effect, promoting the molecules' immunogenicity (which is already higher by the SC route).
- Switching to a different ESA proved unhelpful because the antibody cross-reacted.
- Immunosuppression was tried, with variable success.
- Peginesatide (formerly hematide) ( p. 221) differs in structure and does not cross-react with the antibody. It has been successfully used as treatment.
- PRCA led many countries to abandon epoetin α by the SC route. However, following a change to the manufacturing process, its use remains widespread.

ESAs: target haemoglobin

☞ Although ESAs can be beneficial for patients with CKD-related anaemia, they are not without intrinsic risks. Despite observational data suggesting an association between lower Hb and poorer outcomes, recent randomized trials have demonstrated overall worse outcomes and higher risk of death with ESA treatment, particularly with higher Hb targets.

Influential clinical trials

CHOIR

- Correction of Hemoglobin and Outcomes in Renal Insufficiency study.
- USA; published 2007.
- Hypothesis: using epoetin A to achieve an Hb of 13.5g/dL, compared to Hb 11.3g/dL, would ↓ CV complications and death.
- Randomized, open label design; 1,432 patients, CKD 3–4 (non-dialysis); initial Hb targets 10.5–11.0g/dL and 13.0–13.5g/dL, but a protocol amendment changed the targets to absolute values (Hb 11.3g/dL vs 13.5g/dL).
- 1° outcome: time to all-cause mortality or MI, CVA, heart failure (HF).
- Stopped early; mean 16 months' follow-up.
- Finding: 34% increase in the risk of primary composite outcome in higher target group (mainly HF). Little difference in quality of life.
- Problems: high dropout rate, differences in two groups at baseline, higher target not actually achieved—despite huge ESA doses.

CREATE

- Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin study.
- European; published 2007.
- Hypothesis: early vs late anaemia correction with epoetin α will ↓ mortality and CV morbidity in CKD 3–4.
- Randomized, open label design; 603 patients, CKD 3–4 (non-dialysis); Hb targets 10.5–11.5g/dL and 13.0–15.0g/dL.
- 1° outcome: time to CV event.
- 24 months' follow-up.
- Finding: trend to higher event rate in higher target group (not statistically significant). Quality of life better in higher target group.
- Problems: low CV event rate (6%).

Although both studies had faults, the trends toward poorer outcomes led the US Food and Drug Administration to significantly escalate the label warnings for ESA drugs, strongly cautioning against higher targets.

TREAT

- Trial to Reduce Cardiovascular Events with Aranesp Therapy study.
- Worldwide (24 countries); published 2009.
- Hypothesis: treatment with darbepoietin α would ↓ risk of death, major CV events, and renal events in patients with T2DM and CKD.
- Randomized, placebo-controlled, double-blind; 4,038 patients, CKD 3–4 (non-dialysis) with T2DM.

- 2,012 patients assigned to ESA, with Hb target ~13g/dL (median achieved 12.5g/dL), and 2,026 patients to placebo, with rescue ESA if Hb <9g/dL (median Hb 10.6g/dL).
- 1° outcome: composite of death or a CV event and of death or end-stage renal disease (▶ the death and CV event rate in the trial overall was an incredible 31%—reflecting the huge CV disease burden in this population).
- 29 months' follow-up.
- Finding: no ↓ in the risk of either death or CV event with ESA, but this group did have an ↑ risk of stroke. Modest benefits (↓ fatigue, ↓ transfusion). Authors suggested ESA might be best avoided in T2DM.
- Problems: differences in baseline group characteristics; may not be applicable to non-diabetic population.

Adverse outcomes: putative mechanisms

The mechanism for the apparent outcomes associated with higher Hb targets is unclear, but it is likely that a number of interdependent factors are operative.

- Effect of ↑ Hb (↑ blood volume, ↑ blood viscosity, endothelial damage).
- ↑ BP.
- ↑ platelet aggregation.
- Direct ESA toxicity (particularly with large and rapidly escalating doses).
- Interaction with patient's comorbidity (particularly if poor ESA response and higher doses, e.g. inflammation, CV disease).

The future

Further large, well-designed clinical studies are needed to clarify the safety and efficacy of ESAs. Ideally, target Hb would be individualized, with a risk-benefit assessment based on a patient's specific level of function, life-style, and comorbidity.

Current targets (see Table 3.8)

△ For now, ESA treatment to Hb targets above 11–12g/dL, particularly in those with significant CV morbidity, should be avoided. Some would go further and suggest that, given current evidence, the use of ESAs should no longer be habitual in pre-dialysis patients, especially in relatively asymptomatic patients with mild to moderate anaemia (Hb ~9–11g/dL), and that large ESA doses should certainly be avoided in this situation.

Table 3.8 Guidelines for target indices in CKD-associated anaemia

	Hb target (g/dL)	Iron indices
KDOQI	11.0–12.0 (avoid >13.0)	Ferritin >200 micrograms/L (HD) or >100 (non-HD) TSAT >20%
UK Renal Association	11.0–12.0	Ferritin 200–500 micrograms/L (HD) or >100–500 micrograms/L (non-HD) TSAT >20% or % HRBC <6%

Iron: metabolism and markers

Key facts

- Iron is an essential component of haem, so adequate amounts are obligatory for RBC synthesis.
- Iron deficiency is found in ~40% of patients with advanced CKD and virtually all dialysis patients.
- For optimal RBC production, CKD patients require different targets for iron markers than non-CKD individuals (📖 p. 230).
- ESA treatment leads to almost universal iron deficiency.
- Iron absorption from the gut is lower in CKD patients. Consequently, oral iron is usually ineffective (📖 p. 229).
- Many CKD patients and virtually all dialysis patients require parenteral iron therapy.
- Iron therapy alone may treat anaemia in pre-dialysis CKD patients.

Causes of iron deficiency in CKD

Absolute iron deficiency

- Occurs when body iron stores are genuinely low.
- Characterized by a low serum ferritin.
- Reduced intake:
 - Poor appetite.
 - Dietary restrictions.
- Increased iron loss:
 - GI bleeding (often subclinical).
 - Multiple blood tests.
 - Haemodialysis (may lose up to 2g of iron per year through blood left in the dialyser circuit; 10–20× losses in general population).

Functional iron deficiency

- Despite adequate storage iron, it is not made available at a rate that satisfies demand.
- This is common when the ESA-driven ‘supraphysiological’ rate of erythropoiesis has outpaced the delivery of iron by transferrin.
- Characterized by a normal or raised ferritin and low TSAT (<20%).

Reticuloendothelial (‘inflammatory’) block

- Occurs with infection or inflammation (the ‘anaemia of chronic disease’).
- Iron is trapped in the reticuloendothelial system and is not released to transferrin for Hb synthesis.
- Characterized by ↑ CRP, ↑ ferritin, ↓ TSAT (but current markers are unable to distinguish from functional iron deficiency).

Markers of iron status

Several markers of iron status are available. Unfortunately, they lack sensitivity and specificity to predict the response to iron therapy in the context of CKD. It is generally recommended that ferritin and at least one additional test are used.

- Ferritin:
 - Cellular storage protein and marker of storage iron.
 - An acute phase protein, raised in inflammation and liver disease.

- TSAT:
 - Transferrin is a serum protein involved in iron delivery.
 - $TSAT = (\text{serum iron} / \text{TIBC}) \times 100$.
 - A measure of available iron.
- Percentage hypochromic red blood cells (% HRBC):
 - Measure of the iron incorporated into RBCs.
- Reticulocyte Hb count (CHr):
 - Measure of the iron incorporated into immature RBCs.
- Others: serum transferrin receptor and erythrocyte zinc protoporphyrin levels are mainly research tools at present.

Hepcidin

This recently described, hepatically synthesized peptide has emerged as a key regulator of iron homeostasis.

- Inhibits both GI iron absorption and iron release from the liver and reticuloendothelial system.
- Hepcidin exerts its actions through binding to ferroportin, a cellular iron efflux channel. Binding → internalization and degradation.
- Animal models:
 - Hepcidin knockout → severe iron overload.
 - Hepcidin overexpression → severe iron deficiency anaemia.
- Human haemochromatosis results from either deficiency or failed regulation of hepcidin.
- Plays a key role in the anaemia of CKD, ESA resistance, and the anaemia of chronic disease.
- Synthesis is induced by iron loading and inflammation, and suppressed by erythropoiesis, iron deficiency, and hypoxia.
 - Iron loading/inflammation → ↑ hepcidin → ↓ GI iron absorption + ↓ hepatic and reticuloendothelial iron release → ↓ plasma iron levels.
 - Erythropoiesis/iron deficiency/hypoxia → ↓ hepcidin → ↑ GI iron absorption + ↑ hepatic and reticuloendothelial iron release → ↑ plasma iron levels.
- Hepcidin is eliminated by the kidney, so CKD indirectly causes reduced GI iron absorption and iron store availability.
- Hepcidin levels rise as CKD progresses (highest in dialysis patients). Levels also increase in infection and inflammation.
- Hepcidin could prove to be a useful marker of iron status:
 - Functional iron deficiency → low hepcidin.
 - Reticuloendothelial blockade → high hepcidin.
 - Levels ↑ with iron loading so may help avoid iron overload.
 - Low hepcidin levels may identify those patients likely to respond to oral iron.
- The future: hepcidin antagonists could stimulate iron absorption and mobilization, blocking the inhibitory effect of CKD or inflammation on red cell production (→ ↓ parenteral iron administration and ↓ ESA requirement).

Iron: therapy and targets

► Prescribing an ESA to an iron-deficient patient is a waste of time and money.

Targets

- Ferritin:
 - >200 micrograms/L (haemodialysis).
 - >100 micrograms/L (non-haemodialysis).
 - Generally, aim 200–500 micrograms/L. Δ Avoid >800 micrograms/L, i.e. targets well above the normal physiological range.
- TSAT:
 - >20% (unless ferritin >800 micrograms/L).
 - Generally, aim 20–40%.
- % HRBC: <6% (unless ferritin >800 micrograms/L).
- Reticulocyte Hb content (CHr): >29pg/cell.

Monitoring

Measure iron stores 1–3-monthly, depending on the clinical situation and response to treatment (and no earlier than 1 week after IV iron administration).

Oral iron therapy

- Generally little benefit, particularly in higher CKD stages.
- Ferrous sulfate 200mg tablets contain just 65mg of elemental iron.
- GI side effects, including nausea, dyspepsia, and constipation, are considerable.
- Has to be taken as part from mealtimes and phosphate binders—so challenging for patients already on complex tablet regimens.
- Compliance is often poor.
- Some guidelines (e.g. UK Renal Association) suggest first-line in CKD, but this is rarely the case in practice.
- Consider a trial in pre-dialysis patients, with iron stores checked after 4–6 weeks of treatment.

Intramuscular iron

Δ Avoid: very painful; causes skin discoloration; CKD bleeding tendency → haematomas.

Intravenous iron

- Safe and effective.
- Increases ferritin and TSAT. Decreases ESA requirement.
- Concerns about iron overload (→ oxidative stress, infection risk, and CV damage) not as strong as previously (provided appropriate monitoring in place).
- Defer administration if active infection, as potential risk of compromised neutrophil function.
- Current preparations contain elemental iron enclosed in a carbohydrate shell.

- The elemental iron is released to transferrin and then to the reticuloendothelial system for storage.
- The more stable the preparation, the larger the permissible dose.
- In haemodialysis patients, it is practical to give regular low doses of iron, e.g. 100mg weekly. This is obviously less convenient in pre-dialysis or peritoneal dialysis patients.

► **Adverse reactions**

- Free iron reaction: ↓ BP, nausea, vomiting, dizziness, sweating, myalgia, back pain, arthralgia, pruritus. Often less problematic with slower administration. Usually self-limiting, but consider treatment with hydrocortisone and/or antihistamines.
- ►► Anaphylaxis: risk low, but staff should be appropriately trained and adequate resuscitation facilities immediately available.

Preparations of intravenous iron

Iron III hydroxide sucrose complex (iron sucrose/saccharate)

- Venofer[®].
- Low incidence of adverse reactions. Anaphylaxis very rare (0.05%).
- Test dose unnecessary.
- Widely used, particularly in Europe.
- IV infusion or slow IV injection (20mg/min), often diluted in 100mL saline.
- Typical dosing pre-dialysis or peritoneal dialysis: 200mg every 1–3 months (200mg weekly for three doses, if clinical urgency).
- Haemodialysis: initially 100mg for ten dialysis sessions. Continue weekly if ferritin <500 micrograms/L.

Sodium ferric gluconate

- Ferrlecit[®].
- Anaphylaxis rare. Test dose unnecessary.
- Widely used.
- More iron may be released directly to storage and not to transferrin.
- Usually administered as 62.5–125mg IV over 10min on haemodialysis.
- Diluted for slower administration in pre-dialysis and peritoneal dialysis patients.

Iron dextran

- Higher risk of reactions and anaphylaxis (0.6%), the latter due to the formation of anti-dextran antibodies.
- Popularity declining in view of this.
- ⚠ A test dose is mandatory.
- Total dose of iron infusions of low MW iron (III) hydroxide dextran complex (Cosmofer[®]) (e.g. 20mg/kg over 4–6h) have been used for more rapid iron repletion and to avoid multiple infusions.

Newer preparations

- Include ferric carboxymaltose (Ferinject[®]) and ferumoxytol (Feraheme[®]). Both facilitate the delivery of higher doses of iron in a single administration.

CKD mineral and bone disorder (CKD-MBD)

Definitions (see Table 3.9)

- CKD mineral and bone disorder (CKD-MBD) is a relatively new term that describes the mineral, skeletal, and related CV consequences of CKD (particularly CV calcification).
- This expanded focus has been driven by observational studies suggesting that CKD-MBD (and its treatment) may impact on CV morbidity and mortality.
- Vascular disease is common and progresses rapidly in CKD, particularly at stage 5—usually occlusive lesions due to atheromatous plaques. The full spectrum of arterial disease in CKD is broader, however, including vessel wall calcification with resulting impaired vascular function.
- Renal bone disease (osteodystrophy) is reserved to describe the bone pathologies associated with CKD. Osteodystrophy is a heterogeneous disorder that ultimately leads to diminished bone strength.
- CKD-MBD is invariably present beyond CKD 3, and its management represents a significant clinical challenge.
- There is no single therapeutic intervention that fits all—instead, a package of management, customized to the individual patient, is necessary.
- Several important international practice guidelines have been formulated to help inform the optimal treatment of CKD-MBD (📖 p. 244).

Table 3.9 KDIGO^a classification of CKD-MBD and renal osteodystrophy

Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD, manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism.
- Abnormalities of bone turnover, mineralization, volume, linear growth, or strength.
- Vascular or other soft tissue calcification.

Definition of renal osteodystrophy

- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder that is quantifiable by histomorphometry of bone biopsy material.

^a KDIGO, Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guidelines for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) (2009). *Kidney Int*, **76** (Suppl 113), 1–132.

Classification

(See Fig. 3.4)

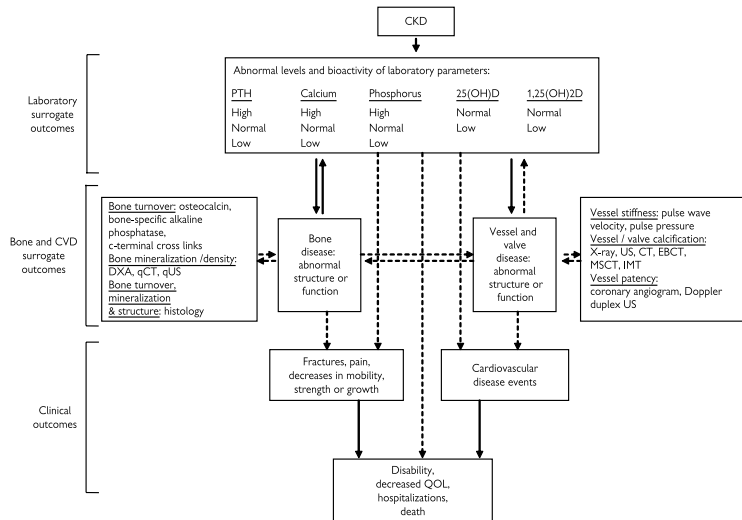


Fig. 3.4 CKD-MBD: an emerging paradigm. Arrows represent relationships and correspond to a question of interest. Solid arrows represent well-established associations. Dashed arrows represent associations that need to be established with greater certainty. CVD, cardiovascular disease; DXA, dual-energy X-ray absorptiometry; EBCT, electron beam CT; IMT, intimal medial thickness; MSCT, multislice CT; (q)CT, quantitative CT; (q)US, quantitative ultrasound; QOL, quality of life. From KDIGO for the diagnosis, evaluation, prevention, and treatment of CKD-MBD. Reproduced from *Kidney International* **76**, S113, 1–132. Methodological Approach, (2009), with permission from Nature Publishing Group.

CKD-MBD: bone disease

Osteodystrophy is a function of bone turnover, mineralization, and volume. Strictly speaking, bone biopsy (usually from the iliac bone) with histological and histomorphometric assessment is required for diagnosis and classification. In practice, biopsies are very rarely performed (invasive, with considerable expertise needed to interpret), and surrogate markers of bone turnover are \therefore (over) relied on (see Table 3.10).

See Fig. 3.5 for the spectrum of renal bone disease.

Secondary hyperparathyroidism (SHPT) \uparrow PTH causes \uparrow bone resorption and formation ('high turnover' disease). Haphazardly organized, weakened bone results (classically, osteitis fibrosa cystica).

Adynamic bone disease Paucity of cells with \downarrow bone resorption and formation ('low turnover' disease). Pathophysiology remains poorly understood, but incidence has \uparrow rapidly over the last two decades.

Mixed uraemic osteodystrophy

This is also relatively common, as is evolution from one form to another.

Osteomalacia

This refers to a defect in mineralization. Uncommon as an isolated finding and not helpful as a clinical description in this situation. Generally related to a deficiency of $1,25(\text{OH})_2\text{D}$, but aluminium intoxication and uraemic acidosis are also important risk factors.

Osteoporosis

Usually defined in terms of bone mineral density (BMD) so has little diagnostic meaning in the context of osteodystrophy where low BMD can coexist with low or high turnover disease. DEXA (dual-energy X-ray absorptiometry) scanning does not predict fracture risk in advanced CKD so is of limited clinical utility in this setting (stages 4–5D). Stage 3 CKD encompasses large numbers of patients, many with age-related declines in GFR, who will exhibit a mixed bag of skeletal pathologies (including mild SHPT, osteoporosis, and vitamin D deficiency). Extrapolating general management from the non-CKD population is \therefore difficult (and not evidence-based), and the role of anti-resorptive agents, such as bisphosphonates, is uncertain. One approach is to gather a dataset of Ca^{2+} , PO_4 , PTH, serum $25(\text{OH})_2\text{D}$, and BMD. Any abnormalities of mineral metabolism can be addressed as described over the next few pages. If none exists, then low BMD can be treated as for non-CKD patients. Stages 1–2 CKD should be treated as per the non-CKD population.

Factors contributing to adynamic bone disease

- Overtreatment with vitamin D.
- \uparrow calcium intake.
- Diabetes mellitus.
- Age.
- Low PTH.
- Aluminium accumulation.
- Acidosis.
- CAPD.

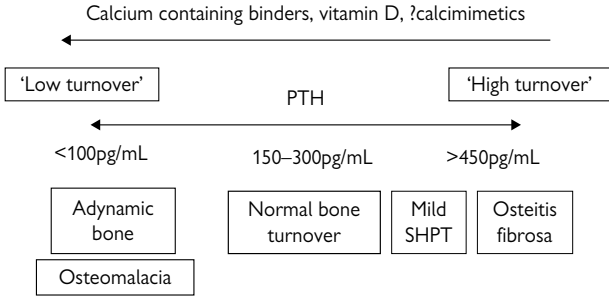


Fig. 3.5 The spectrum of renal bone disease.

Table 3.10 Features of ‘high’ and ‘low turnover’ renal bone disease

	High turnover Hyperparathyroid bone disease	Low turnover Adynamic bone disease	Osteomalacia
Bone biopsy findings	↑ osteoblast and osteoclast activity Fibrosis	↓ osteoblast and osteoclast activity Thin osteoid seams	↓ osteoblast and osteoclast activity Widened osteoid seams Aluminium deposition
PTH	High	Low or normal	Usually low or normal
Alkaline phosphatase	Raised	Normal	Normal
Calcium	Variable	Often ↑	Normal or ↑
Phosphate	↑↑	Normal or ↑	Normal or ↑
DFO test ^a	Normal	Normal	Often elevated

^a DFO test, desferrioxamine test: a non-invasive means of detecting aluminium overload.

Possible indications for bone biopsy include: unexplained fractures, unexplained hypercalcaemia, unexplained bone pain, suspected aluminium toxicity, before treatment with bisphosphonates.

CKD-MBD: physiology

If renal function is intact, concentrations of PO_4 and Ca^{2+} are maintained through interaction between PTH, $1,25(\text{OH})_2\text{D}$ (calcitriol), fibroblast growth factor-23 (FGF-23), and their principal targets: bone, kidney, the GI tract, and parathyroid glands.

Parathyroid hormone

PTH secretion (and parathyroid gland proliferation) are stimulated by $\downarrow \text{Ca}^{2+}$, $\downarrow 1,25(\text{OH})_2\text{D}$, and $\uparrow \text{PO}_4$. PTH acts on three fronts: (i) mobilizing skeletal calcium; (ii) \downarrow urinary Ca^{2+} + \uparrow urinary PO_4 excretion; (iii) \uparrow renal production of $1,25(\text{OH})_2\text{D}$ (in turn $\rightarrow \uparrow$ intestinal Ca^{2+} and PO_4 absorption).

Vitamin D

Inactive vitamin D sterols, e.g. colecalciferol (from dietary sources and UV conversion in the skin), are metabolized in the liver to $25(\text{OH})\text{D}$ (calcidiol) and converted to $1,25(\text{OH})_2\text{D}$ (principally) by the renal 1α -hydroxylase enzyme. $1,25(\text{OH})_2\text{D}$ exerts many important biological effects via its intracellular receptor (VDR) (see Fig. 3.6).

FGF-23

Produced in bone by osteocytes and osteoblasts. FGF-23 levels \uparrow as GFR \downarrow , potently suppressing 1α -hydroxylase and $\therefore 1,25(\text{OH})_2\text{D}$ production. It also \uparrow urinary PO_4 excretion. FGF-23 excess underlies autosomal dominant hypophosphataemic rickets, X-linked hypophosphataemia, and tumour-induced osteomalacia (all characterized by PO_4 wasting, $\downarrow 1,25(\text{OH})_2\text{D}$, and skeletal abnormalities). \blacktriangleright Emerging as a very powerful biomarker for mortality.

Klotho

A putative ageing suppressor gene, encoding a transmembrane protein that forms a complex with the FGF receptor to \uparrow FGF-23 affinity. Expressed principally in the kidney, brain, and parathyroid gland, it is a mandatory cofactor for the actions of FGF-23 within mineral homeostasis. \downarrow Klotho expression is one of the earliest biomarkers for CKD (preceding $\uparrow \text{PO}_4$ and \uparrow FGF-23) and continues to decline as GFR falls.

Bone biology

Bone is not static; it continuously adapts to mechanical and metabolic requirements by a remodelling process centred around the coupling of osteoblastic formation and osteoclastic resorption. Multiple systemic hormones (including PTH and $1,25(\text{OH})_2\text{D}$) and local growth factors (e.g. the RANK/OPG system) influence this process. Bone is the most important body reservoir of Ca^{2+} and PO_4 . See Fig. 3.7 for the pathogenesis of SHPT.

The effect of CKD

- Loss of functioning renal mass →:
 - Phosphate accumulation.
 - \downarrow $1,25(\text{OH})_2\text{D}$ (\rightarrow \downarrow serum Ca^{2+}).
 - \downarrow Klotho expression \rightarrow \uparrow FGF-23 (\rightarrow \downarrow $1,25(\text{OH})_2\text{D}$).
 - 'Nutritional' vitamin D insufficiency is also common in CKD (p. 250).
- Secondary hyperparathyroidism:
 - \downarrow Ca^{2+} + \downarrow $1,25(\text{OH})_2\text{D}$ + \uparrow $\text{PO}_4 \rightarrow$ \uparrow PTH synthesis and release.
 - Prolonged stimulation of parathyroid tissue \rightarrow clonal proliferation of parathyroid cells (with areas of nodular hyperplasia).
 - These clones express less Ca^{2+} -sensing receptor (CaR) and VDR.
 - Refractoriness to treatment is inevitable (termed tertiary or autonomous hyperparathyroidism).
 - In addition, there is relative 'skeletal resistance' to the effects of PTH (mechanisms unclear).
 - Abnormal bone turnover results.
 - \uparrow PTH also has non-skeletal effects, including LVH, cardiac fibrosis, extraskeletal calcification, peripheral neuropathy, impotence.

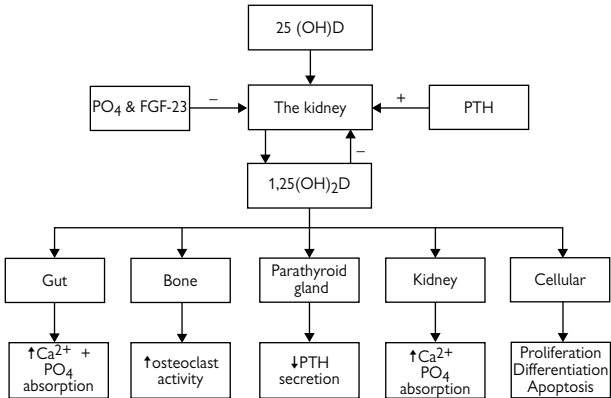


Fig. 3.6 Overview of vitamin D metabolism.

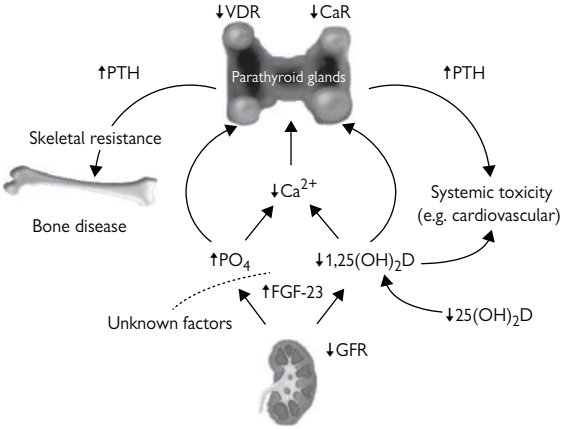


Fig. 3.7 The pathogenesis of SHPT.

CKD-MBD: clinical features

Secondary hyperparathyroidism (SHPT)

- Usually asymptomatic. Clinical sequelae occur late (with significant biochemical and histological disease), including:
 - Bone pain, arthralgia, and muscle weakness (esp. proximal).
 - Pruritus (cutaneous calcium phosphate deposition).
 - Bony deformity (e.g. resorption of terminal phalanges).
- ↑ fracture risk (hip fracture risk ~5× in dialysis patients). Fracture risk is equivalent to a non-dialysis patient 10–20 years older. ► Mortality following a fracture rises by ~2.5×.
- Marrow fibrosis contributes to anaemia and poor ESA response.

Adynamic bone disorder

- Usually asymptomatic and probably no ↑ fracture risk \blacklozenge^* .
- Adynamic bone buffers calcium poorly; ↑ Ca^{2+} is common, particularly if oral calcium intake is significant.
- ↑ risk of soft tissue and vascular calcification.
- ↑ risk of osteopenia post-transplantation (Δ steroids).
- Aluminium-related low turnover bone disease is often painful, with an ↑ risk of spontaneous fracture.

Cardiovascular risk

- ► Poor control of serum PO_4 , serum Ca^{2+} , calcium phosphate product (CaxP), and PTH are all associated with ↑ CV morbidity and mortality.
- ↑ CaxP is associated with soft tissue and cardiac calcification.

Diagnosis

No one marker is perfect, so a clinical dataset is used (see Table 3.11).

Biochemical

- Check Ca^{2+} , PO_4 , and PTH, as in Table 3.11. More often if treatment changes made.
- PTH: the ability of serum PTH to predict high and low turnover disease is actually quite poor though improves at extremes of PTH (<2× upper limit of normal for PTH: low turnover; >9× upper limit of normal: high turnover).
- Calcium: ↓ in untreated SHPT (though rises with vitamin D analogue and calcium-based phosphate binder treatment); often ↑ in ABD.
- Phosphate: raised (early).
- Alkaline phosphatase: ↑ in SHPT and a useful, if underutilized, component of the clinical dataset. It is a marker of bone formation (others, e.g. osteocalcin, are also elevated though not routinely measured).

Radiology

The availability of PTH measurements means X-rays are rarely necessary.

- SHPT: subperiosteal bone resorption (distal and middle phalanges of hands and feet), osteosclerosis (→ ‘rugger jersey spine’ on lateral films), solitary cysts (‘brown tumours’), particularly in jaw, pelvis, or ribs.
- ABD: often normal (osteopenia difficult to detect on standard X-rays).
- DEXA does not predict fracture risk in advanced CKD although may in stages 1–3 (p. 234). Quantitative CT of the spine may prove to have a role in predicting high and low turnover disease.

Table 3.11 KDIGO recommendations for frequency of biochemical testing in CKD

CKD stage	Calcium	Phosphorus	PTH	Alkaline phosphatase	Calcitriol (25(OH)D) ^a
3	Every 6–12 months	Every 6–12 months	Baseline [⦿]	Baseline	Baseline
4	Every 3–6 months	Every 3–6 months	Every 6–12 months	Every 6–12 months	Baseline
5 and 5D	Every 1–3 months	Every 1–3 months	Every 3–6 months	Every 3–6 months	Baseline

⦿ Other guidelines, including those produced by NICE in the UK, do not advocate routine testing of serum PTH in CKD stage 3.

^a Calcitriol (1,25(OH)₂D) is not routinely measured, as it is present in only tiny amounts in serum, and the assay is technically difficult and expensive.

PTH assays

- PTH (1-84) is the active hormone synthesized by the parathyroid glands and released into the circulation.
- PTH (1-84) exerts its biological effects via the type 1 PTH receptor (PTH1R).
- PTH fragments are also present in the circulation. These include a large C-terminal fragment called PTH (7-84).
- Routinely used ‘first-generation’ immunometric assays or ‘intact’ PTH assays detect both PTH (1-84) and PTH (7-84).
- PTH (1-84) has a circulatory half-life of <5min. PTH (7-84) undergoes renal clearance, and its half-life is appreciably longer.
- PTH (7-84) appears to exert an inhibitory influence on osteoclastic bone resorption (probably via a distinct C-PTH receptor). This opposes the action of PTH (1-84) and may be a contributory factor to the apparent skeletal resistance to PTH seen in CKD.
- ‘Second-generation’ immunometric assays, more specific for PTH (1-84), are available and are likely to attract increasing attention as their clinicopathological validation progresses. At present, however, international CKD-MBD guidelines have not supported their routine use.
- There may prove to be a role for combining the different assays, e.g. a PTH (1-84)/PTH (7-84) ratio <1 has been correlated with adynamic bone.

CKD-MBD: vascular calcification

Background

- Vascular calcification may predict, or even contribute to, the ↑ CV morbidity and mortality associated with CKD.
- Prevalence in CKD far exceeds the general population (>80% of dialysis patients). Progression is also much more rapid.
- Appears intimately linked to the aberrant mineral and bone metabolism of CKD (as well as to its treatment ☹️). May explain the association between ↑ PO_4 , ↑ $CaxP$ and ↑ PTH, and adverse CV outcomes in observational studies. The finding of vascular calcification is, in itself, associated with significant ↑ CV risk.

Types

Two types of arterial calcification (often co-localized):

- Intimal—within atherosclerotic plaques. Associated with stenotic lesions and CV events, such as MI and stroke. The calcium content of plaques from CKD patients is greater than age-matched controls.
- Medial—within the intima media; classically, Mönckeberg's calcinosis. This causes vascular stiffness (→ elevated pulse pressure → LVH → LV dysfunction).
- In addition, cardiac valvular, and other soft tissue, calcification is a frequent finding in advanced CKD. Calcification also makes vascular interventions, such as CABG or angioplasty, more challenging.


Should we screen?

The role of screening is unclear at present, as screening criteria are not fulfilled: (i) best therapy is uncertain and (ii) unknown if CV outcomes can be modified. Possible methods, however:



- Electron beam (EBCT) or multislice (MSCT) CT scanning (esp. coronary arteries and aorta) most sensitive and specific. Generate a calcification score for prospective monitoring. Problems: expensive, cannot distinguish intimal and medial calcification.
- Plain X-ray (usually lateral AXR) can document 'pipe stem' calcification, with reasonable sensitivity; quantification more difficult (recommended by KDIGO).
- Vascular ultrasound, e.g. carotid intimal medial thickness.
- Pulse wave velocity yields functional information.
- Echocardiography identifies valvular calcification.

Relationship with osteodystrophy

- Most commonly associated with ABD where the skeleton fails to buffer Ca^{2+} and PO_4 , leaving them 'available for use' in calcification. In SHPT, the release of Ca^{2+} and PO_4 during bone resorption may also favour calcification.
- ☹️ Both calcium-containing phosphate binders and active vitamin D can create a +ve calcium balance, with a risk of ABD and ↑ $CaxP$. There is evidence linking calcium intake to arterial calcification. This has provoked an extremely robust, ongoing debate within

nephrology about the future role of these treatments (both previously cornerstones of therapy) (see  pp. 246–251).

Prevention and treatment

- Follow best practice guidelines for CKD-MBD, as outlined on  p. 244.
- Some evidence that sevelamer HCl, a non-calcium-containing binder, may slow progression of coronary and aortic calcification.
- Calcimimetics may help control PTH without \uparrow CaxP or large doses of vitamin D. A potential future role is currently under study ( p. 252).
- Daily or long-hours dialysis with superior PO_4 control (negating the need for binders) may help, as might transplantation.

Biology of vascular calcification in CKD

A new paradigm that departs from the traditional view of \uparrow CaxP passively promoting calcification has recently emerged, revealing an extremely complex—and closely regulated—process. The evidence trail is as follows:

- Although calcification appears to correlate, in part, with calcium intake, it was frequently encountered prior to the widespread use of calcium-based phosphate binders.
- A poorly understood association between arterial calcification and bone disease has long been recognized in the context of osteoporosis where mineral metabolism is less overtly disturbed.
- The calcium deposited in vessels is in the form of hydroxyapatite crystals—the same as in the skeleton.
- Spontaneous vascular calcification occurs in rodents carrying specific gene deletions (e.g. apolipoprotein-E, fetuin-A, and OPG).
- Certain hitherto ‘bone-specific’ regulatory transcription factors (particularly Cbfa1) and proteins (e.g. osteocalcin, osteonectin, and alkaline phosphatase) have been demonstrated in calcified vessels.
- Several stimuli (including \uparrow PO_4 and uraemic serum) are able to promote the differentiation of vascular smooth muscle cells to an osteoblastic phenotype (via the upregulation of the Na-dependent cotransporter Pit-1). Such cells then form matrix vesicles and initiate the process of matrix deposition and mineralization.
- Regulation of calcification is achieved through a balance of promoters (e.g. BMP-2, RANKL) and inhibitors (e.g. matrix Gla protein, itself inhibited by warfarin, osteopontin, fetuin-A, PTHrP, OPG).
- In addition, \uparrow PTH, \uparrow BP, abnormal glucose metabolism, dyslipidaemia (particularly \downarrow HDL), inflammation (\uparrow CRP, \uparrow IL-6, \uparrow TNF- α , \downarrow fetuin-A), oxidative stress, and natural inhibitor deficiencies are all likely to play a role.
- Further complexity is suggested by the discovery of cross-talk between osteoblasts and adipocytes (via leptin and other hormones) and \therefore bone remodelling and energy metabolism. This may have particular relevance in diabetes where low bone turnover is common.
- This integration of bone and vascular biology may yield novel treatments; for example, BMP-7 has been shown to be efficacious in animal models of vascular calcification and bone disease. OPG and fetuin-A are also potential future therapies.

CKD-MBD: treatment

Goals

- Keep serum Ca^{2+} and PO_4 within the normal range.
- Keep bone turnover and strength as near normal as possible.
- Keep serum PTH appropriate to these objectives.
- Prevent the development of parathyroid hyperplasia.
The standard treatment package comprises:
 - Measures to ↓ serum PO_4 :
 - Dietary PO_4 restriction.
 - Oral phosphate binders (prevent absorption).
 - Removal through adequate dialysis.
 - Measures to suppress PTH synthesis and secretion:
 - Calcitriol or vitamin D analogues (e.g. alfacalcidol, paricalcitol).
 - Calcimimetic agents.
 - Measures to normalize serum Ca^{2+} :
 - Appropriate calcium intake ± supplementation (including calcium-containing binders).
 - Appropriate vitamin D treatment.
 - Appropriate dialysate concentration.

Therapeutic targets

An area of healthy debate within nephrology.

NKF KDOQI (2003) (see Table 3.12)

- Guidelines developed by NKF KDOQI reflected the growing concern that CKD-MBD and its treatment might be associated with a potentially modifiable increase in CV risk.
- Principally opinion-based, they advocated much more rigorous targets for Ca^{2+} , PO_4 , and PTH than previously suggested (see Table 3.12).
- These targets:
 - Proved extremely challenging from the clinician's perspective. Multiple studies, as well as national registry data, showed that current practice fell well short of achieving them.

Table 3.12 NKF KDOQI treatment guidelines^a

CKD stage	GFR (mL/min)	PTH (pg/mL)	Calcium (mmol/L)	Phosphorus (mmol/L)
3	30–59	35–70	Normal	0.87–1.48
4	15–29	70–110 ^b	Normal	0.87–1.48
5 and 5D	<15 or dialysis	150–300 ^b	2.1–2.37	1.13–1.78

^a National Kidney Foundation (2003). K-DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kid Dis*, 42, S1, 51–201 (see <http://www.kidney.org/professionals/kdoqi>).

^b A PTH target above the upper limit of normal reflects observational data that suggest normal bone turnover is most likely to be achieved in uraemic bone when PTH is modestly elevated.

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- Outcome data showing a significant impact on mortality through attaining them have, thus far, not been forthcoming.
- Provided a framework for the pharmaceutical industry to introduce novel and (sometimes) expensive treatments as well as for healthcare purchasers to set reimbursement targets.

KDIGO (2009) (see Table 3.13)

- The more recent KDIGO clinical practice guidelines present a comprehensive and systematic review of available evidence in this area and hope to harmonize international guidelines.
- While not universally accepted, they have generally superseded the NKF KDOQI guidelines.
- The principal differences are:
 - Much less prescriptive.
 - Less emphasis on attaining narrow Ca^{2+} , PO_4 , and PTH targets, e.g. the target for PTH in pre-dialysis CKD is effectively removed beyond treatment of a progressively rising value.
 - The guidelines generally recommend decision-making based on trends, rather than single values.
 - The guidelines suggest there is no evidence to underpin a more stringent PTH target, so focus on avoidance of risk at extremes of PTH, i.e. at $<2 \times$ or $>9 \times$ normal in dialysis patients.
 - A 'multiplication' range of $2\text{--}9 \times$ normal is given, as opposed to an absolute range in pg/mL or pmol/L, because absolute PTH levels can vary significantly between assays.
 - The guidelines read more as a summary of evidence, punctuated by pointers and advice, rather than dogmatic targets.
 - Criticisms: the new broader PTH targets risk 'letting the genie out of the bottle', with progressive hyperparathyroidism that could subsequently prove unstoppable. Additionally, some were expecting (and prefer) more prescriptive guidance.

Table 3.13 KDIGO treatment guidelines^a

CKD stage	PTH (pg/mL)	Calcium (mmol/L)	Phosphorus (mmol/L)
3	No numerical target ^a	Normal range	Normal range
4	No numerical target ^a	Normal range	Normal range
5	No numerical target ^a	Normal range	Normal range
5D	$2\text{--}9 \times$ upper limit of normal range	Normal range	Lowered toward normal range

^a It is suggested that if the PTH is progressively rising and remains persistently above the upper limit of normal, it warrants treatment but not to a specific numerical target because the optimal PTH level in this situation is unknown. From *Kidney Int*, 2009, **76**, Suppl. 113, 1–132.

⚠ Very few statements in either guideline are based on high-quality evidence—in fact, the only two recommendations graded 1A within the KDIGO report are in areas within paediatric practice. This serves to highlight the pressing need for RCTs to inform future guidelines in this area.

CKD-MBD: hyperphosphataemia

Control of phosphate

PO₄ control is the weak link in the therapeutic approach to CKD-MBD.

Dietary restriction

- Phosphate is contained in almost all foods (esp. meat, milk, eggs, cheese, yogurt, bran cereals, cola, chocolate drinks, beer, baked beans, dried peas (e.g. chick peas), nuts, and many convenience foods).
- It is difficult to balance dietary phosphate restriction against adequate protein intake (recommended levels of daily dietary protein provide 30–40mmol of phosphate). Patients are advised to reduce unnecessary PO₄ intake (e.g. cola), so they can maintain an adequate protein intake (e.g. meat, eggs).

Phosphate binders

See Table 3.14.

- Taken with meals to bind phosphate in the gut. The amount taken is proportional to size of meal (and, ideally, to its PO₄ content) as well as to serum PO₄ (usually 1–3 tablets/meal).
- Potency is modest, and some patients require large doses. GI side effects are frequent. ►The most effective binder is one that the patient will take: demanding regimens + unpalatable tablets = poor compliance (>50% dialysis patients do not take their binders regularly).
- Should not be taken at the same time as iron supplements.
- Aluminium hydroxide is the most effective binder, but potential aluminium toxicity (skeletal and neurological) restricts its use (<4 weeks).
- Calcium-containing phosphate binders (CCPBs) have been the mainstay:
 - Not only bind PO₄, but help correct ↓ Ca²⁺ (and ∴ suppress PTH).
 - Patients receiving CCPBs are often in +ve calcium balance, so they have been implicated as contributors to vascular calcification (and adverse CV outcome). This can probably be avoided by limiting CCPB dose (and lowering dialysate calcium, e.g. to 1.25mmol/L).
 - CCPBs should be restricted to 1,500mg elemental calcium/day, particularly if low turnover disease likely (PTH <2 × upper limit of normal).
 - Avoid if hypercalcaemia.
 - Non-calcium-based binders are preferred in patients with severe vascular and/or soft tissue calcifications.
- Non-calcium, non-aluminium-containing binders, e.g. sevelamer hydrochloride (Renagel[®]) or carbonate (Renvela[®]) and lanthanum carbonate (Fosrenol[®]), allow calcium and aluminium to be avoided.
 - They are much more expensive than calcium- or aluminium-based binders.
 - Equally as effective as CCPBs.
 - Sevelamer is associated with slower progression of coronary calcification and possibly with improved survival.
 - Sevelamer lowers LDL cholesterol and may provide additional CV risk reduction.

- Magnesium-calcium combination binders, e.g. calcium acetate + magnesium carbonate (Osvaren[®]), reduce calcium burden and appear cost-effective (SE: GI, including diarrhoea).
- The recent KDIGO guidelines suggest current available evidence does not favour a specific phosphate binder. Choice of agent in a particular patient should \therefore be based on serum biochemistry, presence of vascular calcification, and bone histology (if available). A local policy will usually be in place.
- One strategy is to use a combination of binding agents to reduce PO_4 , avoid excessive calcium administration, and ameliorate the cost of newer binders.

Adequate dialysis

- Dietary intake of PO_4 exceeds daily removal by dialysis.
- A significant amount of PO_4 is in the intracellular compartment, so significant rebound occurs post-HD treatment. CAPD is more efficient at PO_4 removal than HD.
- Poor PO_4 control may be an indication for more frequent dialysis.
- Daily dialysis regimens can control PO_4 , with no binder requirement (supplementation is often necessary!).

Aluminium toxicity

History. In the 1970–80s, clusters of dialysis units reported patients with aluminium toxicity. Investigation identified a high geographic concentration in dialysate water as the cause, and improved purification techniques eliminated this route of exposure. Aluminium-containing phosphate binders were left as the main source.

Presentation. Aluminium toxicity (\rightarrow ↓ PTH secretion, ↓ mineralization, and ↓ osteoblastic activity) previously accounted for the majority of low turnover bone pathology. This was often painful, with an ↑ risk of fracture. Also: ESA-resistant anaemia, encephalopathy, and neurotoxicity.

Current practice. Aluminium-containing phosphate binders should generally be avoided (use for a limited period, e.g. <4 weeks, a possible exception). If extended use is necessary, aluminium levels should be monitored. Serum aluminium should be <20 micrograms/L (0.7 $\mu\text{mol/L}$) in dialysis patients. Levels >60 micrograms/L (2.2 $\mu\text{mol/L}$) suggest aluminium overload. Sequential levels may detect the development of overload in at-risk patients. However, serum aluminium is not a reliable indicator of overall body content, and a desferrioxamine (DFO) stimulation test may be required (\rightarrow rise in aluminium level after IV DFO). Symptomatic patients may benefit from regular DFO chelation treatment. Interestingly, recent data suggest that long-term use of aluminium-based binders in dialysis patients is not associated with toxicity as measured by desferrioxamine (DFO) stimulation test, so perhaps their clinical use is about to go full circle.

Table 3.14 Phosphate binders

Binder	Advantages	Disadvantages	Examples
Calcium-based binders	Inexpensive Help to correct low Ca^{2+} and suppress PTH Calcium acetate has a smaller calcium load per equivalent phosphate-binding dose (though $\uparrow \text{Ca}^{2+}$ is common)	Calcium load may predispose to vascular and soft tissue calcification Hypercalcaemia	Calcium carbonate: Titalac [®] (168mg calcium) Calcichew [®] (500mg calcium) Calcium 500 [®] (500mg calcium) Adcal [®] (600mg calcium) Calcium acetate: Phosex [®] (250mg calcium)
Calcium acetate + magnesium carbonate	Inexpensive Lower calcium load per equivalent phosphate-binding dose Less $\uparrow \text{Ca}^{2+}$	Need for magnesium monitoring	Osvaren [®] Calcium acetate 435mg + magnesium carbonate 235mg
Aluminium-based	Inexpensive Very effective	Risk of aluminium toxicity Need to monitor levels Short-term use only	Alu-cap [®] ($\text{Al}(\text{OH})_3$ 475mg) Aluminium hydroxide suspension
Sevelamer HCl	Non-absorbed, does not accumulate Avoids calcium May slow progression of coronary and aortic calcification Other beneficial effects: \downarrow LDL, \downarrow urate, \downarrow inflammation	Expensive GI intolerance Large doses needed (average 8 tablets/day) Causes a reduction in serum bicarbonate	Sevelamer hydrochloride (Renagel [®]), 1–3 800mg tablets with each meal
Sevelamer carbonate	Similar to sevelamer HCl Better GI tolerance Avoids \downarrow bicarbonate	Expensive Large doses needed	Sevelamer carbonate (Renvela [®]), 1–3 800mg tablets or one 2,400mg powder sachet with each meal
Lanthanum carbonate	Avoids calcium and aluminium Minimally absorbed Lower tablet burden (500mg, 750mg, and 1,000mg available)	Expensive Long-term outcome and safety data currently lacking	Lanthanum carbonate (Fosrenol [®]), 500–1,500mg with meals

Renal bone disease management summary

SHPT


- Check Ca^{2+} and PO_4 , PTH, and 25(OH)D, according to Table 3.11 (📖 p. 241) (more often if treatment changes made).
- If serum 25(OH)D <30ng/mL (<75nmol/L), consider replacement (📖 p. 250).
- Aim to reduce serum PO_4 to the normal range through a combination of diet, phosphate binders, and adequate dialysis (📖 p. 246).
- Once PO_4 controlled, add alfacalcidol or calcitriol, titrating the dose to achieve a locally agreed target PTH, according to CKD stage (📖 p. 244).
- Aim to keep serum Ca^{2+} in the normal range (If $\uparrow \text{Ca}^{2+}$, switch to non-calcium-containing binder; review dialysate Ca^{2+} ; reduce/stop vitamin D, as necessary).
- Uncontrolled SHPT: review diet; review compliance (especially before prescribing multiple expensive therapies); intensify phosphate binder and vitamin D therapy, as serum Ca^{2+} allows.
- Consider paricalcitol (📖 p. 251) and cinacalcet (📖 p. 252) if high calcium limits vitamin D treatment.
- Parathyroidectomy: reserve for those cases refractory to medical management (📖 p. 254).

ABD


- Aim to increase PTH-driven bone turnover:
 - Reduce or stop calcium-containing binders and vitamin D analogues (aim for serum Ca^{2+} in the normal range).
- Lowering dialysate calcium concentration (e.g. 1.0mmol/L for both HD and CAPD) may help $\downarrow \text{Ca}^{2+}$ and $\uparrow \text{PTH}$.
- Exclude significant aluminium deposition, if applicable (📖 p. 247).
- Exogenous PTH (pulsatile administration) and calcimimetics may prove to have an anabolic role in ABD (circadian PTH release is anabolic for bone, whereas sustained PTH release is catabolic).

CKD-MBD: vitamin D treatment


There are two vitamin D treatment strategies in CKD—which are not mutually exclusive.

- The conventional rationale is to suppress PTH and control SHPT.
 - Failure of the kidney to produce $1,25(\text{OH})_2\text{D}$ is a key part of the pathogenesis of SHPT, so it is logical that $1,25(\text{OH})_2\text{D}$ replacement should form part of management.
 - Vitamin D requires 1α -hydroxylation in the kidney for activation. In renal failure, this can be pharmacologically bypassed by using the 1α -hydroxylated analogues calcitriol or alfacalcidol (1α -calcidol).
 - Newer vitamin D analogues, (e.g. paricalcitol or doxercalciferol) provide alternatives.
 - There is evidence (retrospective studies) that mortality ↓ in dialysis patients taking vitamin D, compared with those who do not.
- A newer justification for vitamin D treatment is correction of vitamin D ‘substrate’ deficiency, using non-activated vitamin D products (colecalfiferol, ergocalciferol).
 - Largely based on theoretical benefits (see Box 3.3) and assumes independent benefits for non-activated vitamin D via local conversion of $25(\text{OH})\text{D} \rightarrow 1,25(\text{OH})_2\text{D}$ (autocrine effects) in a wide range of target tissues. See also  p. 208.

Treatment: control of SHPT

- ► **Control serum phosphate first.**
- Start with a low dose (0.25 micrograms/day alfacalcidol PO), and increase, as necessary, over several weeks (rarely, >0.5–1.0 micrograms/day).
- See  p. 244 for treatment targets; local policies may differ.
- Pulsed oral and IV therapy (usually 0.5–2.0 micrograms $\times 3$ /week) are an alternative to daily regimens and appear equally efficacious. Giving therapy, either IV or oral, during a dialysis treatment can aid compliance.

Monitoring Monitor serum Ca^{2+} , PO_4 , and PTH (monthly initially). Avoid ↑ Ca^{2+} and PTH oversuppression.

Side effects and toxicity ↑ Ca^{2+} and ↑ CaxP (↑ GI absorption and ↑ mobilization from bone) frequently complicate treatment. More than just a therapeutic inconvenience, this has implications for bone turnover (→ ABD), soft tissue/vascular calcification, and CV morbidity/mortality ( p. 242).

Treatment: ‘nutritional’ vitamin D deficiency

- Low serum $25(\text{OH})\text{D}$ (calcidiol) levels are very common in patients with CKD (<15ng/mL in ~20% if GFR <30mL/min).
- Probable cause: comorbidity → sedentary indoor lifestyle → insufficient sunlight exposure → ↓ available vitamin D substrate (rather than poor dietary intake or a renal abnormality).
- KDIGO guidelines recommend screening in CKD stages 3–5.
- Serum $25(\text{OH})\text{D}$ <30ng/mL (<75nmol/L) represents insufficiency, but there is no real consensus on what defines ‘adequate’ levels.
- Usually treated with colecalciferol in formulations with calcium, e.g. calcium 600mg with D3 400 units (one tablet bd). An alternative is

colecalfiferol D3 as 20,000 unit capsules: two capsules once daily for 7 days, then maintenance $2 \times 20,000$ unit capsules $\times 1/\text{month}$. However, there is no current consensus on repletion strategies. These doses may actually have limited effects on vitamin D stores.

- The benefits are not clear, but treatment appears very safe (with little risk of $\uparrow \text{Ca}^{2+}$, $\uparrow \text{CaxP}$, or PTH oversuppression, though modest reduction in PTH may be seen).

Box 3.3 Vitamin D: beyond mineral metabolism

- Vitamin D-dependent genes are influenced through an intracellular vitamin D receptor (VDR).
- In addition to its 'classical' role in mineral metabolism, vitamin D is now known to exert various non-classical effects on cell function, including differentiation, proliferation, and apoptosis.
- This occurs across a variety of cell types (including leucocytes, cardiac myocytes, skeletal muscle cells, and pancreatic islets).
- Vitamin D is involved in immune and inflammatory responses, the RAS, and development of myocardial hypertrophy.
- It has been implicated (on epidemiological and biological evidence) in the pathogenesis of several disorders, including psoriasis, various cancers, diabetes mellitus, and $\uparrow \text{BP}$.
- 25(OH)D (calcidiol) is the major circulating form of vitamin D and is measured in routine lab testing. Circulating $1,25(\text{OH})_2\text{D}$ (calcitriol) levels are 1,000-fold lower and much more difficult to estimate.
- 25(OH)D may have benefits independent of renal conversion and is a better indicator of overall vitamin D status than $1,25(\text{OH})_2\text{D}$.

Newer vitamin D analogues

- Much attention has been given to the development of vitamin D analogues that suppress PTH, with less propensity to hypercalcaemia.
- Various mechanisms are proposed for this selective action, including less GI Ca^{2+} absorption.
- They are members of a group of compounds known as vitamin D receptor agonists (VDRAs) or 'active vitamin D compounds'.
- Many have shown potential in the experimental setting, and a few are available for clinical use (e.g. paricalcitol, 22-oxacalcitrol, and doxercalciferol).
- Widely used outside the UK, especially the USA and Japan.
- They potently suppress PTH, but $\uparrow \text{Ca}^{2+}$ and $\uparrow \text{CaxP}$ do still occur.
- Advantages over calcitriol and alfacalcidol remain unproven, though there may be marginal benefits.
- 📌 A large retrospective cohort study suggested a possible survival advantage for patients treated with paricalcitol.
- A therapeutic trial may be warranted in patients prone to $\uparrow \text{Ca}^{2+}$.
- Paricalcitol is given IV on dialysis (initially, dose is baseline PTH in pg/mL divided by 80). An oral formulation is also available.
- Doxercalciferol (not available in the UK) can be given IV or oral.
- Further randomized prospective studies are awaited.

CKD-MBD: calcimimetics

The calcium-sensing receptor (CaR)

First cloned in 1993, the CaR is constitutively expressed across multiple cell types and credited with roles in many aspects of cell function. Its main purpose is the control of extracellular Ca^{2+} concentration and regulation of steady state PTH secretion.

Calcimimetic agents

- Small molecules that bind to the parathyroid CaR and mimic the effect of \uparrow extracellular Ca^{2+} :
 - Type I: include Ca^{2+} itself and other cationic compounds. Directly activate the CaR.
 - Type II: not strictly agonists but allosteric modulators that \uparrow CaR sensitivity to ambient Ca^{2+} . Cinacalcet is currently the only calcimimetic available for clinical use.
- Calcimimetics \downarrow PTH, with a simultaneous \downarrow in serum Ca^{2+} .
- Parallel reductions in PO_4 and CaxP are also seen. In this respect, they differ importantly from other available treatments (see Table 3.15).
- Side effects: dose-dependent upper GI intolerance, modest \downarrow Ca^{2+} frequent (though rarely problematic). Despite the ubiquitous distribution of the CaR, CNS, cardiac, and other side effects not evident.
- Evidence for clinical efficacy using biochemical endpoints is unequivocal and has been shown to facilitate improved compliance with international Ca^{2+} , PO_4 , and PTH targets.
- \downarrow risk of parathyroidectomy, fracture, and cardiovascular hospitalization in short-term studies.
- There is evidence that cinacalcet may improve CV calcification (large vessels and cardiac valves). However, its impact on important CV outcomes remains unknown; in the EVOLVE study, it did not reduce risk of death or major CV events in dialysis patients with moderate to severe secondary hyperparathyroidism.

But:

- Expensive. Uptake in many countries likely to be limited (a NICE guideline in the UK effectively restricts their use to refractory \uparrow PTH where parathyroidectomy is contraindicated).

Role

More data are needed to decide where need is greatest.

- From the biochemical standpoint, therapy (vitamin D or calcimimetic) can be chosen, according to the clinical phenotype of the patient (see Table 3.16).
 - The 'vitamin D phenotype': the SHPT patient in whom serum Ca^{2+} , PO_4 , and CaxP product are all low normal or subnormal. Vitamin D therapy is usually effective in bringing biochemical parameters to target. Risk of \uparrow Ca^{2+} or \uparrow PO_4 is relatively low.
 - The 'calcimimetic phenotype': potentially more difficult to treat. Here, SHPT is accompanied by a high normal or frankly elevated Ca^{2+} , often with \uparrow PO_4 and CaxP product. Treatment with vitamin D will \downarrow PTH but aggravate \uparrow Ca^{2+} and \uparrow PO_4 .

- Vitamin D and calcimimetics work well together. Their modes of action at the level of the parathyroid are different, and effects on PTH suppression appear additive. Calcimimetics may ↓ serum Ca^{2+} , 'making room' for the use of vitamin D analogues.

Dosing: cinacalcet (Mimpara® UK, Sensipar® USA)

Oral; initially, 30mg od, increased incrementally (60mg, 90mg, 120mg, 180mg), as necessary, to maintain target PTH. Check Ca^{2+} 2 weeks after starting treatment and after any dose change. Hypocalcaemia may require dose reduction. Ca^{2+} usually checked monthly for first 6 months and PTH 2–3-monthly.

Table 3.15 Relative actions of current treatments on calcium, phosphorus, CaxP, and PTH concentrations

	Calcium-based binder	Calcium-free binder	Vitamin D sterols	Calcimimetics
PTH	↓↓	↓	↓↓↓	↓↓↓
Calcium	↑↑	↔ or ↑	↑	↓
Phosphate	↓↓	↓↓	↑	↓
CaxP	↓ or ↑	↓	↑	↓

Table 3.16 The two clinical phenotypes of CKD-MBD frequently encountered (designated by appropriate treatment)

	Calcium	Phosphorus	CaxP
'Vitamin D phenotype'	Low normal or low	In target	In target
'Calcimimetic phenotype'	High normal or high	Above target	High

CKD-MBD: parathyroidectomy

► An elevated PTH alone is not an indication for parathyroidectomy.

Indications

- Tertiary or autonomous hyperparathyroidism: failure of hyperplastic, overactive glands to suppress adequately in response to optimal medical therapy.
- Manifests clinically as ↑ PTH (usually >500pg/mL), with persistent ↑ Ca²⁺.
- PO₄ and alkaline phosphatase are usually raised.
- If calcium is low or normal, ↑ PTH indicates SHPT, and further medical treatment is necessary.
- Calcimimetic therapy (📖 p. 252) may prove to have a role in reducing the need for parathyroidectomy and may be an alternative in those in whom surgery has failed, is refused, or is deemed too high risk.
- Inappropriate parathyroidectomy may have deleterious consequences for the skeleton (→ low turnover disease).

Pre-op considerations

Imaging. Isotope scans (e.g. MIBI) allow localization of the parathyroid glands prior to surgery and identify ectopic (e.g. retrosternal) tissue. USS and CT can also be helpful (speak to your surgeon).

ENT. All patients should have their vocal cords visualized preoperatively—there is a risk of damage to the recurrent laryngeal nerve during surgery, so pre-existing dysfunction needs documentation.

Prevention of 'hungry bone syndrome'. Most likely if bone turnover is very high (↑ alkaline phosphatase or subperiosteal resorption on X-ray. High doses of active vitamin D pre-op (e.g. alfacalcidol 5 micrograms daily for 5 days) attenuates/prevents rapid and severe falls in Ca²⁺ post-operatively (caused by calcium influx into bone).

Post-op considerations

Haemorrhage. Rare but may cause tracheal compression. Monitor drains carefully.

Hypocalcaemia. May be profound in the days following surgery. Check Ca²⁺ 2–4h post-op, then 12h for 2–3 days. Give calcitriol or alfacalcidol 0.5–2.0 micrograms/day, with oral calcium (1–3g in divided doses). If serum Ca²⁺ falls below 1.8mmol/L or tetany develops, administer IV calcium (see Box 3.4), and continue high-dose oral vitamin D.

PTH. Measured post-operatively to confirm success (can also be measured intra-operatively).

Box 3.4 IV calcium post-parathyroidectomy

► Start IVI 10% calcium gluconate 50mL in 500mL 5% glucose or 0.9% saline, initially at 50mL/h. Recheck Ca²⁺ at +1h, and adjust infusion rate accordingly. Cardiac monitoring required.

►► If tetany, give 10mL 10% calcium gluconate 10mL (2.2mmol) IVI over 3min (⚠ extravasation—central vein preferable). Repeat if necessary or infusion as described. Cardiac monitoring required.

Parathyroidectomy technique

The amount of parathyroid tissue removed at operation can be varied.

Partial parathyroidectomy. Parathyroid tissue is deliberately left behind in an attempt to avoid the deleterious consequences of absent PTH (principally ABD). Unfortunately, further autonomous PTH secretion often necessitates repeat (and technically more difficult) surgery.

Total parathyroidectomy with reimplantation. Parathyroid tissue is implanted into an extraparathyroid site (usually the arm). This tissue is then more easily accessible if recurrent hyperparathyroidism develops. Unfortunately, parathyroid regrowth in the neck remains common; the implant may fail to 'take', or the implant itself may become autonomous or even locally invasive.

Total parathyroidectomy. Attempted removal of all parathyroid tissue. Leaves the patient hypoparathyroid, with risk of ABD. Serum calcium is subsequently maintained with calcitriol or alfacalcidol. Regrowth of islands of parathyroid cells is not uncommon. Small nests of residual cells often mean that serum PTH will increase with time.

Radiological ablation. Ultrasound localization and ablation through ethanol injection has met with limited success. Direct injection of active vitamin D compounds into the largest gland(s) is successfully used in some countries.

Calcific uraemic arteriolopathy (calciphylaxis)

Definition

Calcific uraemic arteriolopathy (CUA), or calciphylaxis, is a small vessel vasculopathy involving mural calcification, with intimal proliferation, fibrosis, and thrombosis. It occurs predominantly in individuals with renal failure and results in ischaemia and necrosis of skin, soft tissue, visceral organs, and skeletal muscle.

Incidence

First described in 1962, but better recognition in recent years has contributed to an increasing incidence. However, recent estimates of a 4% prevalence in ESRD programmes are probably too high (closer to ~1%).

► Mortality ~45% at 1 year (almost always due to sepsis).

Pathogenesis is poorly understood. Abnormal skeletal and mineral metabolism certainly appears to play an important role, but many patients do not have uncontrolled CKD-MBD at the time of presentation.

Reduction in key inhibitors of calcification (e.g. fetuin-A, matrix Gla protein), an increase in reactive oxygen species, and inflammatory cytokines all contribute. Multiple risk factors, some of which are iatrogenic, have been documented. What creates a 'perfect storm' for the development of CUA in an individual patient remains undetermined.

Risk factors

- Uraemia (though also seen post-transplantation and in primary HPT).
- ♀ > ♂.
- Diabetes mellitus.
- ↑ Calcium phosphate product.
- ↑ PTH.
- Duration of dialysis therapy.
- Vitamin D analogue and calcium-based phosphate binder usage.
- Elevated alkaline phosphatase.
- Caucasian race.
- Obesity.
- Malnutrition and low serum albumin.
- Warfarin.
- Protein C and/or S deficiency.
- Liver disease.
- Corticosteroid treatment.

Presentation

- **Painful** erythematous livedo reticularis-like skin patches and plaques, with violaceous mottling and subsequent ulceration. Panniculitis and 2° infection follow.
- Surrounding soft tissue often feels hard and plaque-like.
- Two overlapping patterns have been described:
 - Ulcers on the trunk, buttocks, or thighs (over adipose tissue in more obese patients).

- Ulceration on the extremities (often in thinner malnourished patients).
- Not just a cutaneous disease—may occur in arterioles supplying other organs (lung calcification on the CXR is common).
- Bone scans often show increased uptake over lesions.
- Awareness is often half the journey to diagnosis.
- Skin biopsy is characteristic: medial calcification of cutaneous arterioles, intimal hyperplasia, endovascular fibrosis, inflammation, thrombosis, luminal occlusion, necrosis, and panniculitis. Calcium stains should be undertaken.
- Differential diagnosis: vasculitis, pyoderma gangrenosum, ulceration 2° to macrovascular disease, cholesterol emboli.

Treatment

⚠ No treatment is of proven benefit.

- ► Appropriate analgesia.
- Scrupulous wound care and avoidance of trauma (e.g. subcutaneous injections).
- Aggressive treatment of sepsis.
- Lower CaxP: avoid calcium-based binders; discontinue vitamin D analogues; daily dialysis; lower dialysate Ca^{2+} .
- Aggressive control of PO_4 with non-calcium-based binders and dietary restriction.
- Parathyroidectomy (or cinacalcet) *may* help if \uparrow PTH and \uparrow CaxP.
- Optimize tissue perfusion; revascularize, as necessary.
- Stop warfarin.
- Investigate for primary hypercoagulable/prothrombotic state.
- Hyperbaric oxygen has been used successfully.
- Interest in sodium thiosulphate has grown recently. Case series have demonstrated enhanced pain relief and wound granulation. Administered IV, with minimal side effects at low infusion rates (\rightarrow nausea, abdominal pain, diarrhoea). Two mechanisms of action:
 - It is a powerful antioxidant.
 - It sequesters calcium ions to form soluble calcium thiosulphate complexes, thus preventing calcium deposition.
- Bisphosphonates have been used but may have deleterious effects on bone metabolism in patients with pre-existing low turnover disease.
- Steroids probably of no benefit (⚠ sepsis).

There are several calciphylaxis registries to which clinicians are encouraged to submit both patient data and tissue specimens. For example, the UK calciphylaxis registry is part of the international collaborative calciphylaxis network and can be accessed at <http://www.calciphylaxis.org.uk>.

Diet and nutrition in CKD

Dietary advice is extremely important in the management of CKD and the maintenance of broader health in CKD patients.

Measurement of nutritional status

► No single parameter should be considered in isolation.

Assessment should include:

- **History and examination** to identify ongoing medical problems that may limit nutritional intake—psychosocial issues may be important.
- **Dietary interview or diary.** Quantitative intake of nutrients.
- **Subjective global assessment (SGA).** SGA is based on subjective and objective assessment of several patient parameters, including factors in the history and examination, GI symptoms, body weight patterns, functional capacity, and the presence of comorbid conditions that may influence nutritional requirements. Patients are assigned to one of three nutritional states: (i) well nourished; (ii) mild to moderately malnourished, or (iii) severely malnourished. This simple score is well validated in CKD and powerful enough to predict outcome.⁴
- **Anthropometric measurements.** BMI, skinfold thickness, estimated % weight loss, and mid-arm muscle circumference.
- **Serum albumin.** Reflects not only protein intake, but susceptible to changes with inflammation or infection. ► A strong predictor of future mortality in new starters on dialysis.
- **Adequacy of dialysis.** Inadequate dialysis is a common contributing factor to malnutrition (uraemic toxins are anorectic and proinflammatory). Dialysis adequacy should be assessed in conjunction with the normalized protein catabolic rate (nPCR), which is a measure of the rate of urea formation. When a patient is in steady state, urea formation correlates with protein intake and protein breakdown.

Fluid restriction

- CKD stages 4–5. Fluid and salt restriction are often important to prevent volume overload.
- On dialysis. When the urine output drops, fluid restriction is vital to minimize weight gains. Aim for weight gains of 1–1.5kg or less/day. In an anuric patient, this means a fluid restriction of 750–1,000mL. ► This must be combined with salt restriction.


Protein intake

- Intake averages ~80g/day in the developed world, although requirements may be only 50g.
- A low-protein diet has been shown to slow the progression of renal failure in patients with CKD (📖 p. 208). Set against this is the danger of patients reaching dialysis with significant malnutrition. Most advocate no more than **moderate** protein restriction. Daily protein targets:
 - 0.8–1.0g/kg per day for CKD stages 4–5.
 - 1.2g/kg per day when on dialysis.
- Protein sources include meat, fish, eggs, milk, nuts, pulses, and beans.

Carbohydrate intake

- Adequate energy intake is essential for patients with CKD, especially those undergoing protein restriction.
- Target 30–35kcal/kg per day.
- Sources: mainly complex carbohydrates, some from mono- or polyunsaturated fats. Combining a diabetic diet with a renal diet can be difficult and requires expert support.
- Examples: sugar, jams, marmalade, specialist high-energy renal drinks.

Phosphate restriction (see also p. 246)


- The kidney is the main route of phosphate excretion. Aim to restrict dietary phosphate to 0.8–1g/day, and target a serum phosphate in the normal physiological range.
- Prescribe phosphate binders if dietary restriction alone fails ( p. 246).
- Phosphate-rich foods include all protein-containing foods, making phosphate restriction difficult to achieve. Examples: milk, cheese, custard, yogurt, ice cream, cola, chocolate drinks, beer, liver, baked beans, dried peas and beans (e.g. chick peas), nuts, wholegrain products, bran cereals, and, many, many convenience foods.

Potassium restriction

- Typical UK intake ~50–120mmol/day. With failing renal function, K^+ excretion falls, making restriction necessary (esp. in patients taking ACE-I, ARBs, and/or mineralocorticoid antagonists, such as spironolactone).
- K^+ -rich foods include dairy products, potatoes (baked, chips, and crisps), some fruits (bananas, grapes, dried fruit, fresh pineapple), fresh fruit juice, tomatoes, sweet corn, mushrooms, chocolate, and coffee.

Salt restriction

- Typical UK intake ~150–200mmol/day (or 9–12g).
- This is a vast excess over physiological needs.
- Salt restriction is helpful if \uparrow BP \pm volume overload (helps reduce thirst and hence fluid intake). Aim for an intake of <100mmol/day (5–6g).
- Na^+ -rich foods include cheese, salted butter/margarine, salted meat (bacon, ham, corned and luncheon meats), tinned meat, vegetables and soups, crisps, soy sauce, many breads and cereals, salted nuts, processed foods, and packaged meals.

There are several resources on the internet that can help patients and their families to understand and adjust to these dietary restrictions. The nutrition section of the US National Kidney Foundation website is a good starting point ( <http://www.kidney.org>), and several cookbooks are available.

Reference

- Steiber A, Kalantar-Zadeh K, Secker D, et al. (2004). Subjective Global Assessment in chronic kidney disease: a review. *Journal of Renal Nutrition*, **14**, 191–200.

Malnutrition in CKD

Malnutrition is common in CKD (affecting up to 50% of dialysis patients) and a powerful predictor of survival. Contributors include:

- Anorectic uraemic toxins (e.g. leptin).
- Chronic low-grade inflammation.
- Dietary restrictions (low-protein diet, unbalanced low-phosphate diet).
- Medication (phosphate binders, oral iron).
- Dialysis itself (esp. CAPD where protein losses into the dialysate may be 1–2g/L or ~10g/day; this would be considered nephrotic range if lost in the urine!).

Managing malnutrition in the CKD patient

- Assess the severity of malnutrition (📖 p. 258).
- Measure current nutritional intake.
- Address correctable factors:
 - ► Correct under-dialysis (e.g. change modality, improve access, increase treatment time).
 - Seek and treat occult infection.
 - Investigate and treat GI problems, e.g. gastroparesis.
 - Define and intervene if psychosocial problems.
- Consider dietary supplements:
 - Wide range available.
 - Renal-specific oral supplements are low in K^+ and PO_4 and are also concentrated (limiting the volume of fluid).
- Overnight nasoenteral (or PEG) feeding may be beneficial in more severe cases of malnutrition when adequate oral intake cannot be maintained.
- IDPN (intradialytic parenteral nutrition). Given on dialysis, it provides amino acids, glucose, and lipids. It is not a substitute for oral supplements but can deliver ~1,500kcal/session (of which at least ~500kcal are lost in dialysate!). However, it can be a useful adjunct if the patient is able to manage 50% of the desired daily intake by mouth. Expensive.
- 🧪 Amino acid containing PD solutions (Nutraeneal®) may offer benefit in malnourished PD patients.
- Total parenteral nutrition (TPN) should be reserved for those who cannot be fed enterally. Electrolyte quantities (particularly potassium, phosphate, and magnesium) should be reduced and monitored daily.
- 🧪 Appetite stimulants/anabolic agents are of uncertain benefit:
 - Growth hormone (costly and long-term benefit uncertain).
 - Nandrolone (an androgen).

Inflammation in CKD

Patients with CKD have ongoing low-grade inflammation, with ↑ acute phase proteins (CRP, ferritin), ↑ inflammatory cytokines, hypoalbuminaemia, and hypercholesterolaemia. Contributors include:

- Repeated infections.
- Oxidant stress (↓ levels of antioxidants, ↑ oxidative and carbonyl stress).
- Accumulation of AGEs.
- Arteriosclerosis and abnormal endothelial function.
- Malnutrition (both a cause and an effect of chronic inflammation).

Protein–energy malnutrition may coexist—there is increasing evidence that chronic inflammation and oxidant stress increase metabolic demands and predispose to malnutrition. The triad of malnutrition, inflammation, and accelerated atherosclerosis has been labelled the MIA syndrome. A vicious cycle may ensue, often culminating in death from cardiac disease. This may account for the apparent paradox that patients on dialysis with a higher BMI tend to survive longer.

Endocrine problems in CKD

Thyroid function

Tests may be difficult to interpret, as thyroid-binding globulin is lost in the urine if heavy proteinuria, causing a ↓ measured T4. Clinical assessment and measurement of T3 and TSH may be necessary for correct interpretation.

Adrenal axis function

Addison's disease is difficult to diagnose in the context of CKD, especially in dialysis patients, as the characteristic electrolyte changes may be masked by renal dysfunction and dialysis. Suspect if persistent hypotension (or postural hypotension). Many renal patients have received corticosteroid therapy, with consequent steroid-related side effects.

Sexual dysfunction (♀)

Reduced libido frequent. Comorbidity (vascular disease, diabetes) and concomitant drug treatment may be relevant. Altered body image and self-perception may also play a role, as may depression and anxiety. Offer counselling. ► Anaemia contributes to reduced libido and should be corrected. Disturbances in menstruation and fertility are common. Amenorrhoea is virtually ubiquitous at ESRD. Gynaecological assessment is often helpful.

Sexual dysfunction (♂)

Erectile dysfunction is common. It may be multifactorial (arterial disease, neuropathy, psychological factors, side effects of drug treatment). Where possible, treat the underlying cause. Testosterone deficiency is not uncommon in dialysis patients and should be corrected with replacement therapy. Phosphodiesterase inhibitors, such as sildenafil, are effective but should be avoided in patients on nitrates, with significant coronary artery disease or hypotension. Vacuum devices or penile implants may be useful, especially if a physical cause for impotence.

Hyperprolactinaemia

Elevated circulating prolactin concentrations, 2° to ↑ secretion and ↓ clearance, are common in advanced CKD. Causes galactorrhoea (♀) and gynaecomastia (♂). Bromocriptine or cabergoline may normalize levels. The contribution of ↑ prolactin to sexual dysfunction in both sexes is unclear. Other causes, such as drugs (e.g. tricyclics, metoclopramide) or a prolactinoma, may need exclusion.

Early menopause

Not associated with CKD per se but may occur in patients treated with cyclophosphamide or other cytotoxic agents.

Growth retardation in CKD





Resistance to growth hormone (GH) is an important consequence of advanced CKD. Although circulating GH levels are normal (or elevated), resistance to its action causes growth retardation in children and muscle wasting in adults. This resistance is the consequence of multiple defects in the GH/IGF-1 axis: GH receptor expression is downregulated, as is the activity of the downstream JAK/STAT signal transduction pathway. The expression and activity of IGF-1 (a major mediator of GH action) are also significantly reduced. Growth delay can now be treated with recombinant GH. Other contributors to growth retardation are steroid therapy, malnutrition, and osteodystrophy.

CKD management overview





General advice (all stages)

- Exclude AKI.
- Explanation, education, and reassurance regarding the causes and consequences of CKD.
- Smoking cessation.
- Weight reduction if obese.
- Encourage aerobic exercise.
- Aspirin 75mg, according to 10-year CV risk estimate.
- Treat lipids, according to best practice guidelines.
- Avoid NSAIDs and other nephrotoxic drugs.
- Limit alcohol to <3 units per day (♂) or 2 units per day (♀).
- Vaccination against influenza and pneumococcus.

CKD stages 1–3

- ► Most of these patients will not progress to kidney failure, so the emphasis should be on CV risk reduction.
- Can usually be effectively managed in primary care setting.
- Suggested criteria for referral to a specialist renal service are shown on  p. 265.
- Stages 1–2—at least annual follow-up:
 - eGFR, urinalysis, and uACR/uPCR.
 - Meticulous BP control; use ACE-I (see  p. 204 for targets).
- Stage 3—at least 6-monthly follow-up:
 - USS of urinary tract if lower urinary tract symptoms.
 - eGFR, urinalysis, and uACR/uPCR.
 - Meticulous BP control; use ACE-I (see  p. 204 for targets).
 - Anaemia management. If Hb <11g/dL, exclude other causes; check iron stores, and refer for consideration of IV iron and ESA therapy ( p. 222).
 - 6-monthly check of serum calcium and phosphate.
 - PTH at baseline; 6–12-monthly if abnormal.

CKD stages 4–5

- Refer to a specialist unit (► urgently if stage 5). Late referral of patients with advanced CKD is associated with poor outcomes.
- Full dietary assessment ( p. 258).
- Anaemia management.
- CKD-MBD management ( p. 249).
- Correct acidosis ( p. 205).
- Immunize against hepatitis B.
- Information and discussion regarding future treatment choices; dialysis modalities, options for transplantation, or conservative/palliative treatment ( p. 266).

When to refer to specialist care

- What do nephrologists do for patients with CKD?
 - Diagnose and manage treatable kidney disease.
 - Identify and control risk factors for progression.
 - Manage 2° complications, such as anaemia.
 - Plan for RRT in patients progressing to kidney failure.
- It is not possible, or necessary, for all CKD patients to be seen in specialist clinics.

Referral guidelines

Even if seen for specialist review, subsequent follow-up can continue in primary care, with appropriate shared care protocols. Consider referral if:

- eGFR <30mL/min.
- eGFR <60mL/min, *and any of*:
 - Progressive fall (>5mL/min in 1 year or >10mL/min in 5 years).
 - Microscopic haematuria.
 - Proteinuria (uACR >70mg/mmol, uPCR >100mg/mmol) unless known to be due to diabetes and appropriately treated.
 - >15% decline in eGFR with commencement of an ACE-I or ARB (? renovascular disease).
 - Suspected systemic illness (e.g. SLE, myeloma).
 - Hb <11g/dL, with no other explanation.
 - Abnormal calcium, phosphate, or PTH.
 - Refractory ↑ BP (>150/90 despite three antihypertensive agents).
- eGFR >60mL/min *and* other evidence of renal disease/damage:
 - uACR >70 or uPCR >100mg/mmol.
 - uACR >30 or uPCR >50mg/mmol and microscopic haematuria.
 - Abnormal renal imaging, e.g. renal cysts.
- Other indications:
 - ► Suspected acute kidney injury.

Advanced CKD care

The transition from CKD to ESRD is a physically and psychologically demanding time (see Fig. 3.8). Such patients are best cared for by a multidisciplinary team (see ~6-weekly, more often in the latter stages), with attention to:

- Ongoing measures to minimize rate of progression.
- Dietary intervention.
- Active management of complications (anaemia, CKD-MBD, malnutrition).
- Pre-dialysis counselling: choice of dialysis modality, individualized advice and support in the decision-making process.
- Pre-dialysis and pre-transplant information and support sessions. Ideally involving expert patients (peer supporters); see 'Education'.
- Preparation for transplantation: education; identify potential living donors. ► Pre-emptive transplantation should be the goal, if possible.
- Formation of dialysis access (surgical review at least 6 months prior to start of dialysis is desirable).
- Access to palliative services for those who elect not to undertake dialysis treatment or to help manage symptom burden.
- Timing initiation of dialysis—avoid symptomatic uraemia.

Composition of an advanced CKD clinic

- Nephrologist.
- Specialist nurses (e.g. pre-dialysis counselling, anaemia management, pre-transplant assessment, dialysis access preparation, palliative care).
- Renal dietitian.
- Vascular access and transplant surgeon.
- Pharmacist.
- Social worker.
- Counsellor.

Education

- Defined education programme, involving specialist nurses and expert patients (peer support).
- Start when eGFR ≤ 20 mL/min (ideally 12 months prior to RRT).
- Use a variety of techniques to impart information—1:1 sessions, group education, culturally appropriate written material, visual aids (DVDs, image library), practical demonstrations, web-based material.
- Include information on:
 - Functions of the kidney.
 - Implications of impaired kidney function.
 - Cardiovascular risk and lifestyle modification.
 - Symptoms to expect as function declines.
 - Concept of integrated care—they may need to move between different treatment modalities over time.
 - Detailed discussion on different dialysis options, with practical demonstrations and visits to PD and HD departments.
 - Transplant options.
- Define treatment plan when eGFR approaches 15 mL/min—allows for timely access preparation and assessment for a home-based therapy, if required.

When to start dialysis

- The IDEAL study compared 'early' (eGFR 10–15mL/min) vs 'late' (5–7mL/min) commencement of dialysis and showed no survival benefit. However, quality of life is just as important a consideration.
- Guidelines recommend considering the commencement of dialysis when GFR <15mL/min. However, this requires careful discussion with the patient and consideration of the risks and benefits associated with RRT. Symptoms and signs of advanced CKD (e.g. persistent nausea and vomiting, anorexia, malnutrition, volume overload, restless legs), comorbidity, functional status, and physical and the psychological and social consequences of starting dialysis all need to be taken into account.
- GFR \leq 5–7mL/min, whether symptomatic or not.
- Refractory hyperkalaemia, acidosis, pulmonary oedema, pericarditis, encephalopathy, and neuropathy are all (urgent) indications for dialysis (the aim should be to start dialysis **before** these are present).
- ► Pre-emptive transplantation is the treatment of choice of ESRD. Consider when GFR <20mL/min. If not possible, discuss whether a home-based therapy (HD or PD) is suitable. Early planning leads to improved choice.

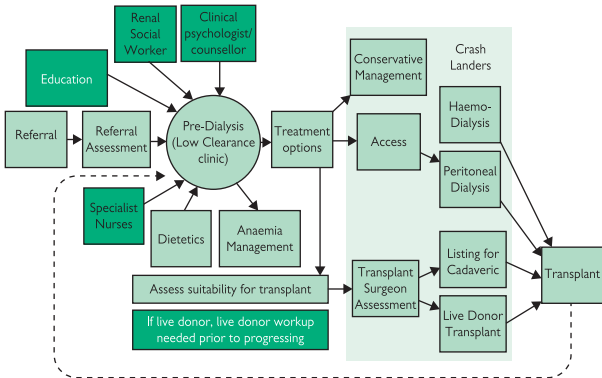


Fig. 3.8 A pathway of care for advanced CKD. 'Crash landers' (or unplanned starters): these individuals are unknown to renal services and present as emergencies within 90 days of needing RRT (~25–30% of patients entering ESRD programmes annually). They miss out on pre-emptive education, usually start on HD with temporary vascular access, and have worse outcomes in general. Reproduced from *Focus on Preparing for End Stage Renal Disease* with kind permission of the NHS Institute for Innovation and Improvement.

Conservative treatment of CKD: symptomatic management of ESRD

As CKD advances, so does the symptom burden. Over half of patients who follow a conservative (i.e. non-dialytic) management pathway report poor mobility, weakness, pain, and pruritus, and over one-third report poor appetite, difficulty sleeping, drowsiness, dyspnoea, and constipation. With proactive identification and management, the distress and disability caused by these symptoms can be considerably eased (see Table 3.17). Many units now run a service specifically for such patients, concentrating resources and care to provide physical and social support. Patients may become increasingly reliant on family members and other carers. District nurses, social workers, home care teams, physiotherapists, occupational therapists, and hospice services should be involved, as required.

Table 3.17 Symptom control in advanced CKD

Symptoms	Causes	Treatments	Comment
Anorexia	Constipation, oesophagitis, nausea, dry mouth, gastroparesis, oral candidiasis, dysphagia, anxiety	Relax dietary restrictions	
		Artificial saliva, ice to moisten mouth	
		Dexamethasone 2–4mg od for up to 4 weeks	
		Medroxyprogesterone 100–200mg daily	Mode of action unknown. Avoid if thromboembolic risk
		Thalidomide 100mg od	SE: neuropathy
		Fluconazole 50–100mg od	If oral candidiasis
Taste disturbance		Consider trial of a zinc salt, e.g. zinc sulfate	
Dyspepsia		Lansoprazole 30mg od or other PPI	
		Ranitidine 150mg bd	
Constipation	Multifactorial Adequate fluid intake and dietary advice are important	Lactulose 10–20mL bd	Osmotic
		Senna 2–4 tablets bd	Stimulant
		Bisacodyl 5–10mg od/bd	Stimulant
		Docusate sodium 100–200mg bd	Stimulant and softener; good choice with opiates
		Macrogols 1–3 sachets daily	Osmotic

Symptoms	Causes	Treatments	Comment
Dyspnoea	Treat anaemia, fluid overload, acidosis, anxiety	IV iron and ESAs, diuretics, bronchodilators, O ₂ advice on sleeping position	
		Lorazepam 0.5mg sublingual 4–6h Midazolam 2.5mg SC 4–6h	Benzodiazepines can be a useful adjunct in dyspnoea, especially if anxiety a factor
Nausea and vomiting	Multifactorial	Haloperidol 0.5–2mg PO od	
		Metoclopramide 5–10mg tds PO	
		Domperidone 10–20mg tds PO	
		Ondansetron 4–8mg bd PO	Constipating
Dry skin and pruritus	Control PO ₄ and ↑ PTH ₄	Emollients (e.g. aqueous cream, E45®, Diprobase®), Oilatum® in bath water	
		Antihistamines, e.g. cetirizine 5–10mg od, chlorphenamine 4mg qds	
		Capsaicin 0.025% cream if localized	SE: burning sensation
		Thalidomide 100mg nocte if intractable	SE: neuropathy
Anxiety and depression		Expert counselling and psychological support	Anxiety
		Lorazepam 0.5–1mg PO prn	
		SSRIs (e.g. citalopram 20mg od)	Low mood
Confusion	► Check for reversible causes	Metabolic (e.g. ↓ Na ⁺ , ↑ Ca ²⁺)	
		Constipation	
		Drug toxicity	Has an incorrect dose been prescribed for level of renal function?
Restless legs	Correct anaemia, iron deficiency and ↑ PO ₄	Clonazepam 250–500 micrograms nocte	
		Co-careldopa 12.5/50 nocte	May give short-term relief, then exacerbate
		Pergolide 25 micrograms nocte	SE: nausea

Conservative treatment of CKD: general

The decision not to have dialysis

- Patients who start dialysis with significant comorbidity and functional dependence typically have a short survival time, which may be filled with hospital admissions, painful illnesses, and unpleasant procedures.
- For such patients, continuing supportive care without commencing dialysis may allow a better quality of life, with little or no reduction in life expectancy.
- The decision whether to commence dialysis at ESRD is ultimately made by the patient (assuming the patient has capacity). The renal team has a duty to ensure that this decision is as informed as possible by explaining the implications of withholding dialysis and the pros and cons of commencing it. Family members should also be involved.
 - The process cannot be rushed. A decision not to accept dialysis should be made over time and be consistently held.
 - Patients may (and often do) change their minds (in either direction).
 - If severely uraemic, a patient may be unable to be involved in the decision-making process.
 - It can be difficult to determine whether debility is uraemic in origin (and ∴ potentially reversible) or 2° to pre-existing comorbidity.
 - Patients referred late have no time to go through the pre-dialysis counselling process and may be denied the opportunity to make informed decisions about their care.

Withdrawal of dialysis

- As with the decision of not to start dialysis, the decision to withdraw should be made by the patient with the help and support of the multidisciplinary team.
- Withdrawal means that death will probably occur within a few days if the patient has no significant residual renal function. The decision to withdraw may be prompted by a catastrophic medical event (e.g. a CVA, loss of vascular access). Less often, it is the culmination of a number of smaller events, which have, in the view of the patient, had unacceptable consequences for their quality of life.
- Depression should be looked for and treated.
- The decision to withdraw should be made over a period of time and be held consistently.

Care of the dying patient

- The patient should be able to die peacefully and with dignity, in a place of his or her choosing, surrounded by loved ones. This requires planning so that care at home, in a hospice, or in hospital can be arranged at short notice.
- Agreed care pathways may facilitate the management of the last few days of life.
- Family support: before death, family members may be involved in the physical care of the patient and need support and help. At the time of death and afterwards, help should be available to cope with the grieving process (this will need to be culturally appropriate).

Analgesia in advanced CKD

- Pain is under-recognized and undertreated in patients with kidney disease. The fact that it is more difficult to treat is no excuse for inadequate management.
- Opiate analgesia is very effective but must be used with caution. Accumulation → significant side effects: constipation, drowsiness, confusion, respiratory depression, twitching, and seizures.
- If uncertain, seek expert pain advice.
- Use the World Health Organization (WHO) analgesic ladder.

Step 1

- Paracetamol: safe and effective in CKD. Requires no dose adjustment.
- NSAIDs:
 - Usually contraindicated (pre-dialysis → deterioration in GFR; dialysis → ↓ residual renal function).
 - Can be an effective short-term measure, esp. musculoskeletal pain.
 - Co-prescribe a PPI, as gastritis common.

Step 2

- Tramadol: 90% renally excreted, so ↓ dose and ↑ interval (start 50mg 12h).
- Avoid codeine and dihydrocodeine if eGFR <15mL/min. ⚠ Hepatic metabolites accumulate in CKD. If used, reduce dose by 50%.

Step 3

Drug choice will depend on acuteness and severity of pain, desirable route of administration, and local availability. SC can be used for rapid relief, with subsequent conversion to oral or transdermal.

- Morphine or diamorphine:
 - ⚠ Avoid, if possible, as breakdown products accumulate.
 - If used short-term—morphine: initially 2.5mg SC 4–12h prn.
- Diamorphine: initially 1.25mg SC 4–12h prn.
- Buprenorphine:
 - Effective. Nausea a prominent side effect.
 - 200–400 micrograms sublingual or transdermal patches.
- Alfentanil:
 - First-line SC opioid in renal failure.
 - SC 250 micrograms 2–4h.
 - Can be given as a continuous infusion.
 - Use fentanyl for breakthrough, as alfentanil has short half-life.
- Fentanyl:
 - <10% renally excreted.
 - SC 25 micrograms 3–6h. Lozenges for breakthrough pain. Transdermal patch very effective once pain controlled by other means.
- Hydromorphone: initially 1.3mg orally 6–8-hourly + 1.3mg prn for more severe pain.
- Oxycodone: start with OxyNorm® (initially 2.5mg 8–12h) for rapid pain control, and convert to OxyContin® for less frequent administration.
- Methadone: hepatic metabolites excreted in faeces. However, large interpatient pharmacokinetic variability means it should probably be reserved for use by physicians familiar with its eccentricities.

Dialysis

- RRT: a brief history 274
- Dialysis: an introduction 276
- Haemodialysis (HD) 278
- Haemodialysis apparatus 280
- Dialysate 282
- Dialysers and membranes 284
- Dialysis prescription and adequacy 286
- Anticoagulation 290
- Dialysis access: AVF/PTFE 292
- Haemodialysis access: lines 296
- Fluid balance on dialysis 300
- Intradialytic hypotension 302
- Extended hours HD treatments 304
- Other HD complications 308
- Peritoneal dialysis (PD) 312
- Types of PD 314
- PD fluids 316
- Prescribing PD 318
- Peritonitis 320
- Peritonitis: management 322
- Other PD complications 324
- PD adequacy 328
- Ultrafiltration (UF) failure 332
- The well PD patient 334

RRT: a brief history

It is only in the last 50 years that it has become possible to keep ESRD patients alive. The challenge now is to allow them a quality of life that approaches, or matches, that of the general population.

1861	Term 'dialysis' first coined
1913	First 'artificial kidney' built and used in animals
1923	First human PD
1924	First human HD
1933	First (unsuccessful) cadaveric kidney transplant
1946	First dialysis in the UK
1946	PD used to treat ARF
1947	First cadaveric kidney transplant. Patient had pregnancy-related ARF. Graft placed externally (on arm) and lasted 6 days (and ARF had resolved)
1948	Kolff–Brigham dialyser developed—a major technological advance
1948	HD used to treat ARF in the Korean war
Early 1950s	Cadaveric transplants for CRF (into thigh with ureterostomy); no immunosuppression—all rejected within 6 months
1954	First successful monozygotic twin transplant*
1959	Non-monozygotic twin transplant (with whole body irradiation as immunosuppression)
1959	Intermittent PD, with repeated abdominal puncture, described
1960	Peter Medawar and Franc Burnet received Nobel Prize for describing principles of immunologic rejection
1960	Scribner shunt—the first access device enabling repetitive use
1960	First long-term HD patients (Seattle, USA)
1962	6-mercaptopurine used successfully for immunosuppression
1963	Steroids and azathioprine used with greater success
1964	First home HD patients
1966	Cross-matching introduced
1966	Forearm AVF developed
1967	First successful liver and heart transplants
1968	Tenckhoff PD catheter introduced
1975	Haemofiltration introduced
1976	Introduction of ciclosporin—1-year graft survival dramatically improves
1977	Continuous AV haemofiltration described
1976	Continuous ambulatory peritoneal dialysis (CAPD) introduced
1982	First kidney pancreas transplant
*1990	Joseph Murray awarded Nobel Prize for his pioneering transplant work
2013	First successful rodent transplantation of a bioengineered kidney

Dialysis: an introduction

Normal functioning kidneys:

- Remove excess salt, water, and acid.
- Remove or regulate other electrolytes (e.g. K^+ , Ca^{2+} , Mg^{2+} , PO_4).
- Remove waste products of metabolism (Ur and Cr are measured routinely, but there are many others).
- Make erythropoietin.
- 1α -hydroxylate (and \therefore activate) vitamin D.

Dialysis acts as surrogate for all but the last two of these (which can be achieved pharmacologically). Even at best, it is only partially effective. Transplantation more completely (but still partially) replaces normal kidney function and should be regarded as the optimum treatment of ESRD. Transplanted patients survive longer and have a better quality of life. However, not everyone is fit for transplantation—ESRD patients are often frail, with appreciable comorbidity, especially vascular disease.

Registry data and international comparisons

In the UK there are now 23,500 prevalent HD patients (365 PMP) and ~4000 PD patients (61 PMP). Annual dialysis growth has been declining in recent years and now stands at ~2% for HD (with a decrease of ~2% for PD). The median age of prevalent patients is 58 years. Incidence rates have been stable since 2006, but with an increase in patients > age 65 (Fig. 4.1).

Resources

Dialysis (and transplantation) are expensive. The cost of RRT is estimated to account for 1–2% of the total NHS budget, even though it affects just

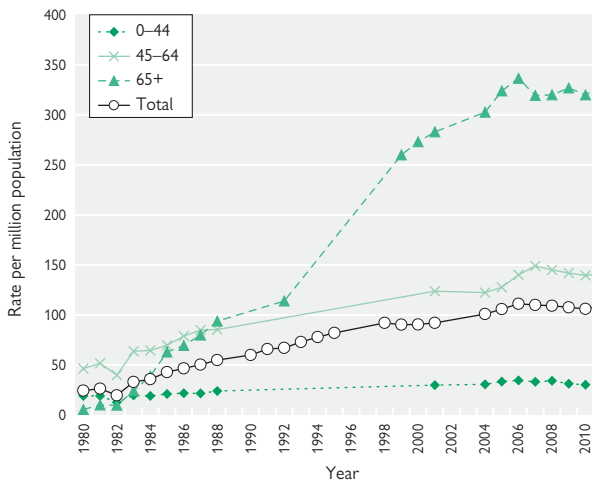


Fig. 4.1 UK incident RRT rates between 1980 and 2010. Reproduced from UK Renal Registry 15th Annual Report: UK Renal Registry (2012), with permission.

0.05% of the population. The tariff for hospital or satellite based HD in the UK is currently ~£23,000 per annum, depending on locality (with a 'best-practice' supplement for those dialysing through an AV fistula). Although all modalities are expensive, transplantation is the most cost effective (but only after the first year). In the US (2011), Medicare expenditure on RRT rose to ~\$30 billion (~\$25 billion HD, \$1.5 billion PD, ~\$3 billion transplantation). Per patient per year the costs were: HD ~\$88,000, PD ~\$72,000, transplant ~\$33,000.

International data

- Prevalence rates of RRT vary across Europe and are often higher than in the UK.
- In the USA there were ~430,000 prevalent dialysis patients in 2011 (HD ~395,000, PD ~31,500). However, the annual growth rate (3.4%) was the lowest for 30 years. Total ESRD prevalence was 1,901 PMP.
- ~101,000 patients started HD therapy in the US (80% of whom started on a dialysis catheter, rather than with an AVF. An astonishing 40% had not seen a nephrologist prior to reaching ESRD), ~7,500 started PD and ~2,500 received a pre-emptive transplant. 16% started RRT with an eGFR of 15mL/min or over.
- The overall adjusted incidence of ESRD in the US was 357 PMP (Caucasian 280 PMP, Black 940 PMP, Native American 453 PMP, Asian 399 PMP, Hispanic 518 PMP). Diabetes mellitus was the most common cause of ESRD, followed by hypertension (source: USRDS Annual Data Report 2013).

Survival

RRT patients age 30–34 have a mortality rate 25x higher than the age matched general population (for patients age >85 it is still ~3x higher). Median survival for patients starting RRT in the age group 45–54 is currently 10.5 years, for age 55–64 it is 5.6 years and for age 65–74, 3 years. The relative risk of death for prevalent RRT patients (UK 2010) was 6.6. Diabetic patients have worse survival than non-diabetic patients. The survival in older age groups is only slightly better than in patients with lung cancer. (See Fig. 4.2 for Kaplan–Meier curve.)

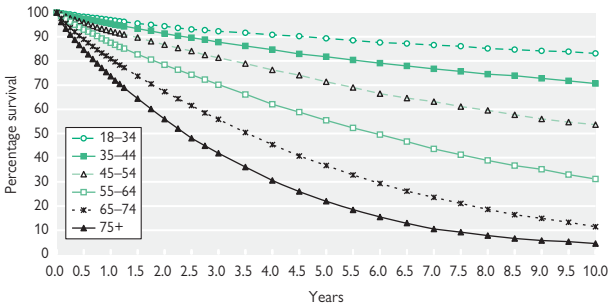


Fig. 4.2 Kaplan–Meier Curve. Survival of incident patients (unadjusted) 1997–2010 cohort (from day 90), without censoring at transplantation. Reproduced from UK Renal Registry 15th Annual Report: UK Renal Registry (2012), with permission.

Haemodialysis (HD)

Overview

- During dialysis, blood is exposed to dialysate (with physiological concentrations of electrolytes) across a semi-permeable membrane.
- Small molecules such as Ur (MW 60Da), Cr (MW113Da) and electrolytes pass through pores in the membrane. Large molecules such as albumin (MW 60,000Da), IgG (MW 140,000Da) and blood cells do not.
- Concentration differences across the membrane allow molecules to diffuse down a gradient. This allows waste products to be removed and desirable molecules or ions (e.g. HCO_3^-) to be replaced.
- Water can be driven through the membrane by hydrostatic force (ultrafiltration, UF).
 - By varying the pressure gradient across the membrane (transmembrane pressure, TMP), water removal can be controlled.
 - In addition to a means to remove water (~1–4L) that has accumulated between dialysis sessions (ingestion of fluid, foods, and by-product of metabolism), UF can also be used as a means of solute clearance by convection.

What is required for haemodialysis?

- Dialysis membrane (📖 p. 284): a biocompatible membrane with adequate surface area/permeability for solute clearance and ultrafiltration.
- Dialysate (📖 p. 282): of sufficient purity and containing the required concentration of electrolytes.
- Effective control and safety mechanisms (📖 p. 280): pumps for blood and dialysate flow, TMP, temperature, detection of blood leaks or air.
- Vascular access: large volumes of blood are removed from a patient, exposed to a dialysis membrane, and then returned. Options are:
 - AVF fistula: optimal form of vascular access (📖 p. 292).
 - PTFE graft: second best (📖 p. 292).
 - Tunnelled, cuffed central venous catheter: ideally not long term (📖 p. 296).
 - Temporary central venous catheter: for immediate use; e.g. in AKI. (📖 p. 180).
- Anticoagulation (📖 p. 290): prevents blood clotting in the extracorporeal circuit.

Haemodialysis and haemofiltration

Haemodialysis

- Solute clearance by diffusion (mainly).
- Dialysate is required.
- Diffusion is maximized by maintaining high-flow rates of blood and dialysate and by pumping the two through the dialyser in countercurrent directions.
- Larger MW (>20kDa) molecules are generally poorly removed.
- Usually administered intermittently (e.g. 4h, 3x/week).

Haemofiltration

- Solute clearance by convection (mainly).
- Achieved by generating a TMP across the membrane.
- No dialysate required.
- Large volumes need to be filtered to achieve adequate solute clearance. This would cause hypovolaemia unless replacement fluid administered (usually pre-prepared 5–10L bags).
- Removes larger MW (30–50kDa) molecules (e.g. vitamin B12 and B2 microglobulin) more efficiently than dialysis.
- Continuous (24h) HF is associated with greater haemodynamic stability and often favoured for RRT in a critical care setting (📖 p. 174).

Haemodiafiltration

- Enhances clearance of middle molecules by combining diffusion (HD) and convection (HF) to obtain the best from both modalities. See figure 4.x.
- Both dialysate and replacement fluid are required. Online HDF (OL-HDF) uses ultrapure dialysate produced by the dialysis machine as replacement fluid. This ↑ convective volume and ↓ cost.
- Benefits potentially include superior removal of higher MW uraemic toxins, greater haemodynamic stability and ↓ ESA requirements.
- HDF may also be associated with ↓ mortality (DOPPS 2006), although two RCTs (CONTRAST and the Turkish OL-HDF study) failed to prove this convincingly (although *post hoc* analysis of CONTRAST did show a 39% mortality risk reduction in patients receiving higher convection volumes (>22L/session)).
- A recent large (>900 patients) RCT with 3-year follow-up (ESHOL) reported that post-dilution (see figure 2.16) OL-HDF improves all-cause mortality (30% risk reduction—principally stroke and infection), in comparison to standard high-flux HD.
 - *Post hoc* analysis showed a 40% and 45% mortality reduction in those receiving convection volumes of 23–25 L/session and 25 L/session, respectively (possibly confounded by better dialysis access and longer hours in this group—both confer a survival benefit).
 - Whether the apparent benefit seen is the result of improved middle MW toxins (e.g. β_2 microglobulin), greater haemodynamic stability, less intradialytic ↓ BP, or other factor is uncertain. Regardless, OL-HDF is likely to become increasingly popular, particularly in the subgroup of patients with no residual renal function and greater propensity for haemodynamic instability.

Potential indications

- Patients with no imminent transplant options; e.g. highly sensitized patients on the deceased donor waiting list.
- Large patients already on 4.5-5h high-flux dialysis with sub-optimal clearance.
- Long-term dialysis patients.
- Patients with symptomatic hypotensive episodes on dialysis.
- Patients with post-dialysis symptoms and long recovery time.
- Patients generally not thriving on dialysis (after other causes excluded).
- ? Dialysis amyloid (📖 page 632).

Haemodialysis apparatus

Principle

Blood is removed from the patient, anticoagulated, pumped through a dialyser, and then returned to the patient (see Fig. 4.3). Within the dialyser, blood and dialysate (flowing in opposite directions) are separated by a semi-permeable dialysis membrane.

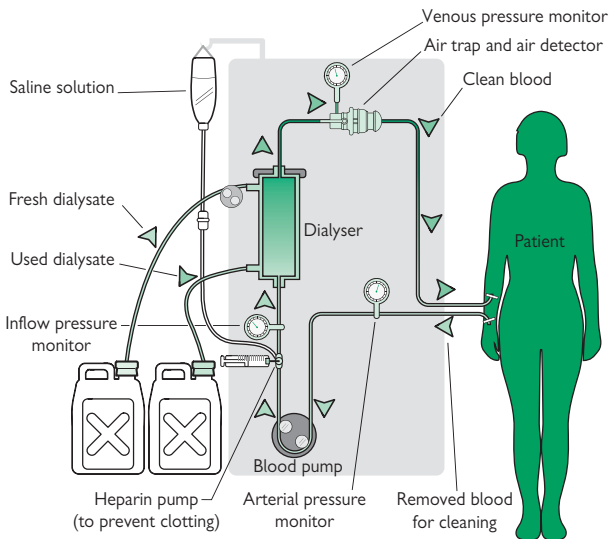


Fig. 4.3 The HD circuit. Schematic of haemodialysis machine. Reproduced with license under the Creative Commons Attribution 3.0 Unported license. Source: Yassine Mrabet.

Apparatus

- Blood pump: usually a roller 'peristaltic' pump.
- Bubble trap: traps air → ↓ risk of air embolism.
- Blood flow rate: usually 200–500 mL/min.
- Dialysate flow rate: up to 600 mL/min.
- Heaters: dialysate and blood are kept at 37°C.
- Dialyser: a rigid polyurethane shell (~30 cm long), containing hollow fibres (capillaries) of dialysate membrane. This arrangement maximizes the available surface area for dialysis (0.5–2.1 m²). Two ports each allow blood and dialysate to enter and exit. Priming volume (saline) ~50–100 mL.
- Dialyser efficiency: depends on membrane thickness, pore size, and dialyser structure. Efficiency of solute clearance is measured as KoA (mass transfer urea coefficient), provided for each dialyser by the manufacturer. KoA varies from 300 to 1,100 (>600 = high efficiency dialyser, requiring higher blood and dialysate flows).

Alarms and monitors

These will stop the blood pump and clamp lines if the situation demands, effectively creating what is known as a 'closed circuit'.

- Air detectors: located distally in the venous circuit, prevent air emboli.
- Pressure monitors:
 - Arterial → detect ↓ pressure 2° to poor access flow and line disconnections.
 - Venous → detect ↑ pressure 2° to resistance to venous return (usually represents an access problem).
 - Dialysate outflow pressure → monitor TMP (to vary UF rate).
- Dialyser integrity.
- Temperature.
- Conductivity:
 - Electrical conductivity is used to monitor proportioning of dialysate to water.
 - Many machines use conductivity to enable changes to Na⁺ concentration.

Newer machines

- Blood volume monitoring: haematocrit (Hct) in the arterial line is used as a surrogate for blood volume (↓ plasma H₂O → ↑ Hct). Used to fine-tune UF and BP control.
- Access recirculation measurements: ensures the same small volume of blood is not dialysed repetitively.
- Delivered Kt/V: Ur concentration in the dialysate outflow line or dialysate conductivity used to calculate delivered dialysis dose.
- Vascular access monitoring: quickly alerts to the possibility that dialysis cannulae or the vascular access device have become dislodged from their normal working position.

Dialysate

Box 4.1 Summary

- A solution of ultrapure water, Na^+ (132–150mmol/L), K^+ (usually 1.0–3.0mmol/L), Ca^{2+} (1.0–1.25mmol/L), Mg^{2+} , Cl^- , dextrose, and buffer.
- Ultrapure water is generated in a treatment plant (involves microfilters, activated carbon, deionization, and reverse osmosis) to exclude particulate matter, ions, and minerals potentially harmful to humans (see Fig. 4.4).
- UK Renal Association standards for water purity are $<0.25\text{IU/mL}$ endotoxin, $<100\text{cfu/mL}$ microbial count.
- H^+ ions have a low plasma concentration and are not removed by dialysis. Buffer (alkali equivalent) is added to dialysate instead.
- Bicarbonate is now preferred to acetate as a buffer.
- HD machines either mix dialysate concentrate, buffer, and water for the individual patient or this is done centrally before distribution around several machines.

Ultrapure water

An average patient is exposed to 560L of water during three HD sessions, so it must be of sufficient purity to enter the bloodstream.

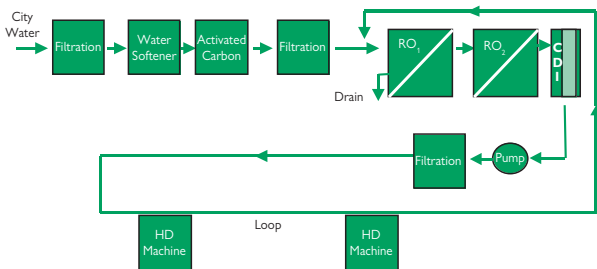


Fig. 4.4 Ultrapure water treatment system for haemodialysis. Reproduced from *Nephrol. Dial. Transplant.* (2002) **17**(suppl 7): 54–61, with permission. RO = reverse osmosis. CDI = continuous deioniser.

Carbon filters removes chlorine/chloramines to $<0.1\text{mg/L}$ (chloramines can lead to haemolysis). *Softeners* remove Ca^{2+} and Mg^{2+} by ionic exchange, as 'hard' water can damage machines and cause muscle weakness. *Micron filters* remove suspended particles. *Reverse osmosis (RO)* removes bacteria, endotoxins, pyrogens, viruses, and solutes (can lead to hypotension, nausea, vomiting.) Regular testing must ensure purity standards (see Box 4.1).


Dialysate concentrates

Dialysate contains pure water as well as several different concentrates: sodium, potassium, calcium, bicarbonate, magnesium, and glucose. In an ideal world, the proportions of each of these concentrates should be individualized for every HD patient.

Potassium (K^+)

Around 80–140mmol is removed per HD session. The gradient of K^+ between serum and dialysate is important, and most K^+ is removed in the first hour. Dialysate K^+ varies from 1 to 3mmol/L. The higher the gradient, the more the K^+ removal which is associated with a greater risk of haemodynamic instability.

Sodium (Na^+)

Dialysate Na^+ concentration controls salt and water removal from the plasma (see  p. 301).

Bicarbonate (HCO_3^-)

HD aims to ameliorate a pre-dialysis acidosis without causing a post-dialysis alkalosis. Dialysate concentrations vary from 36 to 40mmol/L.

Calcium (Ca^{2+})

40% of plasma calcium is bound to protein, the remainder is ionized (1.1–1.5mmol/L) and therefore dialysable. Guidelines recommend lowering dialysate Ca^{2+} to maintain neutral or negative Ca^{2+} balance to prevent vascular calcification. However, higher patient:dialysate gradients are associated with sudden cardiac death. Most units utilise a dialysate Ca^{2+} of 1.25mmol/L.

Dialysers and membranes

Biocompatibility

- Dialysis membranes are not inert. They can activate complement and inflammatory cascades (→ short- and long-term complications).
- A biocompatible membrane is one that elicits the minimum inflammatory response in patients exposed to it.
- Improved biocompatibility may →:
 - ↓ hypersensitivity reactions.
 - Less intradialytic ↓ BP.
 - Slower loss of residual renal function.
 - Improved nutrition.
 - ↓ amyloid deposition.
 - ↓ morbidity and mortality (☹).

Cellulose membranes (e.g. *Cuprophane*®)

- The original membrane and least biocompatible.
- Largely superseded by synthetic membranes.

Modified cellulose (e.g. *Hemophan*®)

More biocompatible.

Synthetic membranes (e.g. *Polysulfone*®, *polyamide*, *polyacrylonitrile*)

- More recently developed.
- Most biocompatible.
- More permeable than cellulose membranes:
 - Solute clearance similar to cellulose membranes.
 - ↑ β_2 microglobulin clearance.

High vs low flux

High-flux membranes are usually synthetic membranes with a large pore size → enhanced clearance of middle and large molecules. ☹ May lead to better outcomes.

Surface area

↑ dialyser surface area (usually 0.5–2.1m²) → ↑ delivered dialysis. See Fig. 4.5.

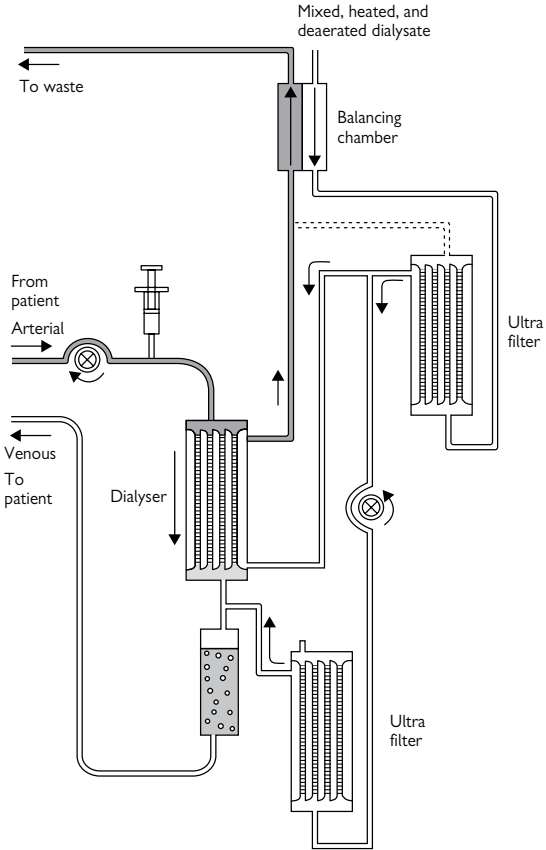


Fig. 4.5 Haemodiafiltration circuit using online ultrafiltration for production of ultra-pure dialysate and replacement fluids.

Dialysis prescription and adequacy

Introduction

Intermittent HD places exacting demands on a patient. As it only partially replaces renal function, fluid and dietary restrictions remain significant and burdensome.

Dialysis can be considered adequate if it provides relief of uraemic symptoms and controls acidosis, fluid balance, and serum K^+ . It should also allow a feeling of physical and psychological well-being.

Aspects of dialysis adequacy

- *Solute clearance.* Small molecule clearance is relatively easy to measure (📖 p. 287). Aim to achieve a target Kt/V of >1.2 or $URR >65\%$ (see box below).
- *Blood pressure and fluid balance.* As a general rule, \uparrow BP in a dialysis patient should be treated by \downarrow 'dry weight' (i.e. post-dialysis weight). This should be the weight at which salt and water balance is optimal. Oligo-anuric patients (majority of long-term HD patients) need to restrict their interdialytic salt and fluid intake in order to achieve this, aiming for weight gains of 1–2.5 kg (maximum) between sessions. It is difficult to achieve prescriptive BP targets in the HD population (lack of evidence and a heterogeneous population). However, pre- and post-dialysis BP $<140/90$ mmHg is desirable. This would preferably be achieved without anti-hypertensive medication. Inter- or intra-dialytic hypotension should be avoided.
- *Nutrition.* Blood Ur levels depend on rate of production as well as rate of excretion. Δ A low pre-dialysis Ur may reflect poor nutrition, rather than good dialysis. Targets:
 - Serum albumin >35 g/L.
 - Normalized protein catabolic rate (nPCR) >1.0 g/kg/day (📖 p. 287).
 - Acceptable anthropometric measures.
- *Clearance of other molecules:*
 - 'Middle' molecule clearance thought to be important to prevent the long-term complications of dialysis. β_2 microglobulin is the most used marker.
 - Phosphate clearance is also important and appears to correlate more with hours of dialysis than rate of small molecule clearance.
- *Quality of life and life expectancy.* There is a potential trade-off to be made between the number of hours spent on the machine (\uparrow dialysis dose) and quality of life. For patients with a limited life expectancy, the latter may be a more important consideration (although reducing hours below 4h 3x week is only rarely indicated).

Measuring dialysis adequacy

In the 1980s, the National Cooperative Dialysis Study (NCDS) established timed average U_r concentration as a determinant of morbidity and mortality on HD. Subsequent mathematical analysis of these data has led to the development of urea kinetic modelling (UKM) as the accepted method of measuring small solute clearance.

Kt/V is a measure of U_r clearance where:

- K = dialyser urea clearance.
- t = time on dialysis.
- V = volume of distribution of U_r (estimated from patient size).

The *single pool* Kt/V assumes that, at the end of dialysis, the concentrations of intracellular and extracellular U_r are equal:

$$spKt/V = -\ln[U_{post}/U_{pre} - 0.008t] + [4 - 3.5U_{post}/U_{pre}] \\ \times UFvol/wt_{post}$$

(U_{pre} , urea pre-dialysis; U_{post} , urea post-dialysis; $UFvol$, volume removed on dialysis)

The *two compartment model* acknowledges that, in reality, it takes time for U_r to be redistributed post-dialysis and that the extracellular U_r concentration is lower than intracellular. An equilibrated Kt/V or eKt/V can be calculated from the $spKt/V$.

A simpler measurement of U_r clearance is the *urea reduction ratio* (URR), which does not take account of the amount of fluid removed by ultrafiltration. It is thus less accurate but has been shown to correlate with outcome:

$$URR = (1 - U_{pre}/U_{post}) \times 100$$

Normalized protein catabolic rate (nPCR)

A measure of U_r generation, which reflects nutritional status. It can only be reliably used in patients who are 'stable' so U_r generation will broadly reflect protein intake. It is felt that patients require an nPCR $>1.0g/kg/day$. nPCR of $<0.8g/kg/day$ is associated with higher mortality.

Residual function

When HD is first commenced, residual renal function may contribute greatly to the total amount of solute clearance (K_{ru}). This is usually calculated with a 24h urine collection. Residual function tends to diminish quickly on HD (secondary to repetitive \downarrow BP \pm bio-incompatibility) (📖 p. 284).

Ensuring adequacy

Kt/V

UK and US guidelines suggest a single pool Kt/V >1.2 for patients dialysed $\times 3$ /week, equating to a URR of $\sim 65\%$. The landmark HEMO study compared two target Kt/V levels. Patients with a target Kt/V of 1.2 had no difference in mortality or cardiac events, compared to those with a Kt/V of 1.6.

► Residual renal function should always be taken into account.

Prescribed vs delivered Kt/V—variables in the dialysis prescription

Most guidelines suggest monthly measurement of Kt/V. Online methods of measuring Kt/V are provided on modern dialysis machines (often using Na^+ clearance to estimate urea clearance).


If Kt/V fails to meet target, options are to:

- Improve vascular access—if flows are poor or if there is access recirculation, it will be hard to improve clearances.
- Increase blood flow/larger needles—beneficial if access reasonable.
- Increase dialyser size—modest impact.
- Increase dialysate flow.
- Increase dialysis time/frequency—major benefit.
- Consider HDF.

Computer modelling software can help decide which elements of the prescription require modification to improve Kt/V.

⚠ HD adequacy is multifaceted. Achieving a desired Kt/V does not necessarily equate to optimal dialysis.

Management of dialysis patients on non-renal wards

- For elective procedures, inform your renal team at the pre-assessment stage. On the day of admission contact them again (arrangements for routine dialysis will need to be made).
- Δ Many dialysis patients are oligo-anuric, so DO NOT routinely administer IV fluids (unless the patient is haemodynamically compromised—if so, use small boluses, assess volume status regularly and call for expert help).
- Δ DO NOT give K^+ supplementation. Discuss with renal team if being considered.
- DO NOT place a urinary catheter unless there is a clear urological indication. Oligo-anuria is virtually universal in this patient group!
- If the patient is clinically overloaded inform the renal team immediately, as the patient may require urgent dialysis.
- Check U+E on admission. If $K^+ > 5.5$ mmol/L inform renal team.
- Δ When considering any new medication, check whether the drug is safe in ESRD and if a dose adjustment is required. Be particularly cautious with opiate analgesia and sedatives (accumulation!). \blacktriangleright See  p. 271 and discuss with the renal pharmacy team.
- Check (and document) daily weight.
- Does the patient have an AVF? NEVER insert an IV cannula into a fistula arm. The back of the hand on the non-fistula arm is the best site.
- If patient has a dialysis central venous catheter (CVC), it should not be used for anything else but HD.
- If a dialysis patient undergoes a general anaesthetic, their K^+ must be checked immediately on return to the ward. This K^+ check cannot wait until the following morning, even if the GA procedure is performed late in the day or out of hours. If $K^+ > 5.5$ mmol/L inform the renal team - the patient may require dialysis.
- Peritoneal dialysis (PD) patients should ideally continue their own dialysis throughout their hospital admission. Occasionally this may be with the assistance of a relative or carer. Liaise with their PD team.
- If there is any concern that a patient will not be able to undertake their own PD (e.g. confusion, neurological event, etc.), inform the renal team ASAP, so that alternative arrangements can be made.

Anticoagulation

Blood exposed to dialysis lines and membranes in an extracorporeal circuit rapidly sees the induction of the extrinsic coagulation cascade. In order to ensure efficient and adequate dialysis, regular anticoagulation throughout the duration of each dialysis session is required. Historically, this was provided by the use of unfractionated heparin (UFH) and, indeed, this is still the case in many parts of the world, including the USA. There has been a trend, in Europe, however, to adopt the low molecular weight heparins (LMWHs) for standard anticoagulation. A 2004 meta-analysis of the safety and efficacy of the LMWHs vs UFH concluded that there was no difference in the number of bleeding events, post-dialysis vascular access compression time, or thrombosis of the extracorporeal circuit between the two.

Unfractionated heparin

- Mixture of glycosaminoglycans between 3 and 30 kDa.
- Highly negatively charged.
- Indirect thrombin inhibitor.
- Narrow therapeutic window and highly variable dose response.
- Metabolized in the liver and by vascular endothelial heparinases.
- No single dosing protocol but usually single bolus 1,000–2,000 IU, followed by infusion of 1,000–1,500IU/h.
- Adjust if weight <50kg or >90kg.
- Monitor using activated clotting time (ACT) at the bedside.
- Short half-life and fully reversible with protamine.

Low molecular weight heparin

- Smaller molecules, typically 4–5kDa.
- Different preparations have variable lengths, weights, and charges (enoxaparin least 'heparin-like', tinzaparin most).
- Primarily work through inhibiting factor Xa.
- Predominantly renally cleared \therefore \uparrow half-life in ESRD.
- Tinzaparin, commonly used at doses of 2,500IU or 3,500IU, is considered safe and effective. Enoxaparin (e.g. 10–40mg) is used in many centres.
- Monitor using anti-Xa activity, aiming <0.4IU/mL (historically slow turnaround in results, but now usually available in 90–120mins).

Heparin-induced thrombocytopenia (HIT) see p. 184

This is a significant complication of heparin use (both UFH and LMWH), associated with major morbidity and mortality. Platelet activation and aggregation results in thrombocytopenia, thrombosis, and infarction. There are wide-ranging reports as to the prevalence of HIT antibodies in dialysis patients, with figures varying between 0 and 18%.

Other

Other options for anticoagulation include regional anticoagulation (UFH/protamine, citrate, epoprostenol), heparin-coated dialyser, heparinoids (danaparoid or dermatan sulfate), or direct thrombin inhibitors (argatroban or hirudin). Some of these may be useful in those patients who develop HIT or those with a high bleeding risk.

Bleeding

► Patients with ESRD have an increased incidence rate of major bleeding. This has been quoted as 2.5% per person-year for patients on haemodialysis. A recent study suggested that this increased to 3.1% with warfarin use, 4.4% with aspirin, and 6.3% with warfarin and aspirin.

⚠ Caution when prescribing these agents in patients on haemodialysis.

Dialysis access: AVF/PTFE

Reliable vascular access is the cornerstone of HD therapy, and timely planning of access creation is a major facet of CKD care (see Fig. 4.6). ~25% of all admissions in the dialysis population relate to access failure or other complication and remain an important source of morbidity and mortality.

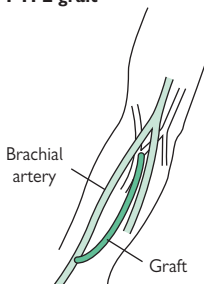
AV fistula

The optimal form of vascular access. Requires surgical anastomosis of an artery and a vein (under LA or GA), either at the wrist (radiocephalic) or elbow (brachiocephalic, brachiobasilic). If the suitability of veins is in doubt, then vascular mapping with USS is desirable. Maturation for 6–8 weeks (minimum) is required prior to needling (∴ advance planning crucial).

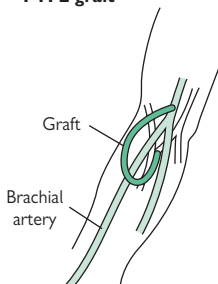
PTFE graft

Second best. A synthetic graft is interposed between an artery and a vein. A larger operation than AVF creation. Necessary if veins inadequate to fashion an AVF (e.g. DM, previous phlebotomy/cannulation). Lower limb sites possible (e.g. femoral loop), in addition to upper limb. Useable within days, but thrombosis and infection (usually necessitating removal) are problematic. Half-life shorter than an AVF.

Forearm straight PTFE graft



Forearm loop PTFE graft



Radial arteriovenous fistula

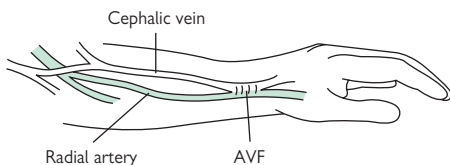


Fig. 4.6 Permanent vascular access for haemodialysis. Reproduced with permission from Levy J, Morgan J, and Brown E (2004). *Oxford Handbook of Dialysis*, 2nd edn. Oxford: Oxford University Press.

Planning

UK Renal Association guidelines suggest that 85% of prevalent haemodialysis patients should be dialysing through either a native arteriovenous fistula or a PTFE graft. At the start of their dialysis career, all patients should have a lifelong vascular access strategy; i.e. a planned approach to vascular access that preserves potential sites for as long as possible. Many centres have a multidisciplinary vascular access team for this purpose.

Clinical examination and vessel mapping (duplex Doppler) help to plan the site of fistula formation. A native fistula takes at least 6–8 weeks to mature. A PTFE graft can often be used within 2 weeks. Primary failure rates for AV fistulae (unusable at 3 months) remain high (up to 50% in some centres). In addition to technical factors, or poor AVF care, this may be caused by a vascular stenosis, either at the AV anastomosis or in the downstream vein. These may be amenable to angioplasty. Grafts have a lower primary failure rate, but are more likely to develop late stenoses—either at the venous anastomosis or in the outflow vein.

Fistula care: what every doctor and patient should know

- Dialysis access is extremely precious.
- Arm veins should be preserved in pre-dialysis patients (no IV cannulae between elbow and wrist).
- Needling should only be carried out by a trained operator (usually a dialysis nurse, ideally the patient).
- Technique: avoid using the same site repetitively (→ false aneurysm formation).
- Never put a tourniquet or BP cuff on a fistula arm.
- Do not use a fistula to take blood.
- Hypotension (and volume depletion) → ↑ thrombosis risk.
- ↑ Hct (too much ESA) predisposes to thrombosis. Keep within recommended guidelines and at the lower end of these, if at risk.
- A clotted fistula or graft requires immediate attention (time to declotting is a major determinant of success).

Surveillance

Alongside clinical monitoring of signs that may indicate stenosis (difficult cannulation, prolonged bleeding post-needle removal), KDOQI have published guidelines for regular access screening. The rationale is that regular surveillance of vascular access should identify a stenosis and allow pre-emptive intervention to prevent thrombosis. The recommendations are that a referral for intervention should be triggered when blood flow <600mL/min in a PTFE or <400–500mL/min in an AVF. While these guidelines are controversial (as they may potentially lead to a high number of unnecessary interventions), they can be helpful when correlated with clinical findings such as access venous pressures and post dialysis bleeding times.

If a stenosis is suspected, investigate further by duplex or angiography ('fistulogram'). The advantage of angiography is the potential ability to proceed immediately to an angioplasty ('fistuloplasty').

Clotted AVF/PTFE

No thrill or buzz in fistula = thrombosis (ensure patients are aware of this) ∴ seek immediate medical opinion. Swift intervention (within 48h) either via interventional radiology (local thrombolysis), or surgery, may be able to salvage the fistula. The longer the time to intervention, the less likely it is to be successful. There is no clear evidence for anticoagulation in the interim. Check U+E and volume status, and insert a temporary dialysis line, if required.

Other complications of fistulae and grafts

- Infection: fistulae rarely become infected beyond a superficial cellulitis. PTFE infection is not uncommon. May be occult, causing weight loss, ESA resistance, and failure to thrive. Antimicrobials rarely successful, and management usually involves surgical removal.
- Aneurysm or pseudoaneurysm formation: may occur at needling sites, especially if sites not rotated. Surgery may be necessary.
 - Bleeding from an infected or aneurysmal AVF or graft is a much feared complication (proceeds under arterial pressure!).
 - ► Wear a gown, gloves, and goggles. Seal the bleeding site with the lid of a universal container, and secure with a tight bandage. Establish wide-bore IV access; check clotting; cross-match blood, and inform a surgeon.
- Distal ischaemia or steal syndrome: flow through the fistula or graft may compromise distal blood supply. Cold or numb peripheries are common but may → infarction or ischaemic pain. Other features include paraesthesia, cyanosis, loss of distal pulses. Patients often elect to wear a glove on the affected hand. AVF ligation or graft removal may be necessary in severe cases.
- Excess flow: may → large ↑ in cardiac output with cardiac decompensation. Surgical 'banding' (plication) of an AVF can ↓ flow.
- Extravasation: blood leakage into the soft tissues. Can cause rapid limb swelling, haemodynamic compromise, compartment syndromes, 2° infection, access thrombosis.

The golden rules of vascular access formation

- Assess the patient for vascular access when dialysis is expected within 12 months.
- Make sure the patient resists venepuncture in the selected limb.
- Use upper limbs before lower limbs.
- Non-dominant arm before dominant.
- Use distal sites (e.g. radiocephalic) before proximal (e.g. brachiocephalic) whenever possible. See Fig. 4.7.
- Use a native vein before prosthetic graft.
- Aim for formation >6 months prior to dialysis. This will give adequate time for maturation (and for repeat intervention in cases of primary non-function).
- Ensure all access procedures and interventions (successful or unsuccessful) are adequately documented.
- Plan ahead—what next? Is peritoneal dialysis an option?



Fig. 4.7 A mature radiocephalic AVF used for hemodialysis.

Haemodialysis access: lines

If a patient has neither an AVF nor a PTFE, the remaining options are:

Temporary dialysis catheter (📖 p. 180)

For immediate use; e.g. AKI, or in a patient with unresolved sepsis. Internal jugular, subclavian and femoral are possible routes. Ideally leave *in situ* for ≤ 2 weeks (femoral < 5 days). These have much higher infection rates than other forms of dialysis access.

Tunnelled (and cuffed) dialysis catheter

A dual-lumen (or two single-lumen) venous catheter is placed in a central vein (internal jugular or subclavian; femoral less common). Available for immediate use and usually left *in situ* for 1–3 months (occasionally longer). Blood flows 300–450 mL/min achievable.

The use of tunnelled central venous haemodialysis catheters (CVC) is common. They are frequently used as a 'bridging' step in those who are waiting for a fistula or in those in whom access surgery has been unsuccessful. They should generally be viewed as a short-term solution, as they are associated with a 3-fold increased mortality, compared with AVFs. In addition, sepsis-related death is 100-fold greater in HD patients than the general population, and infection-related death and all-cause mortality is highest in those dialysing through a CVC.

Malfunction

Catheter malfunction is common. 50% of lines fail within the first year of insertion. Catheter malfunction is defined as one of the following:

- Peak blood flow ≤ 200 mL/min for 30 min in an HD session.
- Mean blood flow ≤ 200 mL/min for two consecutive HD sessions.
- No flow, unable to initiate HD.

Malfunction may be positional (usually ≤ 7 days post-insertion) or mechanical. Mechanical malfunction may be intraluminal (thrombosis), extraluminal (fibrin sheath), or intrinsic to the catheter material/properties.

Fibrin sheaths will start to form within 24 hours of insertion and may eventually completely enclose the catheter. Can cause a one-way valve, manifesting in difficult aspiration despite easy injection.

Primary prevention

Strategies include heparin, rtPA, or trisodium citrate catheter lumen lock between sessions. The PreCLOT trial showed that rtPA for primary prevention of catheter malfunction (1 mg/lumen once/week + heparin for the other two sessions) vs standard heparin (5,000 U/mL to fill lumen) was associated with significantly less catheter malfunction and bacteraemia, with no increase in bleeding events. Trisodium citrate (4, 30, or 46.7%) has also been shown to be more effective than heparin and causes less bleeding, less biofilm formation, and a significant reduction in catheter-related bacteraemia. There are no convincing data for low-dose warfarin, ticlopidine, or other antiplatelet agents with respect to primary prevention.

Treatment

- Initial attempts to restore flow: flush catheter with 10mL syringe of saline; reposition patient; reverse lines. Beware recirculation (repetitive dialysis of the same small volume of blood) and inadequate dialysis.
- Thrombolytic agents: streptokinase/urokinase have largely been replaced by rtPA (alteplase, reteplase, tenecteplase). Differing regimens have been studied: 'push', short dwell (30–60min), long dwell (>2 hours, interdialytic), or infusions. These methods are associated with short-term success of between 40 and 90%, with median patency 14–30 days.
- Fibrin sheath disruption: mechanical disruption of sheath from catheter wall. Published outcomes variable, presumably related to catheter type and operator technique.
- Exchange over guidewire: if previously listed measures unsuccessful, then consider a catheter exchange. Comparable infection rates to *de novo* insertion and preserves vascular access, particularly if a central venous stenosis has developed. Caution—do not use this technique when replacing fractured or 'split' lines due to risk of bacteraemia.

Catheter-related bacteraemia

Catheter-related bacteraemia (CRB) is a serious complication of CVC use. Catheters are associated with a 10-fold increase in bacteraemia rates vs AVF. Incidence of CRB used to range from 2.5 to 6.5 episodes/1,000 catheter days for tunnelled lines and higher for temporary uncuffed lines. Since the advent of antimicrobial catheter locks, most units aim for <1 bacteraemia/1,000 patient days at risk.

- Fever in an HD patient with a line = line sepsis until proven otherwise.
- Causes: ~70% → *Staph. aureus* (▲ MRSA) or *Staph. epidermidis*. Gram –ve organisms more common with femoral catheters.
- Risk factors: poor patient hygiene, previous CRB, recent hospitalization, ↓ albumin, duration of catheter use, *Staphylococcus* nasal carriage or skin colonisation, DM, immunocompromised.

Clinical features

- Usually presents with fever, rigors ± ↓ BP whilst on dialysis. Also N+V, diarrhoea, confusion.
- Examination and investigation:
 - The line: often appears innocent, but check for erythematous or purulent exit site (→ swab for C+S). Is there a tunnel infection?
 - General exam: stigmata of endocarditis, chest signs, other sources of infection; e.g. spinal tenderness (?discitis).
 - Blood cultures: from line and peripheral vein (see Table 4.1).
 - CRP.
 - CXR if chest signs.

Table 4.1 Definitions

Definite	Confirmation of septic thrombophlebitis with single positive blood culture (BC), OR Single positive BC + positive culture of catheter segment with identical organism, OR 10-fold difference in colony count in BC from catheter vs peripheral, OR Single positive BC + positive culture from discharge/aspirate from exit site or tunnel with identical organism
Probable	≥2 positive BC with no other obvious source, OR Single positive BC from <i>Staph. aureus/Candida</i> with no other obvious source, OR Single positive BC for <i>coagulase-negative staph/Bacillus/Corynebacterium jeikeium/Enterococcus/Trichophyton/Malassezia</i> in immunocompromised/neutropenic patient

Adapted from Prevention of catheter lumen occlusion with rT-PA versus heparin (PreCLOT): study protocol of a randomised trial. Hemmelgarn et al. *BMC Nephrol* 2006;7:8

Treatment

- Start antibiotics empirically if fever >38°C, rigors, or ↓ BP.
 - Cover for both Gram +ve and Gram -ve organisms.
 - For Gram +ve cover use either vancomycin (10–20mg/kg IV—usually 1g) or teicoplanin (see [] p. 882).
 - For Gram -ve cover use either gentamicin (see [] pp. 881–2) or third-generation Cephalosporin.
 - Tailor therapy to culture results.
 - Vancomycin is not removed by HD; gentamicin is. Measure gent levels daily (levels will decrease sooner in patients with significant residual function).
Continue 4 weeks for *Staphylococcus* (6–8 weeks if complicated by metastatic infection), Minimum 2 weeks if Gram -ve or *Candida*.
- If fever still present after 12–24h → remove line, earlier if severe sepsis or deteriorating patient.
- Remove in all cases of *Staph. aureus*, tunnel infection, or if infection seeded elsewhere.

Patients with CRB are at risk of developing osteomyelitis, discitis, epidural abscess, septic arthritis, or endocarditis, regardless of whether the CVC is removed or exchanged—consider if ongoing fever or CRP.

Prevention

- Consider IV antibiotics at insertion for patients with Staphylococcal skin colonisation. Sterile placement technique ([] p. 936).
- Meticulous nursing care (KDOQI guidelines: mask and sterile gloves; clean exit site with chlorhexidine each use).
- Eradication of *Staphylococcus* carriage may ↓ incidence (e.g. nasal mupirocin cream).
- Topical antimicrobial ointment: ↓ CRB by 75–93% (e.g. mupirocin).

- Antimicrobial locks: the cornerstone of preventing catheter-related bacteraemia (↓ by 51–99% over 25 trials) though microbial resistance and long term efficacy are concerns.
- The application of chlorhexidine-impregnated foam dressings to catheter exit sites has become popular in many units.

Long-term complications

- Catheters may → central venous stenosis, preventing subsequent catheter placement and compromising AVF maturation and flow. May lead to SVC obstruction, with swollen arms, chest wall, and face. Multiple collateral veins may be visible. Balloon angioplasty ± stent insertion may be successful but recurrence common.

Fluid balance on dialysis

Fluids gains between dialysis depend on:


- Fluid intake during the interdialytic interval (Δ the long interdialytic interval, or the 3-day break that occurs once a week on a standard thrice weekly dialysis regime, is usually associated with the largest fluid gains).
- Residual renal function or urine output.
- Other fluid losses (stoma output, stool losses, etc.).

As a general rule, HD patients should gain no more than 2% of their body weight in fluid between sessions (1.4kg in a 70kg adult). Gains of >4% (2.8kg in a 70kg adult) are described as large interdialytic weight gains. But, as most HD patients will confirm, this is easier said than done. Patients require encouragement and regular tailored advice regarding fluid (and salt) intake.

Dry weight (DW)

- It is the end-dialysis weight thought to best represent a euvolaemic state. It is the body weight in kg against which the ultrafiltration volume is set at each session. For example:
 - HD patient with a dry weight of 70kg.
 - Pre-dialysis weight 72.7kg.
 - Target UF volume = 2,700mL over 4h to achieve DW.

Assessing DW

Can be achieved in a number of ways but should always include clinical assessment. The point at which a patient experiences intradialytic hypotension (or unpleasant cramp) ( p. 302) is a crude (and not always correct) indication that further fluid removal will not be advantageous:

- Examination: to include presence or absence of ankle oedema, lying and standing BP, JVP, and examination of the chest. Hypertension, oedema, and an elevated JVP suggest overload.
- Fluid gains between dialysis sessions.
- Continuous blood volume monitoring (BVM, on-line measurement of the haematocrit on HD where sudden haemoconcentration suggests vascular refill is failing and dry weight has been reached).
- Biofeedback control, a combination of BVM, conductivity, BP, and UF rate, analysed in real time to predict impending hypotension.
- Bioimpedance where resistance to alternating current is used to determine lean body mass and body fluid volume.
- IVC:aorta ratio on ultrasound (predominantly a research tool).

Δ Of these, only the first two have entered routine practice—trials of the other techniques have either been inadequate or results have been inconsistent. A widely applicable, and clinically useful, tool that accurately assesses fluid status is awaited.

Sodium and dialysis

Any individual has a (remarkably stable) 'sodium set-point': if their plasma Na^+ rises above their set-point, osmoreceptors trigger thirst until Na^+ returns to this point. The reverse is also true: if plasma Na^+ falls with total body Na^+ depletion, salt craving increases Na^+ ingestion to regain the 'set-point Na^+ '. So it follows that:

- Δ *Dietary salt intake is a vital part of haemodialysis patients' salt balance!*
- Achieving $<100\text{mmol/day}$ intake (equivalent to 6g NaCl) is difficult on a western diet. The more salt ingested, the more water will be drunk, and the more fluid weight gained between sessions.
- During dialysis, ultrafiltration (convection) removes Na^+ , as does diffusion down a plasma/dialysate gradient. This gradient is not as simple as a patient's measured serum Na^+ , compared to the prescribed dialysate Na^+ :
 - Plasma Na^+ is reported in mmol/L, but only 93% of plasma is free water (so the true Na^+ in that fraction of dialysable water is *higher*).
 - Negatively charged plasma proteins 'resist' movement of Na^+ from plasma into dialysate (Gibbs–Donnan effect), affecting true diffusion.

As long as dietary salt intake is controlled to $<100\text{mmol/day}$

- Lowering the dialysate Na^+ will lead to a negative Na^+ balance over time.
- BUT may be associated with more intradialytic haemodynamic instability over the short term.
- Higher dialysate $\text{Na}^+ \rightarrow$ increased fluid intake and larger interdialytic weight gains over time.
- BUT may be associated with better haemodynamic control during any one session (allows for better capillary refilling during ultrafiltration).

Intradialytic hypotension

A sudden and symptomatic fall in BP during a dialysis session is called intradialytic hypotension (IDH). During ultrafiltration, fluid is removed from the vascular space. This requires prompt refilling from the ECF to maintain blood volume. Healthy adults will tolerate up to 25% reduction in blood volume, but, amongst patients on dialysis, there is large inter- and inpatient variability.

IDH is defined as a fall in SBP $>20\text{mmHg}$ (or MAP >10), associated with symptoms, or a fall to SBP $<100\text{mmHg}$. Symptoms associated with IDH include:

- Cramps, abdominal pain, or nausea (reduced gut perfusion).
- Yawning, sighing, anxiety, or dizziness (reduced cerebral perfusion).
- Chest pain or arrhythmias.

IDH occurs in around 10% of all HD patients and in around 5–30% of these patients' sessions. IDH is always related to the rate of ultrafiltration (i.e. the speed of fluid removal). It is less usual at UF rate $<0.3\text{mL/min/kg}$ and common if UF rate $>0.6\text{mL/min/kg}$. IDH is more likely in:

- Elderly (esp. if with wide pulse pressure and isolated systolic hypertension).
- ♀.
- Diabetic patients (▶ with autonomic neuropathy).
- Cardiomyopathies.
- Occult sepsis.

Immediate management of IDH:

- Stop ultrafiltration (UF).
- Place patient in Trendelenburg position.
- Administer 0.9% NaCl as a 250mL bolus.
- Recheck BP.
- Undertake thorough clinical review (including medications) to prevent future episodes!

Prevent IDH by identifying those most at risk

- Large interdialytic weight gains.
- High salt intake.
- Anuric (no residual renal function).
- Valvular heart disease (aortic valve disease), known systolic dysfunction, or untreated coronary artery disease.
- Those taking dialysis-day antihypertensives (particularly vasodilators).
- Malnourished or hypoalbuminaemic, or those losing flesh weight.
- Large arteriovenous fistulae (flows $>2\text{L/min}$).

Management: preventing IDH

- Maintain residual renal function where possible.
- Confirm cardiac function (ECG, echo) and exclude valvular heart disease.
- Give good dietary salt and fluid intake advice. Patients who do not understand the importance of salt restriction on HD will find controlling thirst and fluid very difficult.
- Avoid eating during HD.
- Stop dialysis-day antihypertensives (but try to continue β -blockers if prescribed).
- Control blood sugars in diabetic patients.
- Correct anaemia, if present, and arrange nutritional input for those who are malnourished.
- Increase dialysis hours or increase number of weekly sessions (i.e. reduce the UF rate or the UF volume per session).

Cooling the dialysate

Dialysis is often a 'warming' event—if the dialysate temperature were set at 37°, the metabolic consequences of the process and of pyrogens and cytokines released through blood–membrane interaction would → a gain in energy.

Warming → peripheral vasodilatation—BP will then only be maintained if heart rate or stroke volume increases (or both).

Patients on dialysis often have a multifactorial uraemic cardiomyopathy—during dialysis, ischaemic regional wall motion abnormalities (RWMAs) are visible on echocardiography in a significant subgroup of patients prone to IDH (as O₂ delivery fails to meet cardiac work).

Reducing the dialysate temperature to 36° or even 35.5° → cooler returned blood during any session, with vasoconstriction, then sustaining or raising blood pressure without tachycardia or increased myocardial contractility.

► Cooled dialysate reduces IDH and prevents RWMAs.

Sodium profiling

Sodium 'ramping', or 'profiling', has not become widely adopted to control IDH—although a higher dialysate Na⁺ during the first hour of dialysis, which then falls on an hour-by-hour (or shorter) basis, should improve haemodynamic stability. The total Na⁺ load tends to be higher than with fixed concentration (standard) dialysate Na⁺. So a higher load then drives intradialytic thirst and fluid gains, setting up a cycle of large intradialytic weight gains requiring ever higher ultrafiltration volumes and more frequent IDH.

Extended hours HD treatments

Background

Dialysis frequency and duration

- For >3 decades in Tassin, France, patients with ESRD have received 8h in-centre dialysis sessions 3x/wk. Patient outcome data with this regime are amongst the best in the world.
- This improved survival (compared to shorter dialysis schedules) is mainly due to lower CV mortality. Other reported benefits include improved nutritional status, better anaemia parameters (with lower ESA requirement) and superior BP control.
- In addition, the 2-day interval between conventional HD sessions is well recognised as a time of heightened risk for CV events.
- In view of these observations, it has been proposed that modern dialysis care should focus on: -
 - ↑ dialysis frequency
 - ↑ dialysis duration
 - Or both of these.
- Strategies to increase the intensity of dialysis include short daily haemodialysis (SDHD), in-hospital nocturnal haemodialysis (INHD) and nocturnal home haemodialysis (NHHD).

SDHD

- 6-7 days/week, 1.5-3 hours/session
- Benefits: improved BP control, ↓LV mass, variable reports on quality of life, anaemia, ↓PO₄, ↓mortality.

INHD

- 3 nights/week, 8 hours/session
- ↓Mortality, ↓hospitalisation, ↓ESA requirements, ↓IDH, ↓PO₄

NHHD

- 5-6 nights/week, 6-8 hours/session
- Improved BP control, ↓ESA requirements, ↓LV mass, No current RCT data on mortality.

Frequent Haemodialysis Network (FHN)

- The FHN, formed in 2005, is responsible for the two most recent RCTs that have examined daily and nocturnal dialysis.
- The trials (short daily haemodialysis (SDHD) v conventional HD (2010) and nocturnal haemodialysis (NHD) v conventional HD (2011)), were designed to test the hypothesis that significant modifications to HD treatment time and/or frequency would have a significant impact on patient outcomes.
- Outcome measures included mortality, change in LV mass, and change in self-reported physical functioning.
- Unfortunately neither of the studies was powered sufficiently to examine the effects of either mortality or risk of hospitalisation. However, they did demonstrate that frequent or long duration dialysis schedules could improve certain clinical parameters and quality of life scores.
- Benefits of increased hours dialysing may, however, be at the expense of vascular access longevity in some patients.

Survival Studies

- RCT design, particularly when studying a therapeutic intervention such as HD, can be challenging - as has proved to be the case for the FHN.
- Recruitment of significant numbers of dialysis patients to RCTs is often difficult. It took 10 years and millions of dollars to recruit 245 patients to the SDHD v conventional HD FHN study (2010).
- However, there are large cohorts of patients undergoing various dialysis schedules and these can provide highly informative data. Table 4.2 summarizes some of the recent survival studies (USA and Canada based) with respect to different extended hours modalities.

Home haemodialysis

- Extended hours treatments are associated with certain barriers (both perceived and actual) for patients and these should be balanced against potential benefits. Some barriers may be overcome through the greater flexibility of a home-based therapy.
- Improving the patient's understanding of the benefits of intensive treatment is fundamental to successful implementation.
- Meticulous attention to care of vascular access is essential for longevity and reduced infection/hospitalization.

Table 4.2 Survival Studies involving intensive hours dialysis treatments.


Modality	Author & year	Comparator & Numbers	Study design	Median Follow up (years)	Outcomes
Nocturnal Dialysis	Pauly et al, 2009	NHD v Transplant NHD: 177 DTX: 533, LTX: 533	Matched retrospective cohort	NHD: 3.8 DTX: 4.6 LTX: 4.3	No difference in the adjusted survival between NHD and DTX (HR 0.87, 95% CI 0.50–1.51; NHD reference group); LTX survival was better (HR=0.51, 95% CI=0.28–0.91).
Nocturnal Dialysis	Nesrallah et al, 2012	NHD v CHD NHD: 338 CHD: 1388	Matched retrospective cohort	NHD: 1.8 CHD: 1.8	13% of NHD treated patients died compared with 21% of CHD treated patients, during the 1.8 year follow up; (6.1 versus 10.5 deaths per 100 persons-years; HR=0.55; 95% CI=0.34–0.87).
(In-centre) Nocturnal Dialysis	Lacson et al, 2012	INHD v CHD INHD: 746 CHD: 2062	Matched intention-to-treat retrospective cohort	INHD: 2.9 CHD: 3.3	2-year survival was 81% for INHD treated patients compared with 73% for CHD patients. INHD had a 25% reduction in the risk for death after adjustment for age, BM, and dialysis vintage (HR=0.75, 95% CI=0.61–0.91)
Short Daily Dialysis	Weinhandl et al, 2012	SDHD v CHD SDHD: 1873 CHD: 9365	Matched intention-to-treat retrospective cohort	SDHD: 5.5 CHD: 5.1	The cumulative incidence of death was 19.2% for SDHD treated patients and 21.7% for CHD treated patient. In the intention-to-treat analysis, SDHD was associated with a 13% lower risk for all-cause mortality than CHD (HR=0.87, 95% CI=0.78–0.97).

NHD, home nocturnal haemodialysis; DTX, deceased donor transplant; LTX, live donor transplant; HR, hazard ratio; CI, confidence interval; CHD, conventional 3x/wk haemodialysis; INHD, in centre nocturnal haemodialysis; BMI, body mass index; SDHD, short daily haemodialysis. Modified from Nephrol Dial Transplant (2012) 27: 4307–4313 – permission needed.

Other HD complications

Acute complications

Cramps

- Very common—usually towards the end of treatment.
- Associated with ↓ BP, ↓ Na⁺, hypovolaemia and hypoxia.
- More common with high UF volumes.
- Management: minimize interdialytic weight gains, reduce intradialytic hypotension, increase dialysate sodium (or sodium profile  p 303).
- Acutely, IV saline or 50% glucose is usually effective. Massage the affected area. Regular quinine sulfate can be helpful for some. Carnitine deficiency is present in some intractable cases and supplementation can be given (usually IV post dialysis).


Nausea and vomiting

- Often associated with ↓ BP.
- Management: administer an anti-emetic. Observe patient through treatment and reassess at completion.


Headache

- May be 2° to ↓ BP, ↑ BP, disequilibrium syndrome or large fluid shifts during dialysis.
- Management: analgesia. Reassure. Review ultrafiltration volumes. Investigate if persistent.

Fever

- Often 2° to dialysis access infection, particularly CVCs ( XXX).
- Patient often rigors prior to temperature rise.
- Management: ► the patient requires a detailed clinical review. Reassure, paracetamol, blood cultures, antibiotics according to local policy.

Haemolysis

- Rare, but potentially serious.
- Causes: overheating of dialysate, dialysate contamination, impure water supply, and dialysis machine malfunction. Multiple patients may be affected. Anaemia and ↑ K⁺ ( can be severe) may result.

Clotting of extracorporeal circuit (blood lines and dialyser)

- Causes: inadequate anticoagulation, low blood flow rates, ↑ Hb levels (high viscosity), intradialytic blood transfusion, or clotted access.
- Warning signs: high (or increasing) venous pressure, the blood circuit darkens, ↑ TMP.
- Action: disconnect the patient from the dialysis circuit and flush their dialysis access with saline. Discard the old circuit and prime a new one. Recommence dialysis. Check FBC.
- Next session: titrate anticoagulation carefully. If anticoagulation is contraindicated, flush the dialysis circuit at hourly intervals with 50-100mL of 0.9% sodium chloride (as permitted by the patient's volume status).

Chest pain

► Assume cardiac in origin until proven otherwise. Reduce blood flow rate to 200mL/min and stop UF. Check observations, perform ECG and commence cardiac monitoring. Administer GTN if prescribed.

Cardiac arrest in the dialysis unit

- Manage as for any non-dialysis cardiac arrest.
- Consider $\uparrow K^+$ and other electrolyte imbalances early.
- Ask dialysis staff to wash back and discontinue dialysis.
- Consider the impact of witnessing an arrest on nearby patients.

Disequilibrium (see also  p. 177)

- Cause: high blood urea levels being reduced too rapidly. Usually occurs during first dialysis session (with high blood flows).
- Prevention: use a dialyser with small surface area, commence blood flow rate at 150-200mL/min. Limit first session to 2h.
- Clinical features: nausea and vomiting, agitation, headache, seizures, loss of consciousness.

First use syndrome/dialyser reaction

- Cause: a reaction to the dialyser membrane or dialysis lines (2° to either sterilizing agents; e.g. ethylene oxide, bacteria, or endotoxins).
- ► Reactions range from severe immediate anaphylaxis, through to milder delayed reactions.
- Clinical features: pruritus, urticaria, breathlessness, cough, nausea, vomiting, flushing, rigors, ► laryngeal oedema, collapse.
- Prevention: careful circuit priming with saline and initial low blood flow (e.g. 100mL/min).
- Management: depends on severity. Summon help. Disconnect the patient immediately without wash back. ► Treat severe cases as anaphylaxis. For milder cases: O_2 and other supportive measures (e.g. antihistamines), close observation.
- Exclude other potential causes; e.g. drug reaction. Send blood cultures, CRP and U+E. Check dialysate visually for contamination and send sample for microbiological testing. Inform the dialysis technical staff. Prior to next dialysis, prime the circuit with 2L saline and re-circulate before patient connection.

Accidental disconnection

- Prevention: ensure all connectors are secured on needle, dialyser and dialysis catheters.
- Check CVC for evidence of deterioration.
- Needles should be fixed securely on the patient's arm and lines taped so that they cannot pull. Do not tape lines to beds or chairs. ► Connections should be visible, do not cover with clothing or blankets.
- Action: if a needle dislodges stop the blood pump and clamp the arterial and venous lines. Apply direct pressure to the bleeding site. Check BP and initiate appropriate treatment for hypovolaemia as dictated by amount of blood loss and the clinical situation.
- Discard all lines and prime a new dialyser and circuit. Re-site needles and secure before recommencing dialysis. Check FBC.

- If a temporary or tunneled CVC becomes dislodged: stop the blood pump and clamp arterial and venous lines. Apply a dressing to the CVC exit site and call for assistance. ⚠ Never attempt to push a dislodged CVC back into place. Discard dialysis lines. Check FBC. Send tip of catheter for culture.

Air embolism

- Air detection systems should prevent air from anywhere in the extracorporeal circuit being returned to the patient.
- If an embolism occurs, air may enter the cerebral venous circulation or the heart and lungs, depending, partly, on the patient's position.
- Clinical features: loss of consciousness, seizures, cough, chest discomfort, breathlessness, patchy cyanosis, ↓ BP, shock.
- Management: clamp the venous line and stop the blood pump immediately. Do not wash back. Place the patient on their left side in the Trendelenburg position (hopefully trapping air in the right atrium). And administer 100% O₂. Summon urgent assistance. Move the patient as little as possible. Check ABGs, ECG, CXR.

Blood leak

- Blood leak may occur due to a breach in the dialyser membrane (which may not be visible); e.g. excessive TMP in a dialyser with a low UF co-efficient.
- Management: the dialysis machine should alarm if this occurs. The patient will need to continue dialysis on an alternative machine.

Hard water syndrome

- Cause: failure of the reverse osmosis (RO) machine or the water-softening plant.
- Clinical features: nausea and vomiting, headache, ↑ BP, flushing. Several patients may be affected simultaneously.
- Management: disconnect from dialysis immediately without wash back. Check observations, send U+E and bone profile. No further patients should be dialysed pending a technical review of the water system.

Long-term HD complications

Cardiovascular Disease

- Dialysis patients are ~20x more likely to die a CV death than the general population. A cardiac cause is implicated in >40% of all deaths at ESRD.
- The cause in dialysis patients is multifactorial and not limited to classical Framingham risk factors (📖 p. 198).

Vascular Calcification (📖 p. 242)

Malnutrition (📖 p. 260)

- Causes: inadequate dialysis dose (→ anorexia, altered taste and reduced enjoyment of food), inflammation, dietary restrictions, nutrients lost via dialysate (~4-8g amino acids lost per session), relative catabolic state, medications (e.g. unpalatable PO₄ binders), impaired absorption of nutrients, gastroparesis.
- Management: early dietetic support, nutritional supplements, parenteral nutrition (intradialytic parenteral nutrition (IDPN) is available, is convenient and does not require additional IV access—but it may not provide sufficient protein and calories to meet the needs of the patient), reduce inflammation (→ treat infection, use biocompatible HD membranes, review water endotoxin levels),

Aluminium toxicity (📖 p. 247)

Dialysis related amyloidosis (DRA) (📖 p. 632).

Withdrawal of HD (see also 📖 p 270)

This is the second most common cause of death in RRT (15%). Several factors may contribute to a patient and/or their physician considering withdrawal, including advancing age, frailty, presence of multiple deteriorating co-morbidities, malignancy, chronic pain, reduced mobility, dementia, difficulties with vascular access, repeated hospital admissions, problems during dialysis itself (e.g. recurrent hypotension) and poor overall quality of life.

If considering withdrawal it is important to consider the following:

- Reversible factors (including depression).
- Assessment of patient's decision-making capacity.
- Identification of any advanced directives.
- Full family or care involvement.
- Involvement of the patient's general practitioner and local palliative services.
- ► Post withdrawal supportive care

Post withdrawal, patients typically survive 1-2 weeks, depending on residual renal function. Palliative support (at home, if possible, depending on the patient's wishes) should include: relaxation of dietary restrictions, continued fluid restriction to avoid distressing pulmonary oedema, appropriate analgesia (see p. 271), management of anxiety and dyspnoea (📖 p. 268).

Advanced directives should be encouraged in dialysis patients.

Peritoneal dialysis (PD)

Introduction

PD is the dialysis modality of 11% of patients worldwide (~250,000 patients). The proportion varies dramatically, however, with <5% in Japan and >60% in Mexico. It is generally accepted that patient survival on PD is similar, compared to HD; in fact, these modalities should be seen as complementary, offering different benefits for individuals at different times in their dialysis history—the so-called ‘integrated dialysis care’ approach.

Advantages of PD

- Preservation of residual renal function.
- No need for vascular access.
- Mobility (e.g. easy to transport dialysis to holiday destinations).
- Patient engagement in treatment.
- Home-based therapy—maintains patient independence.
- Less expensive than HD.
- Less risk of transmission of blood-borne viruses.

Physiology and concepts

The semi-permeable dialysis membrane of the peritoneum comprises the capillary endothelium, supporting matrix, and peritoneal mesothelium. Fluid and solutes move between the fluid-filled peritoneum and blood via, what is termed, the ‘three-pore model’ of PD.

- *Large pores (20–40nm)*: allow macromolecules, such as proteins, to be filtered between compartments (effectively via venular or lymphatic absorption).
- *Small pores (4–6nm)*: responsible for the transport of small solutes, such as sodium, potassium, urea, and creatinine.
- *Ultra-small pores (<0.8nm)*: transport water alone (shown to be aquaporin 1).

It is possible that the small and large pores represent different functional states of a single entity, depending on the density of the glycocalyx.

The net movement of solutes, such as urea, will depend on:

- Net diffusion through small pores and convection through large pores.
- Total volume of dialysate infused.
- Net fluid ultrafiltration (or, under certain circumstances, absorption).

Effective peritoneal surface area

Peritoneal capillary endothelium is the predominant barrier to peritoneal solute transport. However, at any one time, not all capillaries are equally perfused, and not all are close enough to the mesothelium (and thus dialysate) for effective dialysis. The ‘effective peritoneal surface area’ then varies (e.g. with peritonitis or changing dialysate volumes). Increasing the effective peritoneal surface area allows faster rates of small solute transfer but not necessarily better overall dialysis—by increasing dissipation of glucose, ultrafiltration might actually decrease (📖 p. 318).

Ultrafiltration (UF)

The net movement of water (UF) relies on the presence of a high intraperitoneal osmotic gradient (generated by glucose) or oncotic gradient (generated by glucose polymers, such as icodextrin). Any absorption of dialysate via the lymphatics (esp. if ↑ intraperitoneal hydrostatic pressure from patient posture or high instilled PD volumes) will oppose this fluid movement into the peritoneum.

The osmotic gradient is usually generated by glucose and depends on:

- The glucose concentration of the dialysate.
- A patient's blood glucose.
- The rate of absorption of glucose itself from PD fluid.

UF is optimized by:

- Ensuring normoglycaemia (relevant for diabetic patients).
- Adjusting the tonicity of the PD solution (glucose concentration).
- Altering the duration of each dialysis dwell.
- Adjusting dwell volumes; ↑ volume often (but not always) leads to ↑ UF (see next paragraphs).

As an alternative to glucose-based solutions, glucose polymers (such as icodextrin) are poorly absorbed and slowly metabolized—these PD solutions provide a sustained *oncotic* gradient over longer dwells and permit ↑ UF, particularly for patients designated as high transporters (📖 p. 316).

↑ dwell volumes of dialysate may maintain the glucose gradient for longer, but ↑ intraperitoneal pressure may ↑ lymphatic return. Also, ↑ volume might increase effective peritoneal surface area, with more rapid absorption of glucose, lessening the glucose gradient and reducing UF.

Contraindications to PD

Absolute

- Patient or carer unable to train adequately in the technique.
- Inguinal, umbilical, or diaphragmatic hernias (esp. pleuroperitoneal leak).
- Ileostomy or colostomy.
- Abdominal wall infections or intra-abdominal sepsis, e.g. active diverticular disease.

Relative

- Abdominal surgeries (adhesions). The more extensive the surgery, the more likely PD will be unsuccessful.
- Morbid obesity (inadequate clearance).
- Huge polycystic kidneys (insufficient intraperitoneal space).
- Severe gastroparesis (worsening vomiting).
- Severe lung disease (diaphragmatic splinting).

Types of PD

Introduction

Intermittent PD was originally developed for the treatment of AKI in situations where HD facilities are not available (📖 p. 188). Rapid exchanges over a 24-hour period are repeated twice or more times a week. The peritoneal catheters used for treatment of AKI are often different from those used for patients with ESRD (although standard cuffed tubes can be used). See Fig. 4.8 for types of PD.

PD regimens for ESRD

Continuous ambulatory PD (CAPD)

Consists of 3–5 exchanges, with dwell times of 4–10 hours over 24 hours. Usually performed by the patient connecting and disconnecting the PD catheter to dialysate bags. A night-time exchange can be performed with a machine (such as Quantum®). Advantages of CAPD include simplicity, ease of training, and flexibility—the timing of exchanges can be adjusted to times of convenience for patients (although dwells <3 hours are generally discouraged).

Automated PD (APD)

Uses an automated machine to perform exchanges at night whilst the patient is asleep. The machine is usually programmed to perform at least four exchanges over 8 hours (can be more, depending on individual tolerance).

At the end of the overnight exchanges, the machine can be programmed to leave the patient 'dry' for the daytime (sometimes termed night-time intermittent peritoneal dialysis, NIPD). Alternatively, the machine can perform a 'last fill', leaving PD fluid in the peritoneum. Patients may then perform a further exchange during the day (either manually or using the APD machine (sometimes termed continuous cycling peritoneal dialysis or CCPD)).

Tidal APD

Has the machine programmed to only partially drain out PD fluid at the end of any dwell during the nightly cycles ('75% tidal' indicates that the machine will stop draining fluid out when 75% of the expected drain has been extracted). Although efficiency of dialysis is reduced, it is useful for patients whose sleep is disturbed through the discomfort experienced when 'dry' or near dry.

Assisted APD

Poor strength, limited dexterity, decreased vision, or cognitive impairment may mean that some patients are unable to perform PD themselves, although they may potentially benefit from a home-based therapy. In this circumstance, a family member or trained health care assistant can assist with lifting of the bags of dialysis fluid and the connection/disconnection of APD.

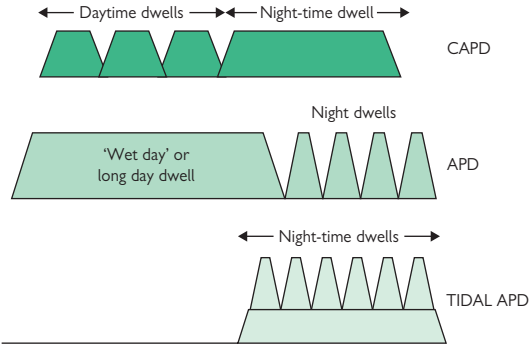


Fig. 4.8 Types of PD. Reproduced with permission from Levy J, Morgan J, and Brown E (2004). *Oxford Handbook of Dialysis*, 2nd edn. Oxford: Oxford University Press.

CAPD technique

Disconnect, flush-before-fill Y-systems are now the norm. The ‘connectology’ has been refined over the years to minimize peritonitis risk through touch contamination. At the time of an exchange, the patient connects a Y-shaped set with a sterile drain bag and a fresh dialysate bag. Patients are taught to make this connection using a sterile technique, although various assist devices are available to aid patients with dexterity or visual problems (e.g. UV Flash Compact®). After the waste dialysate is drained into the empty bag, the Y-connector is flushed (theoretically, flushing away any contaminating bacteria in this portion of the giving set), using a small volume of fresh dialysate. The remaining dialysate is infused into the patient’s abdomen. (See Fig. 4.9)

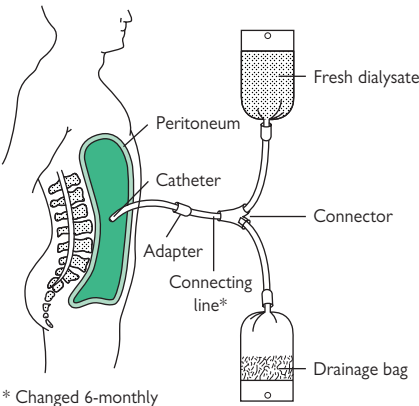


Fig. 4.9 ‘Disconnect’ PD system. Reproduced with permission from Levy J, Morgan J, Brown E (2004). *Oxford Handbook of Dialysis*, 2nd edn. Oxford: Oxford University Press.

PD fluids

Introduction

Peritoneal dialysate needs to remove uraemic toxins, normalize electrolytes, correct acidosis, and remove fluid. Ideally, fluid should be compatible with long-term peritoneal health.

- *Volume*: usually 2L but 1.5, 2.5, or 3L also available.
- *Glucose concentration*: three standard concentrations, usually about 1.5, 2.5, and 4.0% (roughly 25g, 50g, and 75g glucose per bag).
- *Sodium*: Na^+ 135mmol/L (although lower concentrations may improve salt, and thus water, removal).
- *Electrolytes*: Ca^{2+} ranges from 1.25 to 1.75mmol/L (and 0.25mmol/L of magnesium).
- *Buffer*: bicarbonate is not compatible for storage with calcium and magnesium in PD bags, so lactate (which is rapidly converted to bicarbonate in the liver) is widely used instead, at 35–40mmol/L.
- Newer solutions may contain:
 - Bicarbonate alone or in combination with lactate as buffer (using bags mixed immediately pre-infusion).
 - Icodextrin (for an oncotic gradient), rather than glucose (as an osmotic gradient), to achieve UF.
 - Amino acids as nutritional supplement. ⚠ May cause systemic acidosis.

Biocompatible solutions

PD fluid is sterilized through heat treatment. During this process, at the pH of lactate-based glucose solutions, glucose degradation products (GDP) and advanced glycation end-products (AGE) are formed. These are believed to damage the peritoneal membrane: AGE exposure correlates with fibrotic change. Thus, more 'biocompatible' solutions have been developed in an attempt to ameliorate this.

One such solution depends on a twin-bag system; heat sterilization of the compartment containing glucose (at very low pH) generates very low levels of GDP and AGE. The second compartment contains the acid buffer, e.g. predominantly bicarbonate in the case of Physioneal[®] or lactate in the case of Balance[®].

Retrospective analysis of registry data suggested patient survival was better in the group treated with biocompatible solutions, while prospective trials have shown that biocompatible fluids may preserve native urine output volumes (although not solute clearance) as well as reduce rates of peritonitis. However, definitive evidence to support their use (and increased cost) is lacking.

Solutions that rely on molecules, other than glucose, to provide the osmotic gradient have no GDP or AGE. In this respect, they can be considered biocompatible.

Commercially available PD solutions (UK)

- Baxter:
 - Dianeal[®]—glucose-/lactate-containing (see Table 4.3).
 - Physioneal[®]—glucose-/bicarbonate-containing.
 - Nutrineal[®]—contains amino acids. Osmotically equivalent to 1.36% glucose solutions.
 - Extraneal[®]—(7.5%).
- Fresenius:
 - Staysafe[®]—glucose/lactate in single compartment (see Table 4.2).
 - Staysafe Balance[®]—glucose/lactate in twin-bag system.
- Gambro:
 - Gambrosol trio 10[®].

Table 4.3 Range of glucose concentrations commercially available in the UK

	Baxter	Fresenius
'Light'	1.36%	1.5%
'Medium'	2.27%	2.5%
'Heavy'	3.36%	4.25%

Prescribing PD

Introduction

Aim for 'adequate' dialysis with as little impact on the patient's social or psychological well-being as possible. Dialysis adequacy (📖 p. 328) and UF failure (📖 p. 332) are discussed separately. The choice of CAPD or APD will depend on patient choice, lifestyle, and peritoneal transport status.

- '*High*' transporters allow rapid movement of urea and other small

The concept of 'transporter' status

High concentrations of glucose generate an osmotic gradient across the peritoneal membrane. During the dialysis dwell, glucose is gradually absorbed, leading to a fall in glucose concentration and dialysate osmolality within the peritoneal cavity.

The rate of glucose dissipation correlates with the rate at which creatinine equilibrates across the peritoneal membrane and can change over time (termed the '*transport*' status of the patient). This can be measured during a peritoneal equilibration test (PET, 📖 p. 330).

molecules across the peritoneal membrane (through small pores, 📖 p. 330). However, they also absorb glucose rapidly, dissipating the osmotic gradient so that net UF at the end of a dwell is likely to be low.

- This means that a high transporter often has difficulty achieving adequate small solute clearance.
- High transporters are particularly suitable for APD, as frequent short dwells maximize UF and total solute removal.
- '*Low*' transporters benefit less from very short dwells on APD.
- Introducing a fifth PD exchange may be preferable (either manually or using an automated machine to deliver an additional exchange at night, 📖 p. 314).
- Most patients start CAPD on four 'light' (1.36–1.5% dextrose) PD bags.
- If this fails to provide adequate UF, one exchange is changed to a higher glucose concentration bag or icodextrin containing Extraneal®.
- Further increases in glucose concentration may be necessary to achieve adequate dialysis and UF (but see 📖 p. 319).
- With long-term PD, changes in the peritoneal membrane create a tendency for low transporters to evolve into high transporters.

Following characterization of a patient's membrane transport characteristics (via a PET, 📖 p. 330), computer software can be used to predict small solute clearance and UF. These can be particularly useful when considering the necessary changes to a PD prescription in response to a reduction in UF or solute clearance.

⚠ Increasing the volume of a PD exchange can increase solute clearance, but the consequent rise in intraperitoneal pressure may adversely affect UF.

Avoiding peritoneal glucose exposure

High peritoneal glucose exposure over time (often years) predicts the development of UF failure, and causality has been suggested.

An alternative to glucose-containing dialysis solutions dialysate is icodextrin (Extraneal®).

Icodextrin is a 20-glucose polymer with potent colloidal effects (similar to albumin).

Icodextrin is particularly suited to high transporters. It acts at the small intercellular pores and is only slowly lost from the peritoneal cavity, meaning that the oncotic gradient is maintained. It ∴ produces gradual and sustained UF over long dwell periods (overnight dwell in CAPD or daytime dwell in APD).

⚠ Ensure diabetics have glucose-specific monitors, as icodextrin may cross-react with some glucometers, showing falsely high readings (i.e. there is a risk of undetected hypoglycaemia).

Peritonitis

Introduction

Peritonitis is the major complication of PD, leading to significant morbidity and mortality. Repeated episodes of peritonitis will also accelerate peritoneal membrane failure, often necessitating a transfer of modality to haemodialysis. The incidence of peritonitis has declined from about 3 episodes/patient/year in the 1980s to 0.6–0.7 episodes/patient/year (or ~1 episode every 18 months), attributed to improved patient education and better catheter technology. The disconnect 'flush-before-fill' system has also been an important advance. In addition, 'standard care' for all PD exit sites usually includes chlorhexidine-containing disinfectant wiping of plastic and daily application of a topical antibiotic ointment (such as mupirocin).

Risk factors

- T2DM, other significant comorbidity.
- Catheter type and implantation technique.
- Connection systems.
- Nasal carriage of *Staphylococcus aureus*.

Clinical features

- Abdominal pain, nausea, and vomiting.
- 'Cloudy' PD effluent is very highly suggestive.
- High fever, systemic sepsis with signs of an ileus, and peritonism may be present.

Diagnosis

- PD fluid for microscopy and Gram stain:
 - Preferably after dwell time of 4h.
 - >100 WBC/mm³ ($>50\%$ neutrophils).
- Microscopy and culture of PD fluid (discuss with microbiology) and blood.
- FBC (\uparrow WCC) and \uparrow CRP.

Patients should be taught to report cloudy effluent immediately. Abdominal pain can be severe. Rapid peritoneal flushing can improve symptoms, but samples from the original cloudy bag should be sent for microbiology (and rapid flushing should be avoided once IP antibiotics have been administered).

▶▶ Always consider other causes of peritonitis (e.g. perforation, strangulated hernia, etc.).

Bacteriology

- Gram +ve cocci: ~45–75% (coagulase-negative staphylococci, *S. aureus*), often introduced after touch contamination of the connections or following catheter exit site infection. Colonization of catheter biofilms can lead to recurrence of peritonitis and necessitate catheter exchange.

- *Gram -ve organisms*:~15–25% (*Pseudomonas*, coliforms). Usually of bowel origin. Air in the peritoneum is common and may not indicate bowel perforation. Suspect perforation if mixed organisms on culture, and arrange appropriate imaging and/or exploration.
- *Culture negative or 'no growth'*: ideally, cultures should be positive in >85% cases. Higher yields may be obtained by inoculating blood culture bottles with PD fluid.
- *Mycobacterial infections*:~1%. Consider in patients with culture-negative peritonitis not responding to empiric antibiotic therapy. Smears of PD effluent are rarely positive for acid-fast bacilli, and diagnosis is usually made on culture (6-week) or at laparoscopy/otomy, with confirmation on peritoneal biopsy.
- *Fungal*:~3%. Usually *Candida* spp. Peritonitis is infrequent but has a poor prognosis. It often follows antibiotic therapy in at-risk (e.g. malnourished) patients. PD catheter removal is mandatory.

Allergic peritonitis is well described and often found following prescription of icodextrin solutions (although it can occur with glucose-based solutions). In general, the elevation of WCC is modest, and the proportion of eosinophils in PD effluent may be high (>10%). Does not respond to antibiotics. Withdrawal of icodextrin usually helps.

Complications of peritonitis

- *Relapsing peritonitis*. A second episode of peritonitis with the same organism within 4 weeks of completing antibiotic therapy. Prolonged antibiotics (particularly for relapses secondary to *Staphylococcus*) are required. *Recurrent peritonitis* refers to a second episode of peritonitis within 4 weeks with a different organism.
- *Antibiotic treatment failure*. Consider infected, encysted fluid collections and frank abscess formation if no response to protocol antibiotic therapy (→ CT abdomen and pelvis). ⚠ PD catheters will generally require removal, and a laparotomy should be considered, especially if there is a suggestion of other intra-abdominal pathology.
- *Acute and chronic UF failure*. Inflammation → vasodilatation → ↑ glucose absorption, ↓ glucose gradient, and impaired UF. Repeated bouts of peritonitis can lead to long-term changes in the structure and function of the peritoneal membrane, causing chronic UF failure.
- *Malnutrition*. Peritoneal protein loss through the inflamed membrane can be high. Anorexia and prolonged ileus can further impact on nutritional status.

Peritonitis: management

► Empiric antibiotic therapy should always be initiated in cases of definite peritonitis without waiting for the results of cultures. Many therapeutic protocols are available and will be influenced by local experience—discuss with your microbiologist.

The International Society of Peritoneal Dialysis (2010) recommends:

- Gram +ve cover with vancomycin or a cephalosporin, *plus*
 - Gram –ve cover with an aminoglycoside or third-generation cephalosporin.
- IP administration is more effective than IV.
- In the UK, despite concerns surrounding the development of vancomycin resistance, most units utilize vancomycin-based regimens. Protocols differ from unit to unit, but, as an example:
- Vancomycin 2g IP on day 1, with a further dose on days 3–7, depending on trough vancomycin levels (aim to keep trough level >15 micrograms/mL, *plus*)
 - Either gentamicin 0.6mg/kg IP daily (adjusted against trough gentamicin levels on days 3–5; ⚠ ototoxicity) or, alternatively, to spare potential aminoglycoside toxicity, ceftazidime 1g IP daily.

Once culture result and sensitivities known:

- *If Gram +ve*: continue vancomycin according to levels. If *S. aureus*, add in rifampicin 300mg PO bd. Stop gentamicin/ceftazidime.
 - *If Gram –ve*: continue ceftazidime or gentamicin. Although concerns about aminoglycosides affecting residual renal function exist, this is not borne out by current evidence. However, if the patient still has a significant UO (e.g. >500mL), many centres may prefer ceftazidime over gentamicin. Stop vancomycin.
 - *If culture negative*: continue both Gram +ve and Gram –ve cover, doses adjusted according to trough levels.
 - *If mixed Gram –ve growth*: add in metronidazole, and consider laparotomy (► suspect bowel perforation).
 - Treat for 14–21 days.
- ⚠ PD programmes with a high incidence of fungal peritonitis after antibiotics may consider prophylaxis with oral fluconazole.
- Mupirocin ointment administered to the catheter exit site can prevent exit site infection and, potentially, *S. aureus* peritonitis.
- Every episode of PD-related peritonitis should prompt a root cause analysis and review of aseptic technique.

Special considerations for APD

Even in the absence of peritonitis, long day dwells may be 'misty'. However, because cycling times are shorter, cloudy overnight dialysate may not occur, even in the presence of peritonitis. Moreover, in some cases, PD effluent is drained directly into a sink.

This means it is very important for APD patients to recognize potential symptoms of peritonitis and to perform a dwell of at least 2 hours (for visual inspection and sampling of fluid for M, C+S).

Treatment also requires some modifications to normal APD technique. One option is to convert patients to CAPD for the duration of the episode. More preferable is to give antibiotics into the last dwell on the machine (sometimes called the first ambulatory dwell).

Indications for PD catheter removal during infection

- ► Refractory peritonitis (cloudy bags persists after 5 days of appropriate antibiotic therapy).
- Relapsing peritonitis (📖 p. 321).
- Fungal peritonitis.
- Persistent exit site or tunnel infection.
- Potential:
 - Multiple episodes of peritonitis in an individual patient.
 - Mycobacterial peritonitis.
 - Peritonitis caused by multiple organisms of likely enteric origin.

Other PD complications

Catheter exit site infection

A purulent \pm bloody discharge from a PD catheter exit site, often associated with erythema and pain. Crusting alone is not indicative of an acute exit site infection. Scoring systems have been developed, including this one recommended by the ISPD (see Table 4.4).

Table 4.4 Exit site infection scoring system

	0 points	1 point	2 points
Swelling	No	Exit only; <0.5cm	>0.5cm and/or tunnel
Crust	No	<0.5cm	>0.5cm
Redness	No	<0.5cm	>0.5cm
Pain	No	Slight	Severe
Drainage	No	Serous	Purulent

Reproduced from Piraino, B, Bailie, GR, Bernardini, J, et al. Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int* 2005; 25:107.

Causes

- Usually *S. aureus*, *Pseudomonas*.
- The use of prophylactic topical exit site ointment (e.g. mupirocin) reduces such infections. Reducing nasal carriage of *S. aureus* is also helpful.

Treatment

- Swab for culture, and confirm PD fluid is clear.
- *Empiric therapy*: start flucloxacillin 500mg PO qds or ciprofloxacin 500mg PO bd if there is a history of Gram $-ve$ infection.
- Topical antibiotics are not sufficient.
- Adjust therapy once culture result and sensitivities known.
- *Gram +ve organisms*: continue flucloxacillin, unless sensitivities dictate otherwise. Treat for 14 days. If *S. aureus* confirmed, consider adding rifampicin 300mg bd.
- *Gram $-ve$ organisms*: ciprofloxacin 500mg PO bd for 14 days.
 ⚠ If *Pseudomonas*, dual treatment is often recommended (e.g. add IP gentamicin or ceftazidime), and catheter change is often required.

Exit site trauma increases the likelihood of infection—it should \therefore be protected from this (including dressings that immobilize the catheter, thereby preventing pulling on the exit site).

Increasing the frequency of exit site care (to daily or twice daily dressings) is often advocated during infections. Crusts or scabs should not be forcibly removed.

A tunnel infection is defined as erythema and/or tenderness over the subcutaneous catheter pathway \pm intermittent discharge from the exit site. Diagnosis of tunnel infection is usually obvious clinically but can be confirmed by ultrasound examination. Treatment usually involves removing the catheter, as peritonitis is a common complication.

Drainage problems

This needs to be differentiated from the more serious UF failure. Catheter flow problems can present with either slow drainage (drainage takes >15–20 minutes under gravity) or incomplete drainage (high residual volume measured on PET or drain volume is less than the infused volume of a ‘rapid’ exchange).

Causes include:

- Constipation.
- Catheter malposition (usually migration out of the pelvis).
- Catheter occlusions (kinking, thrombus, fibrin, and omental wrapping).
- Fluid leaks into subcutaneous tissue via hernias or at the catheter insertion site.

Inflow problems can also occur for similar reasons—and also if the catheter tip is trapped in an area of intra-abdominal adhesions. Clinical assessment will usually determine the majority of causes. If necessary, plain KUB can be performed to exclude catheter malposition and constipation.

The majority of drainage problems can be improved without surgical intervention:

- Laxatives (most PD patients require regular laxatives, e.g. senna and lactulose, but a short course of a stronger aperient, such as sodium picosulfate, may be required).
- Intracatheter heparin locks (e.g. 500 units as a lock or 500 units/L in exchanges), particularly if visible fibrin in catheter or drainage fluid.
- Thrombolytics, such as urokinase, may be instilled in the catheter lumen.
- Endoluminal brushing (⚠ infection!).

If surgical repositioning of the PD catheter is required, a concomitant adhesiolysis and omentectomy should be considered.

Peritoneal leaks

Dialysate may leak down the catheter tunnel and spread into the subcutaneous tissues (or leak around the exit site). A patent processus vaginalis may allow PD fluid to track into the scrotum, mimicking a hernia or hydrocele. Small diaphragmatic hernias may permit PD fluid to enter the pleural space (usually on the right side).

Clinically, local oedema ± peau d’orange skin appearance may signify a subcutaneous leak. Pleural taps or aspirates from hydroceles can be tested for glucose concentration to confirm it is dialysis fluid. If in doubt, perform CT peritoneogram, e.g. infuse 100mL of non-ionic contrast into a 2L PD bag, and drain in 1L. Perform CT 1–2 hours thereafter.

Leaks around the catheter often heal with temporary (2–4 weeks) discontinuation of PD (temporary HD will usually be required). PD can be restarted, using smaller exchange volumes to reduce intra-abdominal pressure. If leaks recur, the PD catheter can be repositioned with a new insertion site. Hernias should be repaired in a standard manner. APD with a dry day (NIPD) can be particularly successful to minimize recurrence.

Sclerosing encapsulating peritonitis (SEP)

SEP is a feared complication of long-term PD therapy, with a poor prognosis. It is extremely rare before 3 years and has an incidence around 5% at 5 years.

The peritoneal cavity becomes encased in fibrous tissue, with bowel wall thickening and peritoneal calcification. It is thought to be multifactorial in origin, with prior severe/recurrent peritonitis, foreign body reactions to plasticizers on catheters, and long-term PD exposure to high concentration glucose-containing solutions all suggested to be pathogenic.

Clinically

- Symptoms of intermittent bowel obstruction (abdominal pain, nausea, vomiting).
- Poor UF or UF failure (📖 p. 332).
- Malnutrition is frequent and may be severe.
- Symptoms may occur after peritonitis and often after stopping PD (e.g. post-transplantation).

Investigation

- CT abdomen is the investigation of choice, demonstrating peritoneal thickening and calcification with entrapped bowel loops.
- Laparoscopy and peritoneal biopsy is diagnostic.

Management

- Evidence is limited:
 - Stop PD (symptoms may paradoxically worsen).
 - Early specialist dietetic input. Nasogastric feeding or TPN may be required.
 - 🧪 Drug therapy: immunosuppression (steroids, CNIs, azathioprine) and tamoxifen (antifibrotic) have all been tried, but evidence of efficacy is anecdotal at best.
 - Surgery (enterolysis) is an option but only in specialist centres.
 - Renal transplantation—some reported cases of improvement.

Prevention

- There are no effective screening tests, and onset may be rapid.
- Currently, there is no optimal duration of PD therapy, and decisions should be tailored to the individual.
- Switching to HD may be advisable, based upon episodes of peritonitis and/or deteriorating membrane function/UF failure.

PD adequacy

Introduction

Although the term dialysis adequacy is often restricted to the formal calculation of delivered dialysis dose in terms of weekly clearance of urea (Kt/V) and creatinine (CrCl) (📖 p. 286), the measurement of dialysis adequacy should mandate a more global assessment of health, including:

- Absence of uraemic symptoms.
- Nutritional status, appetite, weight, serum albumin.
- Fluid status.
- Quality of life (e.g. by subjective global assessment scoring).
- Improved biochemistry and correction of the complications of uraemia, such as anaemia.

Delivered dialysis dose can be formally measured by calculating weekly clearance for urea (Kt/V) and creatinine (CrCl) (📖 p. 286). The utility of Kt/V, a kinetic measure derived from HD practice, remains contentious in PD. Commercially available computer programmes will helpfully calculate urea and creatinine clearances, based on dialysate and plasma urea and creatinine values obtained during a PET (📖 p. 330) or other standardized regimen.

The current US and UK PD adequacy targets are very similar:

- US KDOQI:
 - Measure after 1 month, then 4-monthly.
 - If residual urine output >100mL/day: combined urine and peritoneal weekly Kt/V should be >1.7.
 - If residual urine output <100mL/day: peritoneal weekly Kt/V should be >1.7.
- UK Renal Association:
 - Measure 6-monthly (or more frequently, if indicated).
 - Combined urinary and peritoneal Kt/V $\geq 1.7/\text{week}$ or CrCl $\geq 50\text{L}/\text{week}/1.73\text{m}^2$.
- Although there is no evidence that increasing the dose above these targets improve survival, it is generally accepted that they should be viewed as minimum treatment standards and that the dialysis dose should be increased as clinical circumstances dictate.

▶ The most powerful predictor of patient survival on PD is not dialysis adequacy, but the presence of residual renal function.

Preserving residual function is extremely important:

- Control BP, with preferential use of ACE-I or ARB.
- Avoid nephrotoxins, e.g. NSAIDs, aminoglycosides, contrast, etc.
- Avoid dehydration and hypercalcaemia.

How to improve a low $Kt/V \pm CrCl$

Tailor changes, according to transporter status (📖 p. 318) Increasing dialysate osmolality to increase UF and drain volumes will also improve total clearance.

CAPD

- If high or high average transporter:
 - The osmotic gradient is lost quickly, so reduce dwell times (possibly allowing an additional exchange).
 - Consider converting to APD to allow rapid cycling overnight.
 - Increasing dwell volumes is unlikely to help, as it will slow down exchanges and may reduce UF.
- If low or low average transporter:
 - More time is required, as solute clearance is slower.
 - Increasing dwell volumes and dwell times may help.
 - Consider an overnight dwell.

APD

- Optimize cycle duration in accordance to patient transport status, as described in 'CAPD' section (short cycles for high transporter). This might necessitate increasing total duration of APD. Consider the use of additional daytime exchanges.

The peritoneal equilibration test (PET)**The test**

- The evening prior to PET, the patient performs a standard CAPD exchange. The exchange should dwell for 8–12h.
- Drain overnight dwell over 20min, and note volume.
- Prepare a 2L 2.27%/2.5% dialysate solution bag at body temperature, and infuse over 10min, with the patient in a supine position.
- After 10min, dialysate samples are collected as follows: drain 200mL dialysate back into the fill bag, and mix sample by inverting bag 2–3 times. Using aseptic technique, withdraw 10mL dialysate sample, and send for determination of creatinine and glucose.
- Repeat at 2h.
- At 4h, completely drain the exchange over 20min. Weigh drain bag, and record volume drained.
- Invert bag 2–3 times; send samples for creatinine and glucose.
- PET calculations:
 - D_{cr}/P_{cr} = dialysate concentration of creatinine at 0, 2, and 4h, divided by serum concentration of corrected creatinine.
 - D/D_0 = dialysate glucose concentration at 2h and 4h, divided by dialysate glucose concentration at 0h.
- Residual renal function is estimated on 24h urine collection.

Interpretation

- If protocols are strictly followed, this is a highly reproducible assessment of peritoneal membrane transport function.
- The ratio of dialysate and plasma creatinine concentrations (D_{cr}/P_{cr} ratio) after a 4h dwell is a measure of solute equilibration.
- High transporters are defined by a $D_{cr}/P_{cr} > 0.8$ and low transporters < 0.5 .
- In between these are high average (0.65–0.8) and low average (0.5–0.64).

Since glucose absorbed from the dialysate is very quickly metabolized, D/P ratio for glucose is meaningless. Instead, the fraction of glucose absorbed from the dialysate at 4h is compared with the initial dialysis solution (D/D_0). This is also a useful indicator of transport status.

A PET is also a useful objective assessment of ultrafiltration. However, a UF volume $< 400\text{mL}$ after modified PET, utilizing a 3.86% glucose dwell, is more specific for UF failure (📖 p. 332).

Ultrafiltration (UF) failure

PD patients with fluid overload are either struggling to be compliant with a realistic fluid restriction or have inadequate UF. Inadequate UF might be the result of an inappropriate dialysis prescription or the failure of an appropriate prescription to remove adequate fluid volumes; the latter is termed *UF failure*.

PD patients are asked to achieve an ideal dry weight through a fluid restriction and the use of hyperosmolar PD bags to produce UF. Residual urine output (which may be stimulated with diuretics) is also very important.

As a general rule, a patient should be able to UF $\geq 1\text{L/day}$. If they are anuric, (defined as $\text{UO} < 100\text{mL/day}$), then minimum daily UF should be 750mL.

Approach

(See Fig. 4.10)

- Consider modified PET (sometimes called standardized permeability analysis) to differentiate UF failure from other cases of fluid overload. ► Net UF $< 400\text{mL}$ at 4h with 3.86% glucose defines UF failure.
- Determining transporter status can also help diagnose the cause of UF failure; in particular, is the patient a high transporter (📖 p. 318)?
- Evaluate the residual peritoneal volume during PET: a 'normal' residual volume is up to 200–250mL. Higher volumes might suggest catheter-related drainage problems, rather than UF failure (i.e. the patient may be removing fluid through UF, but it does not drain out adequately from their peritoneal cavity). Also check drain time during the PET.
- Exclude 'mechanical' catheter or APD equipment problems (📖 p. 325).
- Avoid long dwells ($> 4\text{h}$) with low glucose concentrations.
- Use icodextrin, instead of glucose, for the longest dwell.
- If on APD, consider additional short day exchange.

Causes

- High transporter status (often seen in long-standing PD patients).
- If not high transporter, consider:
 - Leaks (📖 p. 325).
 - Reduced effective peritoneal surface area from peritoneal adhesions.
 - Increased lymphatic absorption.
 - Aquaporin deficiency or failure (indicated by loss of sodium sieving during modified PET/standardized permeability analysis).
 - Patients with ultrafiltration failure will usually need to be switched to HD permanently. However, peritoneal membrane function can sometimes be improved by resting PD (for 4–12 weeks) and might be considered where quality of life on long-term HD will be poor (e.g. excessive travel times).

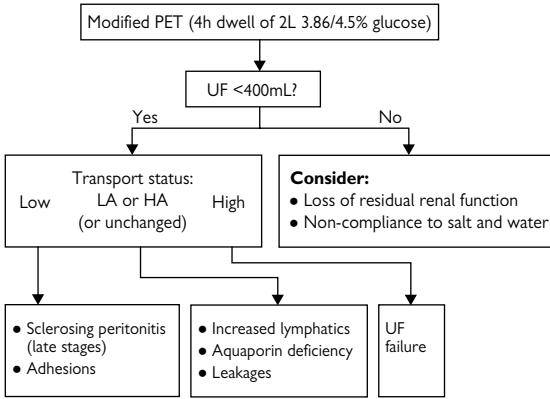


Fig. 4.10 Algorithm for diagnosing the cause of hypervolaemia in PD. LA = low average. HA = high average.

The well PD patient

Introduction

Adequate dialysis: maintain residual renal and peritoneal membrane function.

- Dialysis adequacy should be measured in terms of clearance of small solute clearance (including Kt/V and CrCl) and nutritional parameters.
- Aim for normotension by good salt and water removal—generally, achieving minimum daily fluid removal of >750mL.
- Preserving residual renal function (basically, UO) makes these goals easier to achieve and may improve outcomes (making an argument for use of ACE-I for ongoing renoprotection and avoiding nephrotoxins in PD patients; ► residual urine matters).

Changes in patients' transport status over time (📖 p. 318) may make the maintenance of satisfactory UF and small solute clearance difficult without imposing onerous dialysis regimens and unrealistic fluid restrictions on them. High intraperitoneal glucose concentrations, with consequent exposure to GDP or AGE, is suggested to accelerate peritoneal membrane changes, so the use of low GDP solutions, such as twin-bag 'physiological' solutions, icodextrin, or amino acid solutions, *may* be desirable (👁️).

Complications

Minimize peritonitis episodes and exit site infections through education and good technique. This includes teaching the patients to identify peritonitis at an early stage. Monitor nutritional status closely. The initial stages of sclerosing encapsulating peritonitis (SEP) may be reversible; early diagnosis relies on high index of suspicion.

Social rehabilitation

PD is a home-based treatment that allows patients to retain their independence. It is important to grant individual PD patients a degree of flexibility, e.g. adapting the timing of PD exchanges to work environments (perhaps negotiating a dedicated area and delivery of fluids to the work place). Travel (either within the same country or abroad) improves patients' sense of well-being and should be encouraged. Support for the other family members, including children and spouse, must never be overlooked.

Transplantation

- Transplantation: benefits and challenges 336
- Transplantation outcomes 340
- Basic transplant immunology 346
- Pre-transplant work-up 350
- Compatibility: matching donor and recipient 360
- Live donor transplantation 372
- Immunosuppression: overview 380
- Immunosuppression: induction 382
- Immunosuppression: maintenance 386
- Perioperative care 392
- The transplant operation 400
- Surgical complications 402
- Graft dysfunction 404
- Acute rejection 408
- Chronic allograft dysfunction 414
- Recurrent disease 418
- Long-term transplant follow up 422
- Post-transplant infections 426
- Cytomegalovirus (CMV) 430
- BK virus nephropathy 436
- Post-transplant UTI 438
- Post-transplant malignancy 440
- ABO- and HLA-incompatible transplantation 444
- Kidney–pancreas transplantation 446

Transplantation: benefits and challenges

Introduction

For many patients with ESRD, transplantation is undoubtedly the treatment of choice. However, for some, the risks of transplantation (the surgery itself plus subsequent immune suppression) will outweigh potential benefits. Suitability for transplantation has no set criteria but should reflect the recipient's physical status ('fitness'), likely quality of life post-transplantation, and, wherever possible, the patient's wishes (which assumes adequate education).

Benefits of transplantation

- Improved patient survival:
 - It is not fair to make a straight comparison between the survival of dialysis patients and the survival of transplanted patients, as many dialysis patients are elderly ± have comorbidities that preclude transplantation.
 - However, if the playing field is levelled and patient's survival post-transplant is compared to a matched transplant-listed dialysis cohort, there remains a significant survival advantage, once the initial risk of surgery is overcome (Fig. 5.1).
 - Much of this improvement appears to stem from a reduction in CV mortality.
- Improved quality of life:
 - Freedom from the constraints of dialysis treatment, including the time commitment and both dietary and fluid restrictions.
 - Improved overall sense of well-being.
 - Improved exercise capacity.
 - Improved quality of life for close family.
- More complete and physiological correction of the uraemic milieu, including complications, such as anaemia and CKD-MBD.
- Improved sexual function and fertility, including the potential for successful pregnancy in ♀ (📖 p. 864).
- Better for the health economics: transplantation is less expensive than dialysis (after the first year).

🔍 The risk-benefit ratio of renal transplantation is changing, although much of the currently available data may not adequately reflect this. There is a significant difference between transplanting a 70-year-old dialysis patient from a live donor and with an organ from a marginal deceased donor, particularly if the recipient is thriving on a state-of-the-art daily home dialysis therapy. Preliminary outcome data suggest satisfactory, albeit less good, early outcomes, but patients must be very carefully selected, given appropriate (and realistic) information and education and longer-term outcomes, including quality of life, need further evaluation.

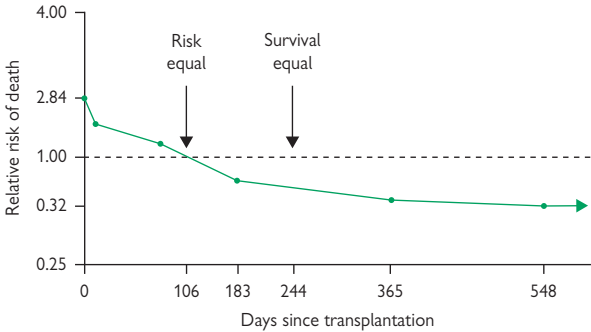


Fig. 5.1 This much reproduced graph shows survival in transplanted patients, compared to those remaining on the waiting list. Reproduced with permission from R. Wolfe et al. *NEJM*; 341, 1725–1730.

Challenges

- The number of patients listed for transplantation globally has plateaued in recent years after an extended period of relentless growth. Demand continues to outstrip the supply of organs (see Figs 5.2 to 5.4).
- This inevitably leads to longer waiting times for deceased donor transplantation (mean ~3 years in the UK).

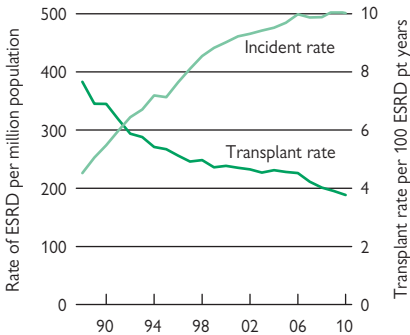


Fig. 5.2 The number of candidates awaiting transplant continues to increase, but transplant rates per 100 dialysis patient years continue to decline (despite a progressive increase in the number of transplants; see Fig. 5.5). Reproduced from USRDS 2012 annual report, used with permission.

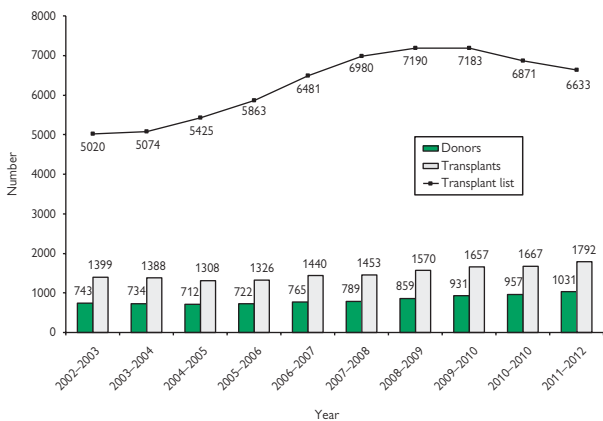


Fig. 5.3 Number of deceased donors and all solid organ transplants in the UK, 2002–2012 and patients active on the transplant list. Reproduced from UK Blood and Transplant Annual Report 2012, with permission.

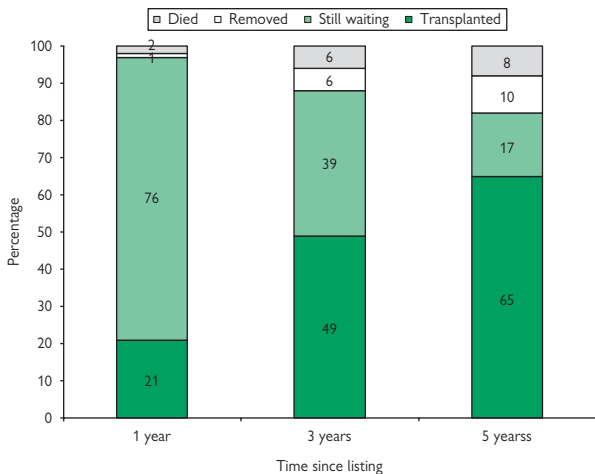


Fig. 5.4 Post-registration outcome for 3,055 new adult kidney only registrations in the UK, 2006–2007. Reproduced from UK Blood and Transplant Annual Report 2012, with permission.

- This disparity has encouraged the use of organs from more marginal donors, e.g. donation after cardiac death (DCD) and elderly donors with acknowledged comorbidity (📖 pp. 366–8). (See Fig. 5.5)
- Other efforts to expand the donor pool include the growth of live donor programmes (including altruistic donation), dual transplants (📖 p. 401), ABO- and HLA-incompatible grafts, and paired schemes (📖 pp. 444–5).
- The CKD population is ageing. The median age of prevalent dialysis patients in the UK is ~65. This more elderly population is also more comorbid, making selection for successful transplantation (and appropriate matching of organs) more challenging.
- The ultimate goal is to prolong both patient and graft survival post-transplantation. This requires:
 - More effective and less toxic immune suppression.
 - ↓ morbidity and mortality from infection, malignancy, and CV disease (▶ better transplant function → lower CV mortality).

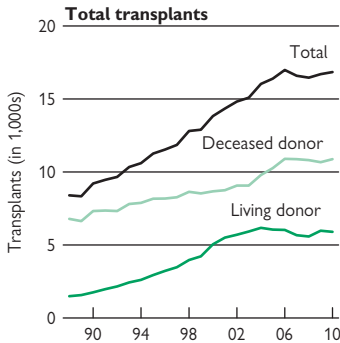


Fig. 5.5 The number of both live and deceased donor transplants has increased significantly over the last two decades and plateaued in recent years. Increases in deceased donor transplantation reflect higher rates of donation after cardiac death (DCD) and the use of extended criteria donors (ECD)—a trend that is likely to see further increases over the next decade. Reproduced from USRDS 2012 annual report, with permission.

Transplantation outcomes

Renal transplant outcomes are traditionally measured in terms of:

- Graft survival (see Fig. 5.6).
- Patient survival.
- Graft function (e.g. SCr \pm eGFR at 1, 3, or 5 years).

Data come from large national and international registries. The most important of these are:

- US Renal Database System (USRDS).
- The Collaborative Transplant Study (CTS).
- United Network of Organ Sharing (UNOS).
- The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).
- UK National Transplant Database (maintained by NHS Blood and Transplant).

Box 5.1 Key facts

- The 1-year survival for deceased donor renal transplants is ~91%. Patient survival is >95%.
- The 1-year survival for live donor renal transplants is ~97%. Patient survival is >98%.
- This has steadily improved over the last two decades.
- The 5-year survival for deceased donor renal transplants is ~70%. Patient survival is ~80%.
- The 5-year survival for live donor renal transplants is ~82%. Patient survival is ~90%.
- The 10-year survival for deceased donor renal transplants is ~45%. Patient survival is ~60%.
- The 10-year survival for live donor renal transplants is >55%. Patient survival is ~75%.

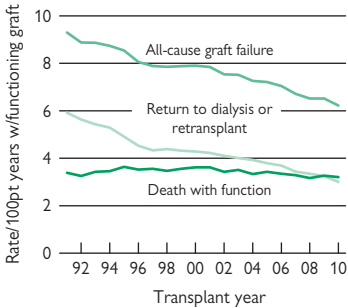


Fig. 5.6 The overall graft failure rate among adult (age >18) transplant recipients per 100 patient years is falling year on year, although the percentage that die with a functioning graft remains unchanged. Reproduced from USRDS 2012 annual report, with permission.

Patient survival

The principal causes of death post-transplantation are CV disease, infection, and malignancy (see Fig. 5.7).

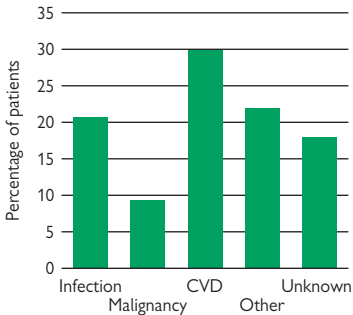


Fig. 5.7 Causes of death in patients with a functioning graft. Reproduced from USRDS 2012 annual report, with permission.

Factors influencing graft survival

- Delayed graft function (DGF):
 - Variably defined (p. 404).
 - ~3% in live donor and ~20% in deceased donor kidneys (the rate will vary significantly, e.g. ~30% for ECD kidneys and ~40% for DCD kidneys).

- DGF is itself a function of \uparrow donor age, \uparrow cold ischaemic time, and the presence of significant anti-HLA antibodies (📖 p. 405).
- DGF is associated with \downarrow graft survival, \uparrow mortality, \uparrow rejection (\rightarrow probably enhanced graft immunogenicity post-reperfusion).
- HLA matching:
 - For deceased donor kidneys, better HLA matching is associated with improved graft survival.
 - This falls progressively with increasing mismatch (see Fig. 5.8).
 - The effect is much less pronounced for live donor kidneys, whether related or unrelated.
- Timing of transplantation:
 - Pre-emptive transplantation provides a survival benefit for both graft and recipient.
 - Graft survival deteriorates, with longer times on dialysis pre-transplantation. Reasons: more recipient CV disease, higher incidence of DGF, socio-economic factors.
 - In the UK, $\sim 35\%$ of adult live donor and just $\sim 10\%$ of deceased donor transplants are pre-emptive.

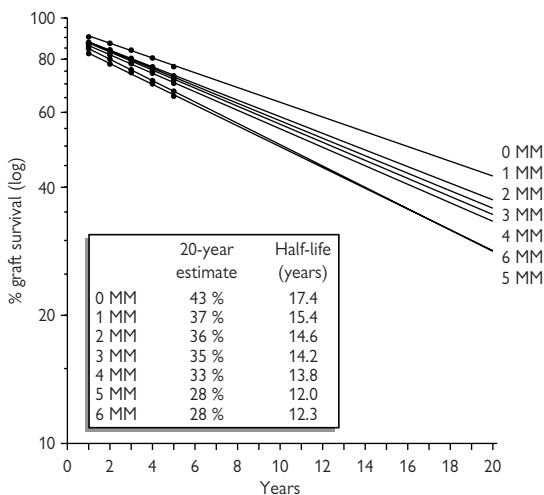









Fig. 5.8 Percentage survival HLA A + B + DR mismatches: first cadaver kidney transplants, 1985–2011. Reproduced from the Collaborative Transplant Study (🌐 <http://www.ctstransplant.org>), with permission.

- Donor factors:
 - Age: 5-year survival of a deceased donor kidney from a donor age 18–34 is ~80%, compared to ~55% for donor age >65. ⚠ This is a very important issue, as the average donor age is progressively increasing.
 - Living donor grafts last longer than deceased donor grafts (less cold ischaemia, better health of donor, often less time on dialysis accruing CV disease and other complications, higher nephron mass, better recipient compliance). See Box 5.1 on  p. 340.
 - Donation after brain death (DBD) kidneys have better outcomes than those donated after cardiac death (DCD) ( pp. 365–8).
 - ECD kidneys have poorer, if acceptable, outcomes overall (although this can be difficult to predict at the time of transplantation).
 - ↑ cold ischaemic time (CIT) → ↑ DGF → ↓ graft survival. This risk is particularly high when CIT >18h. The time it will take to transport a kidney is usually taken into account in organ allocation schemes ( p. 365).
- Recipient factors:
 - Age. The commonest cause of graft loss beyond age 65 is death with a functioning transplant.
 - Race. In the USA, black recipients of deceased donor transplants have poorer outcomes than Caucasian recipients. This is partly due to ↑ DGF in black recipients as well as inferior HLA matching (the donor pool is predominantly Caucasian).
 - Obesity and other comorbidities (↑ BP, CV disease) ( pp. 370–1).
 - The nature of the recipient's original native kidney disease and the risk of this disease recurring in the transplant.
- Rejection episodes ( p. 408):
 - ► A single episode of rejection reduces 5-year graft survival by ~10%.
 - The greater the number of episodes, the worse the outcome.
- HLA antibodies ( p. 361–4):
 - About ~20% recipients develop anti-HLA antibodies post-transplantation.
 - The development of such antibodies *trebles* the risk of graft failure (whether or not they are donor-specific).
 - Donor-specific anti-HLA antibodies (DSA) are associated with chronic antibody-mediated rejection ( p. 414–6).
- Proteinuria:
 - As in native kidneys, a marker of renal injury, the risk of progressive renal dysfunction, and overall CV morbidity and mortality. May also herald recurrent native disease.
- Number of previous transplants (see Fig. 5.9).

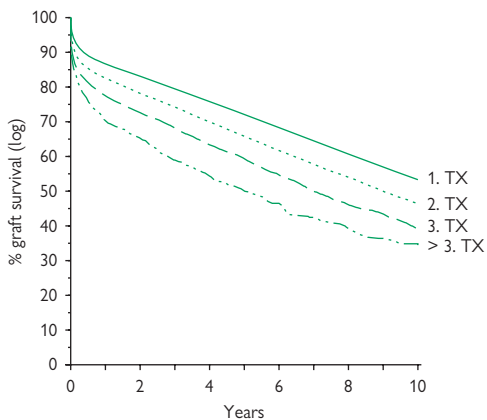


Fig. 5.9 Graft survival over time, according to number of previous transplants in an individual. Reproduced from the Collaborative Transplant Study (<http://www.ctstransplant.org>), with permission.

Basic transplant immunology

Introduction

A transplanted kidney will be antigenically distinct from its new host and recognized as foreign and initiate an immune response, unless it is from a genetically identical individual (essentially, an identical twin). In the context of transplantation, these antigens are known as alloantigens (and the donor kidney is often referred to as an allograft). The most relevant alloantigens to transplantation are a group of histocompatibility genes known as the major histocompatibility complex (MHC). Minor histocompatibility antigens are also relevant although less important. Alloantigen recognition triggers immune cell activity and the activation of multiple potent effectors of the immune response.

Histocompatibility and allorecognition

The MHC presents fragments of 'non-self' proteins to T cells in order to initiate an immune response. In humans, the MHC genes on chromosome 6 encode a polymorphic group of proteins called human leucocyte antigens (HLA). Their main function is to present antigens to T cells. There are two classes:

- Class I HLA includes HLA-A, HLA-B, and HLA-C and is present on all nucleated cells, including vascular endothelium. They exist as a heterodimer with β_2 microglobulin. Class I molecules present non-self peptides to cytotoxic CD8⁺ T cells, leading to their activation. Self-antigens are not recognized, as immunological tolerance, to them, has developed during T cell maturation.
- Class II HLA includes HLA-DR, HLA-DQ and HLA-DP and is present mainly on antigen-presenting cells (APCs), including macrophages, mesangial cells, and dendritic cells. Other cells can be induced to express class II HLA during conditions of inflammation. They are also heterodimers but consist of two polymorphic chains (i.e. no β_2 microglobulin). Class II antigens present peptides to CD4⁺ T cells, leading to their clonal expansion. In addition, activated CD4⁺ cells release cytokines that activate CD8⁺ cells.

Each individual inherits an HLA allele from each parent (a haplotype).

The recognition of transplanted HLA by recipient T cells is by *direct* and *indirect* pathways (see Fig. 5.10).

- *Direct pathway.* Donor (passenger) APCs present foreign peptides to recipient cytotoxic CD8⁺ T cells, leading to their activation. This pathway is largely responsible for early acute cell-mediated rejection.
- *Indirect pathway.* Donor cells or donor proteins shed from cell surfaces are engulfed by recipient APCs and presented to recipient CD4⁺ helper T cells. This is thought to mediate more chronic graft damage.

The binding of a T cell to an APC leads to the initiation of the immune reaction. This process requires three distinct steps or 'signals':

- *Signal 1 (TCR activation).* Binding of APC MHC-peptide complex to the T cell receptor (TCR) activates multiple intracellular pathways. One of these pathways involves the phosphatase calcineurin (\uparrow intracellular

Ca^{2+} → activation of calcineurin → activation of nuclear factor of activated T cells (NFAT) → IL-2 release (but only in the presence of signal 2).

- **Signal 2 (co-stimulation).** Binding of complementary co-stimulatory pathway molecules present on APC and T cells (e.g. CD40:CD40 ligand and ICAM:LFA1) → activation of tyrosine kinase, which, together with signal 1, leads to induction of IL-2 and other T cell activation genes. Other interactions, such as B7:CTLA4, are inhibitory.
- **Signal 3.** Signals 1 + 2 → induction of cytokine, cytokine receptors, and cell activation genes (including IL-2 and IL-2R) → clonal proliferation.

If signal 1 occurs without the subsequent signal 2, then T cell activation is not initiated, and instead *apoptosis* results.

T cell activation

T cell activation involves their proliferation and clonal expansion (meaning all cells express the same TCR), prior to differentiation into effector cells (which no longer require co-stimulation for activation) (see Fig. 5.11).

CD4+ effector cells include TH1, TH2, regulatory and memory cells:

- TH1 cells activate macrophages, provide help to B cells, and synthesize several important cytokines.
- TH2 cells mainly provide B cell help (including immunoglobulin class switching).
- TH17 cells are involved in inflammatory responses (e.g. to bacteria).
- Regulatory T cells (Tregs) suppress T cell responses.
- Memory T cells are a component of immunological memory (the ability to respond promptly and intensely, following antigen representation).

CD8+ cells develop into a single cytotoxic effector cell population, involved in the killing of both infected cells and tumour cells.

B cells

B cells are responsible for antibody production. B cell activation follows antigen recognition via the B cell receptor (BCR—itsself a type of antibody) and requires additional T cell help (provided by CD4+ TH1 and TH2 cells—see above). B cells represent the antigen that has triggered them (with MHC class II), so T cells reactive to the same antigen provide the help. Activation leads to proliferation prior to differentiation into antibody-producing plasma cells (usually found in bone marrow). A small proportion of activated B cells will become memory B cells.

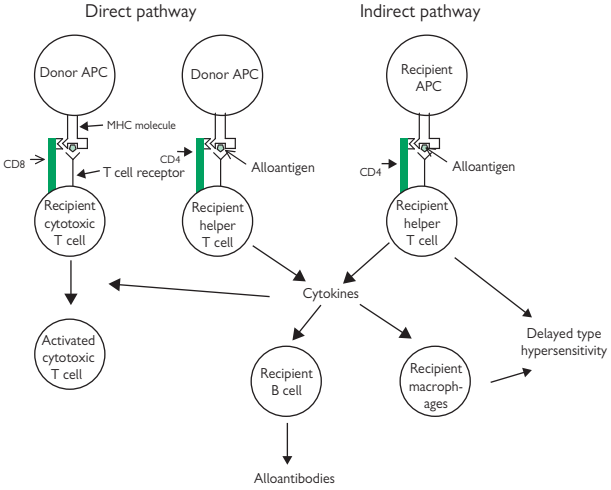


Fig. 5.10 Direct and indirect recognition.

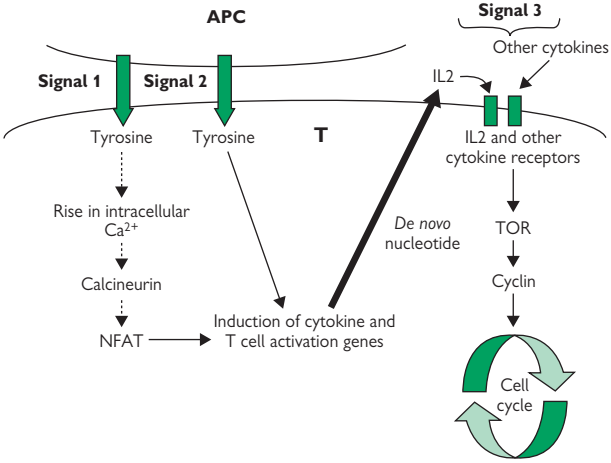


Fig. 5.11 T cell activation. TOR, target of rapamycin (sirolimus).

Tolerance

- The holy grail of organ transplantation: permanent survival of a transplant without the need for maintenance immunosuppression.
- Tolerance implies that alloreactive cells have either been deleted or do not respond to transplanted alloantigens.
- An important and exciting focus of international research efforts in transplantation (see <http://www.immunetolerance.org>).
- Rare cases of tolerance are recognized in renal transplantation (usually in the context of non-compliance!).
- The induction of tolerance has proved possible in rodent models but remains elusive in humans, probably because we have a much more extensive immunological memory.
- Many reports claim partial tolerance, based on the minimal use of immunosuppressive drugs (e.g. lower levels of maintenance immune suppression, following induction with alemtuzumab).
- Complete tolerance has been described in the context of renal after bone marrow transplantation (BMT) from the same donor. This is because BMT may result in the total replacement of the recipient's bone marrow (and \therefore haematopoietic cells) with the donor's—a state known as full chimerism.
- Similar principles have been applied with some success to patients with multiple myeloma and ESRD undergoing combined BM and renal transplantation.
- It is also known that infusion of donor-derived bone marrow cells can improve graft survival, and there is interest in translating this into immunosuppressive strategies.
- Successful protocols have been reported, utilizing donor cell infusions (CD34 +ve progenitor cells and CD3 +ve T cells), but they require formidable conditioning regimens (total lymphoid irradiation and T cell depletion) so are unlikely to be universally accepted.
- In addition, these protocols involve well HLA-matched transplants. It is not clear how such approaches will translate to the much more challenging setting of HLA-mismatched transplantation (BMT across HLA barriers is problematic \rightarrow \uparrow rejection and graft vs host disease).
- A likely future approach will be to specifically bioengineer cell therapy with haematopoietic stem cells (e.g. see <http://www.onestudy.org>).

Pre-transplant work-up

Patient selection

All patients approaching ESRD should be considered for transplantation, unless there is an absolute contraindication. The first step is appropriate education so that they understand the need to proceed through a series of structured investigations.

Contraindications

UK BTS guidelines suggest the following absolute contraindications:

- Uncontrolled malignancy.
- Uncontrolled infection.
- ☹️ Life expectancy of <5 years.

Additional potential contraindications

- Cirrhosis (unless combined liver and kidney transplant).
- Primary oxalosis (unless combined liver and kidney transplant).
- Substance abuse.
- Morbid obesity (☹️ cut-off BMI unclear).
- Recent MI or coronary intervention (see Assessment for cardiovascular disease, 📖 p. 352).
- Ejection fraction <30%.
- Habitual, irremediable, non-compliance.

Note: age alone is not a contraindication to transplantation.

Patient education

Before formal pre-transplant investigations, potential transplant recipients should ideally attend a local education session. The purpose of this forum is to provide patients (and relatives) with a greater insight into the following:


- Risk and benefits of renal transplantation.
- Live donor transplantation vs deceased donor transplantation.
- The nature and rationale for work-up investigations. How long these may take.
- Waiting time for deceased donor kidneys.
- Different types of deceased donor; DBD, DCD, ECD.
- What to expect in the post-operative period.
- The nature and frequency of outpatient follow-up.
- Immunosuppression and its side effects.
- The crucial importance of compliance with medication.

The sessions should be hosted by members of the entire transplant team, including nurse specialists, pharmacists, physicians, and surgeons.

It is also an opportunity to introduce the patient to others who have previously undergone transplantation.

Pre-transplant assessment

Potential recipients must be fit to undergo surgery and long-term immune suppression. Routine assessment starts with a detailed history and a

thorough physical examination. Most transplant centres have a checklist of work-up investigations (for example, see  p. 352).

This assessment is a multidisciplinary process, during which both a nephrologist and a transplant surgeon should review the patient and the results of their investigations. Transplant coordinators, specialist nurses, psychologists, urologists, cardiologists, and tissue typists will also play important roles in the work-up of patients to a greater or lesser extent, depending on individual need.

► In the UK, patients may be listed for deceased donation when dialysis is predicted within the subsequent 6 months. It is important to avoid unnecessary delays (and investigations)—annual mortality whilst awaiting a transplant is ~6%.

Goals of transplant work-up

- To determine physical fitness for transplantation (esp. CV fitness).
- To confirm that a transplant is surgically (+ urologically) feasible.
- To identify any potential impediments to transplantation and any corrective interventions that might remove them.
- To provide adequate and ongoing patient education.


Goals of medical assessment

- Assessment for CV disease.
- Assessment of other medical comorbidities.
- Review of thrombosis/bleeding history.
- Assessment of infection risk/history.
- Review of any previous malignant disease.
- Review of underlying native renal disease.
- Review of immunological history (anti-HLA antibody status).

Goals of surgical assessment

- Assessment of vasculature, particularly iliac and peripheral vessels.
- Previous abdominal surgery and hernias.
- Previous renal transplant history.
- Assessment of BMI and surgical risks.
- Assessment of previous urological history or current symptoms.
- Is the recipient's bladder function likely to be adequate post-transplant? Is bladder outflow adequate?
- Assessment of native kidneys, e.g. do large polycystic kidneys require removal?
- Which side will the graft be placed?

General

- Assessment of compliance.
- Assessment of mental health (see Assessment of mental health,  p. 359).
- Plans for pregnancy in ♀ of childbearing age.
- Social factors: employment, family support, etc.

Box 5.2 Typical recipient work-up**Immunological**

- Blood group.
- HLA type.
- HLA antibody screen.


Virology

- HIV.
- Hepatitis B.
- Hepatitis C.
- Epstein–Barr virus (EBV).
- Cytomegalovirus (CMV).
- Varicella zoster virus (VZV).
- Toxoplasma.
- Syphilis.
- HTLV 1 and 2 (only for Caribbean/Japanese or HIV +ve).

Haematology



- FBC, platelet count, PT/INR/APTT.
- Thrombophilia screen (if previous thrombotic event, relevant FH, SLE, or recurrent miscarriages).
- Serum and urine protein electrophoresis and immunofixation (age >60 years).

Other

- CXR.
- ECG.
-  echo.
- Additional cardiac assessment (see following ‘Assessment for cardiovascular disease’).
- Iliac (arterial and venous) Doppler studies. Further imaging, such as CT or formal angiography, may be required if abnormal.
- Carotid artery Doppler (if previous TIA/CVA).
- Ultrasound of native kidneys.
- Urological (e.g. satisfactory bladder function).
- PSA (if age >50 or FH of prostate cancer).
- Smear test/mammogram (as per national cervical/breast screening).
- FOB (if age >60 as per national bowel cancer screening).
- Lung function testing (based on previous history).

Assessment for cardiovascular disease**Cardiovascular disease burden in CKD**

Advanced CKD is associated with a high risk of CV disease, ranging from coronary artery disease (CAD) and heart failure to PVD and stroke. Potential renal transplant candidates need to be scrutinized for CV disease and CV risk factors and to have them proactively treated to maximize graft and patient survival post-transplantation.

- CV disease is the leading cause of death after transplantation.
- ~50% of deaths with a functioning graft occurring within 30 days of transplantation are due to CAD.
- The relationship between CKD and CV disease is described on  p. 198. Certain risk factors are discussed in the following section, as they are relevant for risk stratification and guiding choice of pre-transplant cardiac investigations.
- CV assessment prior to transplantation is considered an essential exercise by most transplant centres—however, optimal investigations and interventions remain controversial.
- Most centres take into consideration: (i) current cardiac symptoms; (ii) prior history of established cardiac disease; (iii) risk factors.
-  All potential recipients have a degree of CV risk, as relative risk of CV disease is disproportionately high in young ESRD patients.

Risk factors

Many centres use a single risk factor from the list below as a trigger for non-invasive cardiac stress testing. ↑ BP (± LVH) and ↑ lipids are not included, as they are so highly prevalent in ESRD patients.

- Diabetes.
- Age >50.
- Previous coronary revascularization.
- Established non-cardiac vascular disease (i.e. PVD or CVA). (See Table 5.3.)
- Abnormal resting ECG (other than LVH).
- Smoking.
- Dialysis duration >12 months.
- Previous renal transplant.

Approach to CV assessment

- *History.* Angina, ↓ exercise tolerance, breathlessness, claudication, and symptoms suggestive of cerebrovascular disease. Traditional cardiac risk factors.
- *Examination.* Evidence of cardiac failure, murmurs, and review of peripheral vasculature (palpable aortic aneurysm, vascular bruits, missing pulses, distal limb ischaemic changes).
- All patients will need a CXR and an ECG.
- Echo if clinical suspicion of a valve lesion, cardiac failure, pericardial effusion, significant LVH on ECG, or cardiomegaly on CXR.
- An ejection fraction <30% is considered a contraindication to deceased donor transplantation (→↑ perioperative mortality, poor early graft perfusion, and increased risk of transplant vein thrombosis).
- Cardiopulmonary exercise testing (CPET) can identify patients at high risk of post-operative complications.

Risk stratification

Based on the CV assessment, patients can be stratified as follows:

Symptomatic patients

- Symptomatic patients should be referred to a cardiologist for coronary angiography.

- Additional functional tests, such as dobutamine stress echocardiography (DSE), may be considered, but the key symptomatic and prognostic question is whether the patient will benefit from coronary revascularization.
- ⚠ The risks of contrast nephropathy ± cholesterol emboli need careful consideration in this group of patients. Patients may be rendered temporarily, or permanently, dialysis-dependent.

Asymptomatic patients with risk factors

- Whilst there is no convincing evidence that anatomical or functional testing is of either diagnostic or prognostic value in asymptomatic patients *without* renal failure, it is generally accepted that patients *with* renal failure are a unique group and that such assessment is highly desirable.
- ⚠ The absence of symptoms is not always reliable—many patients with ESRD have limited exercise capacity, and volume overload may obscure myocardial ischaemia.
- In diabetic patients, symptom burden is a poor indicator of ischaemia (autonomic neuropathy → defective ‘anginal warning’).
- Asymptomatic patients with any of the risk factors listed should ∴ undergo stress testing, with either a DSE or a myocardial perfusion scan (MPS).
- The interpretation of non-invasive cardiac investigations must be guarded in the context of ESRD (see Table 5.1). The sensitivity, specificity, and positive and negative predictive values of these investigations are shown in Table 5.2.
- Head-to-head comparison of DSE vs MPS reveals that neither is better nor perfect, but both are superior to alternatives.
- The FAME study highlighted the importance of combining anatomical findings with functional tests:
 - Fractional flow reserve (FFR) may help to guide management of a coronary stenosis in an asymptomatic dialysis patient.
 - If the stenosis is associated with downstream ischaemia (identified either by an abnormal FFR or a reversible perfusion defect), the patient should be offered revascularization.

Asymptomatic patients without risk factors

- Resting ECG and CXR to determine the need for either an echo or MPS/DSE. Otherwise, no further investigation is usually necessary.

Table 5.1 The utility of non-invasive cardiac investigation in advanced CKD

Non-invasive tests	Potential problems
Resting ECG	Normal ECG does not exclude CAD. Abnormal ECG predicts CAD but non-specific (up to 40% of dialysis patients have an abnormal ECG).
Exercise stress testing (EST)	Poor exercise performance—several studies have documented that only 7–53% of dialysis patients achieve the target heart rate. A high proportion of patients have baseline ECG abnormalities. Not recommended for transplant cardiac assessment.
Myocardial perfusion scan (MPS)	Balanced ischaemia does not show on an MPS, as the technique measures relative, as opposed to absolute, perfusion. However, an abnormal test suggests a high risk of significant CAD.
Dobutamine stress echo (DSE)	Operator-dependent, and adequate acoustic window is not possible in ~20% of patients. Many dialysis patients do not achieve target heart rate (→↓ sensitivity of the test—although failure to attain maximal stress may itself be a risk factor for subsequent cardiac events).
CT coronary angiogram	Low specificity due to high coronary artery calcium burden.
Cardiac MRI	Avoidance of gadolinium due to risk of nephrogenic fibrosing dermopathy (see p. 51) makes this of limited use.
CPET	A non-invasive measurement of haemodynamic variables and gas exchange but not used to predict presence of CAD.

Adapted from Nicholas Torpey *et al.* (Oxford Specialist Handbook) *Renal Transplantation* (2010), with permission from Oxford University Press.

Table 5.2 Sensitivity, specificity, and positive and negative predictive values of non-invasive cardiac investigations in advanced CKD

Cardiac test	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Resting ECG	67–77	52–58	43	47
EST	35	64	63	36
DSE	47–88	85–95	63–90	66–89
MPS	37–80	37–73	53–58	60–67

Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.

Rescreening

- Patients may wait for several years for a transplant, so regular assessment is essential.
- Data concerning the annual incidence of cardiac events in CKD patients after normal stress imaging test suggest rates increase from 4–12% within 2 years to 10–30% beyond 2 years. This implies cardiac rescreening should be undertaken every 2 years (sooner if symptomatic).
- It is interesting to note that cardiac event rates, following a normal MPS in the general population, are <1% per year, underlining the increased CV risk for patients with advanced CKD.

Revascularization


- The purpose of CAD intervention (either by surgical means or percutaneously through the use of stenting) is to restore blood flow to an ischaemic area of myocardium. Revascularization procedures do not alter the pathophysiological processes involved in CAD but simply serve to improve blood flow and prevent infarction.
- The best method of revascularization for patients with ESRD has not been established. Studies can only be extrapolated from the general population, but support both surgical and percutaneous options as effective in symptomatic disease.
- CABG complication rates are ~10% higher in ESRD patients. However, it is the treatment of choice for patients with multivessel disease and LV dysfunction (→ symptomatic and prognostic benefit).
- Any patient who has had a STEMI/NSTEMI, but not required revascularization, should not be considered for transplantation until cleared by a cardiologist 6 months after the event (this will usually involve further investigation).
- Stented patients need to wait until dual antiplatelet therapy has ceased (→ intraoperative bleeding risk). Generally, 12 months for a drug-eluting stent and 3 months for a bare metal stent.

Table 5.3 Important non-cardiac issues

Respiratory	Pulmonary function tests (PFT) if asthma, COPD, or parenchymal lung disease ± anaesthetic assessment. ⚠ Stop smoking!
GI	GI symptoms may require further evaluation to exclude malignancy. Persistent vomiting or malabsorption (e.g. pancreatic insufficiency) may cause problems with immunosuppression. Cholecystitis post-transplant can be severe. Screen patients with a relevant history for gallstones.
Hyperparathyroidism	Parathyroidectomy post-transplantation is associated with graft dysfunction through uncertain mechanisms (∴ control hyperparathyroidism pre-transplant).

Thrombotic or bleeding tendency

Pro-thrombotic tendency

- Any evidence of a pro-thrombotic tendency should be investigated with a thorough thrombophilia screen. Examples:
 - Previous transplant loss due to arterial or venous thrombosis.
 - Recurrent AVF thrombosis.
 - History of DVT/PE.
 - SLE (associated APS,  p. 664).
 - Recurrent miscarriages.
- A pro-thrombotic history or condition does not preclude transplantation, but patients should have an agreed treatment plan established in advance, with the aim of minimizing thrombotic complications and early graft loss.



Bleeding tendency

- Thrombocytopenia or prolonged INR or APTT warrant haematological investigation.

Anticoagulant and antiplatelet drugs

- Anticoagulation should be reversed prior to transplantation:
 - IV unfractionated heparin should be started as soon as is deemed surgically acceptable post-transplant in high-risk patients (e.g. prosthetic valve or thrombotic tendency).
 - Aim APTT 1.5–2.0.
 - Avoid LMWH until GFR has normalized post-transplant.
 - Re-anticoagulate prior to discharge
- Antiplatelet drugs:
 - Aspirin may be continued peri-transplantation.
 - Dual antiplatelet therapy is considered a relative contraindication to transplantation in many centres.

Infection risk and infection history

- Ensure serological screening has been undertaken. See Box 5.2,  p. 352.
- There should be no active infection at the time of transplantation; in particular, check:
 - Diabetic foot ulcers.
 - Recent dialysis catheter infections or PD-related infections, such as peritonitis, have been fully treated.
 - UTI.
- Any recent significant infectious disease contact, e.g. TB.
- Renal transplantation in patients with HIV, HBV, and HCV is discussed in  Chapter 8.

Review of previous malignancy

- Uncontrolled or recent malignancy is a contraindication to transplantation.
- The use of immunosuppression is associated with an increased risk of both *de novo* and recurrent malignancy in transplant recipients.
- As a general rule of thumb, patients with treated malignant disease should be recurrence-free for ≥ 2 years (≥ 5 years in some situations).
- Helpful guidance for specific tumours can be obtained from the Israel Penn International Transplant Tumor Registry (J[®] <<http://ipittr.uc.edu>>).
- For the common cancers, see Table 5.4.

Table 5.4 Common tumour types and transplant listing

Cancer type \pm location	Condition	Waiting time
Cervical carcinoma <i>in situ</i>	If cure at time of transplantation	None required
Basal cell carcinoma	If cure at time of transplantation	None required
Squamous cell carcinoma (skin)	If cure at time of transplantation	None required
Bladder carcinoma		2yr recurrence-free
Uterine carcinoma		2yr recurrence-free
Renal cell carcinoma	<5cm	2yr recurrence-free
Renal cell carcinoma	>5cm	5yr recurrence-free
Breast carcinoma	Depends on staging	2–5yr recurrence-free
Lymphoma	Depends on staging	2–5yr recurrence-free
Colorectal carcinoma	Depends on staging	2–5yr recurrence-free
Cervical carcinoma	Depends on staging	2–5yr recurrence-free

Pre-transplant cancer screening

- In ♀, ensure cervical smear testing and mammography are current.
- Encourage self-examination of breasts and testes.
- Bowel screening with FOB testing is now national practice in the UK for all those aged >60.
- Patients with a long history of ESRD often develop acquired cystic disease in their native kidneys, which is associated with malignancy—screening native kidneys is included in work-up protocols.
- Most centres use PSA to screen ♂ patients aged >50 or if strong FH of prostate cancer.
- Serum and urine protein electrophoresis and immunofixation for patients aged >60 should be considered.

Native renal disease

- Many primary renal diseases may recur (📖 p. 418). Patients need to be counselled regarding the risk for their particular native disease.
- Certain disorders must be in remission prior to transplantation, e.g. systemic vasculitis (📖 p. 647), anti-GBM disease (📖 p. 657), SLE (📖 p. 663).
- Patients with ESRD, caused or complicated by urinary tract obstruction (\pm urinary infection), require urological assessment.

Assessment of mental health

Introduction

- Due attention should be given to psychosocial issues as they may impact on quality of life (and compliance) post transplant. When identified, many are correctable—either with individualized treatment or through social intervention.
- The uncertainty of transplant listing may in itself cause anxiety. Furthermore, dialysis may have already affected a patient's ability to work, their social engagement, and their self-esteem.
- Psychosocial support, including counselling, formal psychiatric input, and social work may be necessary.
- Evaluation of a patient's social situation, relationships, and financial situation can be valuable, as many of these factors may be modifiable in anticipation of a transplant.
- Rarely, the capacity of a patient to consent to treatment may require assessment.

Pre-existing psychiatric illness

- Evidence suggests that transplant outcomes in patients with pre-existing mental health issues are suboptimal.
- However, a psychiatric disorder is not an absolute contraindication to transplantation, although careful evaluation is required.
- With adequate social support, good insight, reliable interpersonal relationships, and coping strategies in place, patients with mental health issues can be considered for transplantation.
 - Chronic illnesses, such as schizophrenia or bipolar affective disorder, may still have a good outcome in selected stable patients.
 - Severe personality disorders are considered a contraindication by most transplant centres.
 - Substance misuse may interfere with compliance.
 - Long-standing anxiety or affective disorders do not appear to predict worse outcomes after transplant.

Drug issues

- ⚠ Corticosteroids have well-recognized neuropsychiatric adverse effects, including depression, mania, psychosis, and delirium. A minority of patients may suffer from neuropsychiatric ciclosporin (CIC) toxicity. Tacrolimus (TAC) has been associated with sleep disturbances and irritability.
- It is important to identify potential interactions between immune suppression and psychiatric medication prior to transplantation.
- Lithium should ideally be avoided post-transplant (nephrotoxicity), but any change in treatment will require a period of assessment to ensure mood stability.

Compatibility: matching donor to recipient

Introduction

Five fundamental issues must be considered:

- Blood group.
- Tissue type (HLA).
- Anti-HLA antibodies (particularly donor-specific antibody, DSA).
- Donor characteristics.
- Recipient characteristics.

Blood group

ABO antigens are cell surface glycoproteins expressed not just on red blood cells, but on many cell types, e.g. vascular endothelial cells—including those in a transplanted kidney. Naturally occurring anti-blood group antibodies to non-self ABO antigens develop in early life (probably in response to exposure to bacterial antigens).

- Group O individuals develop both anti-A and anti-B antibody.
- Group A and B individuals develop anti-B or anti-A antibody, respectively.
- Group AB individuals do not develop antibodies.

Circulating anti-A or anti-B antibody at the time of transplantation will recognize and bind ABO antigens on donor endothelium, activate complement, and cause catastrophic vascular injury (→‘hyperacute’ rejection).

For this reason, ABO-incompatible transplants are generally avoided, particularly in deceased donor transplantation. The same rules apply for transplantation and blood transfusions, i.e. group ‘O’ are universal donors and ‘AB’ universal recipients. However, ABO-incompatible transplants can be contemplated in certain circumstances (📖 p. 444).

Tissue typing

Many hundreds of HLA antigens exist, and HLA nomenclature (based on recognition with specific antisera and, more recently, DNA sequencing) has been gradually refined over time. HLA antigens are allocated numbers as they are identified. Where newer antisera have allowed a refinement of previous specificities, the antigens are referred to as split and shown in brackets, e.g. the antigen formerly known as HLA-A9 has been split into A-23 and -24 and written A-23(9) and A-24(9).

DNA technology has revealed multiple different HLA alleles, and these are shown with an *, e.g. HLA-A*0101 is an allele of HLA-A1. However, these alleles are usually still described more broadly, using the wider ‘traditional’ serological groupings.

If an individual inherits the same HLA antigen from each parent, they are *homozygous* for that locus. Some antigens are inherited together more often than might be anticipated by chance; this is known as *linkage disequilibrium*.

Relevance

The most relevant HLA antigens to clinical transplantation, particularly organ allocation, are the ~50 encompassed serologically by HLA-A and -B (class I) and HLA-DR (class II). These were the antigens observed to most significantly influence outcome in the early days of HLA typing, although their effect is probably less powerful with contemporary immune suppression.

The degree of *mismatch* (rather than *match*—and, yes, this is very confusing!) between the donor and recipient is usually quoted at these three loci, i.e. HLA identical donors are a 0-0-0 mismatch, whereas donor:recipient pairs who share one HLA-A, one HLA-B, and one HLA-DR are referred to as a 1-1-1 mismatch. If all are different, it is termed a 2-2-2 mismatch. There are a number of minor HLA antigens, but their clinical impact is minimal.

Benefits of a well HLA-matched graft

- ↓ incidence of acute rejection (less evident with modern immune suppression).
- ↓ incidence of DGF.
- ↑ long-term graft survival. HLA-DR matching appears the most powerful in this context, but the number of mismatches is important (see Fig. 5.8). This still holds true for live donor pairs, particularly for 0-0-0 mismatches, but it is *much* less powerful (📖 p. 373).
- ↓ subsequent formation of anti-HLA antibodies (📖 pp. 361–4).

▶ Each mismatched HLA antigen is likely to initiate an immune response, which might be especially relevant if repeat transplantation is ever necessary. Recipients may develop anti-HLA antibodies or memory T cells against mismatched antigens, making organs with these antigens subsequently ‘unacceptable’ for a given recipient.

Anti-HLA antibodies

HLA matching alone is not sufficient. Anti-HLA antibodies present in the recipient at the time of transplantation may cause aggressive rejection, particularly if directed against particular HLA antigens in the transplanted kidney, termed *donor-specific antibody* (DSA).

Patients are ‘sensitized’ (i.e. develop anti-HLA antibodies) when previously exposed to non-self HLA antigens. HLA antibodies may recognize an epitope that is shared by multiple HLA molecules and are ∴ often cross-reactive.

Key sensitization events

- Previous organ transplant (▶ the degree of mismatching is very important: a 0-0-0 mismatch is less likely to become sensitized).
- Previous pregnancy (directed against paternal HLA antigens).
- Previous blood transfusion.
- Unknown (possibly caused by cross-reactivity with microbial antigens).

Screening for HLA antibodies

Historically, HLA antibody screening was undertaken with the complement-dependent cytotoxicity (CDC) assay and described in terms of *panel reactivity*.

Panel reactive antibodies (PRA)

PRA measures the antibody specificities in an individual serum sample against a panel of HLA antigens.

CDC assay: the patient's serum is incubated with lymphocytes from a panel of representative donors in the presence of complement. The PRA is expressed as the percentage of wells with cell lysis, e.g. a PRA of 45% implies recipient antibodies against 45% of the most commonly occurring antigens in that population. A PRA >10% generally defines a sensitized recipient and >85% highly sensitized.

► The higher a patient's PRA, the more likely they will have a positive cross-match (📖 p. 363) at the time of transplantation.

In more recent years, the CDC assay has been superseded by less cumbersome, and more sensitive, solid phase assays.

HLA antibody screening with solid phase assays

- These are either ELISA- or flow cytometry-based.
- Advantages over CDC: rapid, quantitative (strength of the fluorescent signal indicates amount of antibody present), highly sensitive, fewer false +ves, easier to identify antibody specificities, does not require lymphocytes, can detect non-complement fixing antibodies.
- ELISA: purified HLA antigens are bound to wells of an ELISA plate.
- Flow cytometry: purified HLA antigens are bound to fluorescently labelled microspheres. Now the gold standard technique. Luminex® is the most commonly used commercial system. Results are reported as units of median fluorescence intensity (MFI) that reflect the amount of antibody to specific HLA sensitivities present in the serum.
- Solid phase assays report individual antibody specificities but can generate the equivalent of a PRA, based on known population antigen frequencies—termed calculated PRA or reaction frequency.
- The sensitivity of solid phase assays means that the calculated PRA is higher than a CDC PRA.

Non-HLA antibodies

- Antibody-mediated rejection and transplant glomerulopathy (📖 p. 415) can develop despite an absence of anti-HLA antibodies.
- Non-HLA antibodies, directed against non-HLA donor antigens (including proteins on donor vascular endothelium), appear capable of stimulating graft inflammation and have been associated with worse outcomes.
- It is possible that reperfusion injury (and graft inflammation from other causes) exposes previously sequestered kidney antigens.
- Whether such non-HLA antibodies are always pathogenic or if they might prove useful biomarkers for the prediction of transplant outcomes remains to be seen.

The role of HLA antibody testing

Pre-transplantation

- HLA antibodies should be measured at the time of listing for transplantation and about every 3 months thereafter.
 - If present, the antibody specificities will identify *unacceptable antigens*. Recipients will not be offered a kidney possessing these antigens.
 - HLA antibodies may be identified that subsequently disappear. These antigens are no longer *unacceptable*, but close surveillance for recurrence is required post-transplantation.
 - ⚠ The concern is rejection; this may be immediate and aggressive ('hyperacute'), if pre-formed antibody is present in large amounts (▶ cross-matching should prevent this), or early post-transplant if there are lower amounts of antibody initially, but a B cell (or memory T cell) response is initiated.
 - High sensitivity flow cytometric assays can detect antibody in such low amounts that it may not be sufficient to cause a positive cross-match. Although a concern, these antibodies may not preclude transplantation. However, they mandate very close post-transplant surveillance.

Post-transplantation

- Measure monthly for the first 3 months (weekly in selected cases), then 3-monthly for the first year, then annually.
- Also measure if acute or chronic antibody-mediated rejection is suspected.
 - ⚠ 20% will develop anti-HLA antibodies post-transplantation, increasing the risk of graft loss 3-fold.
 - These outcomes are worse, whether or not the antibody is donor-specific (DSA).
 - DSA is associated with both acute antibody-mediated rejection (📖 p. 409) and transplant glomerulopathy (📖 p. 415).
 - The complement-binding capacity of DSA may help identify patients at higher risk for graft loss and help improve risk stratification when planning management.

Cross-matching

- ▶ Cross-matching is used to determine whether recipient serum reacts with donor T and B lymphocytes immediately prior to transplantation.
- The principle was established before the more refined identification of specific anti-HLA antibodies discussed on 📖 p. 362.
- It can be undertaken with complement-dependent cytotoxicity (CDC-XM) or by flow cytometry (FC-XM):
 - CDC-XM is performed separately for T and B cells.
 - Dithiothreitol (DTT) is added to serum to disaggregate IgM, as IgM antibodies are not relevant to transplantation.

- Sensitivity can be increased by adding goat anti-human antibody (binds recipient antibody → improved antibody cross-linkage and fuller complement activation).
- FC-XM is more sensitive and has reduced the early incidence of antibody-mediated rejection.
- FC-XM also distinguishes between T and B cells (by using fluorescent anti-CD3 and anti-CD19 antibodies, respectively).
- The flow cytometer mixture consists of prepared donor lymphocytes (lymphocytes are used, as donor lymphocytes are relatively easy to isolate), recipient serum, and anti-Fc antibodies tagged with a fluorescent dye.
- Fluorescence intensity quantifies positivity.
- *Note:* A virtual cross-match involves determining the presence or absence of DSA through the comparison of the patient's known HLA antibody specificity profile to the HLA type of the potential donor, without carrying out a 'hot' or 'acute' CDC-XM or FC-XM.

Interpreting the cross-match result


- T cells express class I HLA, and B cells express both class I and II HLA.
- HLA antibodies against class I will ∴ be active against both T and B cells.
- ► Since class I HLA is expressed on all nucleated cells, including donor vascular endothelium, a positive T cell cross-match is a contraindication to transplantation, as it implies pre-formed antibody will react with donor endothelium.
- 🦋 The significance of an isolated positive B cell cross-match is less clear, but it is probably an oversimplification to suggest that it indicates the presence of class II HLA antibodies that do not pose a threat to the graft.
- Furthermore, donor endothelium will express class II HLA under certain circumstances, especially inflammation.

CDC-XM and FC-XM are often performed (and interpreted) together.

This interpretation is made easier if a recent recipient anti-HLA antibody screen is available, as antibodies causing a reaction in the cross-match might not always be anti-HLA.

- *Positive T cell CDC-XM:* a positive T cell CDC-XM almost always indicates anti-class I HLA antibodies. Transplantation is contraindicated.
- *Positive B cell CDC-XM:* may be a false positive, and transplantation may proceed under certain circumstances. However, transplantation is contraindicated if class II HLA DSA is known to be present (esp. if specific for HLA-DR).
- *Positive FC-XM and negative CDC-XM:* this implies antibody is present at low titre. However, a positive T cell FC-XM contraindicates transplantation.
 - 🦋 A positive B cell FC-XM is a more controversial area, and protocols differ from centre to centre.
 - Live donor transplantation can provide the opportunity to proceed with transplantation despite a DSA ± a positive cross-match (📖 p. 444).

Donor characteristics

There are several types of kidney donor. Live kidney donation is discussed on  p. 372. Deceased donors are the commonest source of transplant in many countries, including the USA and UK, although live donor programmes in some centres have recently exceeded deceased donor rates.

Deceased donors are classified according to mode of death.

Donation after brain death (DBD)

Previously referred to as 'heart-beating' donors. The most important donor type historically. Once brainstem death has been diagnosed, the patient is legally dead and can be managed as a potential donor on ITU. This management aims to maintain organ suitability for transplantation.

Essentially, the donor has irreversible structural brain damage and is unresponsive, in a coma, and ventilator-dependent. Systemic perfusion is preserved, and organ retrieval occurs whilst some degree of cardiac output remains (meaning ischaemic injury is minimized).

See Academy of Medical Royal Colleges. *A Code of Practice for the Diagnosis and Confirmation of Death*, October 2008.  <http://www.aomrc.org.uk/publications/reports-a-guidance.html>.

Donor management on ITU

- Treatment of infection.
- Line care.
- Airway management.
- Maintain MAP >60mmHg.
- Meticulous fluid balance.
- Most need vasopressor support (e.g. dopamine \pm then noradrenaline).
- Maintain core temp >35°C.
- Common complications:
 - \downarrow BP.
 - Arrhythmias.
 - Hypothermia.
 - Diabetes insipidus (\rightarrow diuresis, \uparrow Na⁺); treat with vasopressin.
 - Electrolyte abnormalities.
 - Acidosis.
 - Pulmonary oedema.
 - Hypothyroidism (\rightarrow haemodynamic instability); treat with T3 or T4 infusion).
 - Hyperglycaemia (insulin resistance).

Warm and cold ischaemic time

- *Warm ischaemic time*: period between circulatory arrest and start of cold storage. WIT is extremely injurious to the kidney.
- *Cold ischaemic time*: period of cold storage before transplantation.

Donation after cardiac death (DCD)

Previously referred to as 'non-heart-beating' donors. The number of DCD donors has increased significantly over recent years. DCD involves donors who are not brain-dead, but in whom treatment is withdrawn, as there is no prospect of recovery. This usually occurs in an ITU setting but may also be undertaken in accident and emergency departments. Organs are harvested at subsequent cardiorespiratory arrest. The time between treatment withdrawal and cardiorespiratory arrest will determine if the organs are viable for transplantation.

The inevitable delay between cardiac arrest and organ perfusion results in a longer period of warm ischaemia time (WIT). WIT is extremely harmful to kidneys, so, in some countries, kidneys are allocated locally to prevent an additional lengthy period of cold ischaemia.

Prolonged WIT increases DGF, but graft survival rates appear comparable to DBD if donors are carefully selected. 📖 However, outcomes for DCD donors using more extended criteria (📖 p. 368) are uncertain.

DCD kidneys are classified, according to the Maastricht classification:

- Category I: dead on arrival in hospital.
- Category II: unsuccessful resuscitation.
- Category III: expected cardiac arrest.
- Category IV: cardiac arrest in brainstem-dead donor.
- Category V: unexplained cardiac arrest in hospital.

Categories II and III are the most common scenarios. DCD can only occur in hospitals that have invested in the expertise, resources, and infrastructure necessary to support such a programme.

Between 2011 and 2012, in the UK, there was an 8% increase in the number of deceased donors to 1,088 (the largest number ever). The number of DBD donors increased by 2% to 652, while the number of DCD donors increased by 17% to 436 (see Fig. 5.12).

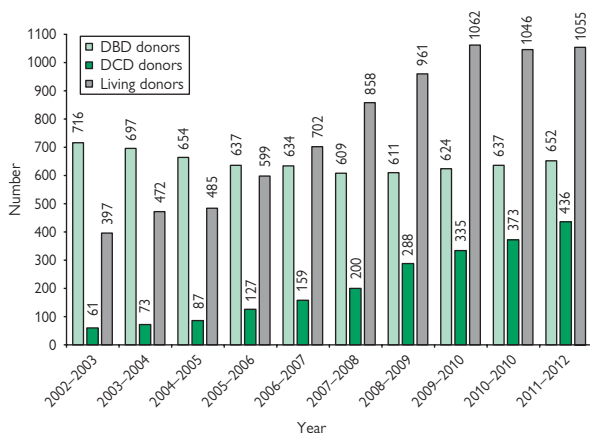


Fig. 5.12 Number of deceased and living donors in the UK, 2002–2012. Reproduced from UK Blood and Transplant Annual Report 2012, with permission.

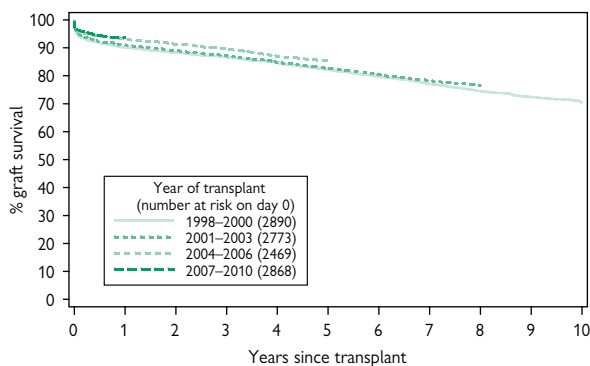


Fig. 5.13 Long-term graft survival after first adult kidney-only transplant from DBD donors, 1998–2010. Reproduced from UK Blood and Transplant Annual Report 2012, with permission.

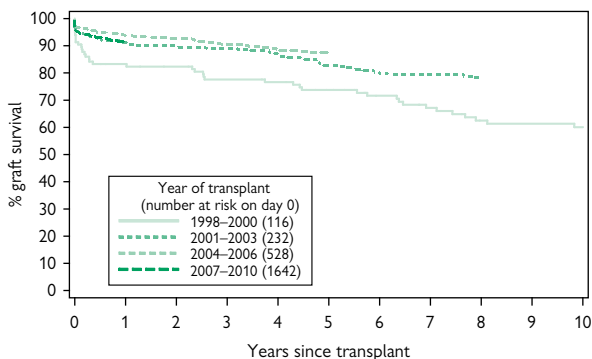


Fig. 5.14 Long-term graft survival after first adult kidney-only transplant from DCD donors, 1998–2010. Reproduced from UK Blood and Transplant Annual Report 2012, with permission.

Figs 5.13 and 5.14 show graft survival estimates (and confidence intervals) for 1, 2, 5, and 10 years post-transplant. There has been a significant improvement in 1-, 2-, and 5-year survival over the time periods shown ($P < 0.01$ in each case).

Note: 1-year patient survival is comparable for DBD and DCD donor transplants in the most recent time periods.

Extended criteria donors (ECD)

• The use of ECD is increasing rapidly as a means of expanding the available donor pool. Previously not considered for transplantation, they now represent ~25% of donors (see Fig. 5.15).

Criteria

- Age >60.
- Age 50–59 and ≥ 2 of the following:
 - \uparrow BP.
 - $\text{SCr} > 133 \mu\text{mol/L}$ (1.5mg/dL).
 - Cerebrovascular cause of death.

'Super'extended criteria donors

- Age >70.

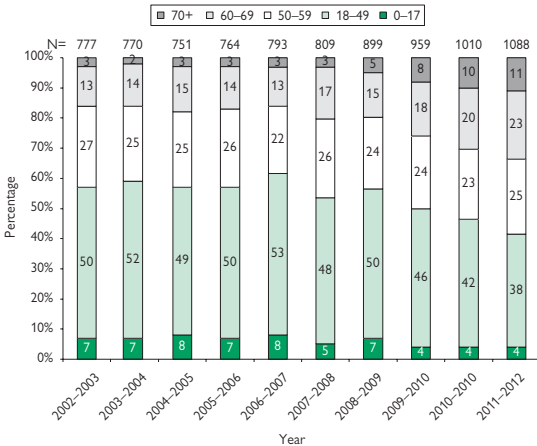


Fig. 5.15 Age of deceased donors in the UK, 2002–2012. Reproduced from UK Blood and Transplant Annual Report 2012, with permission.

Contraindications to deceased donation

- Active or untreated malignancy. A history of past treated cancer is more contentious.
 - Primary brain tumours are an exception.
- Active infection, e.g. encephalitis, TB, HSV, CMV, syphilis:
 - Donation may be possible if the organism and sensitivities are known and treatment has been established prior to donation.
 - In some cases, HBV, HCV, HIV may be allocated to appropriate recipients (📖 pp. 684, 690, 679 respectively).
- Medical comorbidity:
 - 📌 This is an increasingly controversial area, as factors, such as age >60, diabetes mellitus, and ↑ BP, are no longer considered contraindications in many transplant centres (for ECD, see 📖 p. 368).

Deceased donation: opting in or opting out

Organ donation requires consent of the donor or next of kin. In some countries, e.g. most of the UK, potential donors may have given consent during their lifetime, so-called ‘opt in’. Such systems often utilize resources, such as donor cards or donor registries (increasingly online).

Although the next of kin may not have the automatic right to overrule the previously expressed wishes of a potential donor, it would be usual practice to take their wishes into account.

In other countries, e.g. France, Spain (and Wales from 2015), potential donors are presumed to have given consent, unless they previously ‘opt out’. Advocates of this system point to increased donation rates in these territories, although critics suggest this is more a function of transplant coordination systems that are more sophisticated overall.

Recipient characteristics

The median waiting time for a deceased donor kidney is ~1,200 days or 3.3 years. This waiting time is significantly influenced by blood group, with blood groups AB, A, B, and O having median waiting times of ~600, ~950, ~1,300, and ~1,400 days, respectively.

The major factors that influence allocation of a kidney to a potential recipient's are:

- Time on the waiting list, with priority to those that have waited the longest.
- Age: priority to those younger than 18.
- HLA mismatch, with priority to a zero antigen mismatch.
- HLA antibodies, with priority to those with a high PRA or calculated RF.
- Medical priority, e.g. a patient has limited options for sustainable dialysis access.

There is a move toward more sophisticated scoring systems that attempt to improve outcomes by matching donor and recipient more effectively, particularly in terms of patient and graft survival. Such systems usually focus on criteria, such as: (i) estimated survival that a recipient of a specific donor kidney may expect vs remaining on dialysis; (ii) time already spent on dialysis; and (iii) more objective measures of donor organ quality.

Donor and recipient should be as closely 'biologically' matched as possible; for instance, kidneys from elderly donors do not, on average, last as long as those from younger donors and may sensitize younger recipients to subsequent (better matched) grafts.

Specific recipient issues

- Age:
 - The proportion of wait-listed patients aged >50 is increasing.
 - This not only reflects longer waiting times, but also larger numbers of more elderly patients being considered for transplantation.
 - This mandates a regular (re) assessment of both fitness for, and the risk:benefit ratio of, transplantation.
 - The commonest cause of graft loss beyond age 65 is death with a functioning transplant. This means that long-term graft outcomes may be less important, and appropriate attention must be given to issues, such as quality of life.
 - There is usually an attempt to match the age of donor with the recipient to ensure a suitable 'nephron dose'.
- Race:
 - Ensuring equal access to transplantation is a significant challenge internationally, as is encouraging donation from all ethnic backgrounds to support HLA matching.
 - The proportion of patients waiting for a kidney from black, Asian, and Hispanic backgrounds is increasing.
 - In the UK, ~4% of donors are from ethnic minority groups while such groups represent ~8% of the UK ESRD population.
 - Median UK waiting times are Caucasian patients ~1,100 days; Asian patients ~1,400 days; black patients ~1,450 days.

- Comorbidity:
 - Diabetes is the commonest cause of ESRD amongst those wait-listed, followed by ↑ BP.
 - This has implications for associated CV morbidity. Careful work-up is essential (📖 p. 352)
- Size:
 - A large recipient ideally requires adequate 'nephron mass' to achieve a satisfactory post-transplant GFR. A kidney from a small donor (e.g. paediatric) may not achieve this.
 - It may be technically difficult to implant a kidney from a large donor into a small recipient.
 - Large recipient polycystic kidneys may limit placement of the new organ (uni- or bilateral native nephrectomies may be necessary before activation on the waiting list).

Live donor transplantation

Introduction

► Living donor transplantation is the treatment of choice for ESRD.

Living donors enjoy better graft function and patient survival (📖 p. 340). They are the commonest donor type in many countries, and numbers have increased significantly globally in recent years (now approaching 50% of all renal transplants).

Live donors may be related or unrelated, although there is generally an established emotional relationship between the pair (e.g. spouse or close friend). Exchange schemes and protocols to reduce recipient ABO or HLA antibodies are helping to expand the live donor pool (📖 p. 444).

Non-directed altruistic ('Good Samaritan') donation refers to the allocation of a live donor kidney to a patient on the deceased donor list, or in the kidney exchange pool (📖 p. XXX) (with donor/recipient anonymity).

Advantages

- Better graft and patient survival than deceased donor transplantation—regardless of genetic relationship and HLA mismatch.
- Pre-emptive transplants (i.e. pre-dialysis) have the best outcome of all.
 - Time on dialysis is associated with poorer transplant outcomes.
 - ~35% of live donor transplants in the UK are pre-emptive.
- Live donor transplantation is elective surgery and easier to organize.
- Laparoscopic donor techniques have helped acceptability (📖 p. 378).
- Closer HLA matching *may* be possible.
- Live donor transplantation expands the overall donor pool—leaving deceased donor kidneys for those with no other options.
- There is minimal ischaemic damage to graft (∴ ↓ DGF).
- Less potent immunosuppression (possibly).
- Psychological benefits (better compliance, sense of well-being, etc.).

Disadvantages


- Perioperative donor mortality is ~1 in 3,000 (causes: occult cardiac disease, venous thromboembolism).
- Major complications occur in ~2% (intraoperative bleeding, wound problems, DVT).
- Minor complications occur in ~20%.
- Stress to donor (and family).
- ☠️ Later development of donor ↑ BP, proteinuria, or CKD (mean donor GFR after 25 years is ~70% of that prior to donor nephrectomy).
- Difficult to guarantee 'freely given' consent—has the donor been coerced? Potential donors should be assessed in isolation from recipients and allowed to withdraw (without explanation) at any stage.

Assessment of a potential live donor

This is subject to several comprehensive guidelines, e.g. 🌐 <http://www.bts.org.uk>.

A successful live donor programme requires a multidisciplinary team approach.

- Willing to donate? Information and discussion are of paramount importance. This should be delivered through a mixture of culturally appropriate written and visual material as well as face-to-face consultations. A dedicated live donor team, separate from the potential recipient's nephrologist, would usually undertake this. The risks of the live donor process, how the pathway works, and the nature of the necessary investigations should all be clearly explained.
- ABO compatibility (📖 p. 360).
- HLA typing and donor-specific HLA antibodies (📖 pp. 360–3). The impact of HLA matching is much less powerful in live donor transplantation: a 1 haplotype mismatched live related graft 1-1-1 (e.g. parent to child) has similar outcomes to a 2-2-2 mismatched live unrelated graft (e.g. from a spouse)—and, in all cases, the outcomes are as good as for a 0-0-0 mismatched deceased donor kidney. However, HLA matching can help to select between multiple potential donors: 0-0-0 mismatched grafts still have the best outcomes, and poorly HLA-matched grafts risk the subsequent development of DSA, with potential implications for subsequent repeat transplantation in younger patients.
- Medical evaluation: the goals are to protect the health of the donor and to prevent transmissible disease (malignancy and infection) to the recipient.
 - History, clinical examination.
 - BP.
 - Urinalysis (at least $\times 2$ on separate occasions), MSU, and uPCR.
 - U&E, SCr, eGFR.
 - FBC, clotting, LFTs, bone \pm Hb electrophoresis (? sickle cell trait).
 - Fasting glucose \pm glucose tolerance test (if fasting value 6–7mmol/L, \uparrow BMI, or family history of T2DM).
 - PSA (σ^{r} > age 60).
 - Estimation of GFR (📖 p. 374).
 - ECG \pm ECHO if \uparrow BP \pm stress testing if age >60.
 - CXR.
 - HIV, Hep serology, CMV, EBV, syphilis and HTLV-1 and 2.
 - Age appropriate cancer screen.
- Psychosocial evaluation. This is a complex area, and many live donor programmes will have considerable expertise within their multidisciplinary team. Many donors find donation a positive act, associated with increased self-esteem. However, this is not universal. Psychosocial assessment and support may be required (including formal psychiatric review in some cases). Support may need to continue post-donation. Formal mental health assessment is recommended for all non-directed altruistic donors in the UK.
- Donor anatomy:
 - Renal USS: to check there are two normal-sized kidneys.
 - Isotope renography (e.g. DMSA): for split renal function. If there is a difference, the kidney with less function would generally be selected for transplantation.

- Arterial and venous anatomy: CTA is now generally favoured over the more invasive, but less revealing, angiography (CT also yields additional anatomical information; e.g. the IVU phase will identify a duplex ureter). Some centres may prefer MRA.
- How many arteries and veins? Multiple arteries usually require bench reconstruction prior to transplantation. Will laparoscopic surgery be possible? The left kidney is generally favoured as the renal vein is longer.
- Informed consent. The donor should meet the donor surgeon.
- In the UK, it is a mandatory requirement of the Human Tissue Authority (HTA) that all potential live donor transplants undergo evaluation by an 'independent assessor'. The assessor must be satisfied that adequate information has been provided (and understood), that consent has been freely given (no coercion or rewards), and that the relationship between the pair is as described. The transplant must then proceed within a certain time frame (usually 6 months).
- If a donor is unsuitable, it is important that the reasons why are clearly explained (and that any necessary follow-up is organized).
- Donor nephrectomy. For techniques, see  p. 378.
- Donors should be seen 4–6 weeks post-surgery and then reviewed annually (check eGFR, BP, and urinalysis \pm uPCR). This could be undertaken in primary care (but it is important that outcome data are collected by the transplant centre).

Renal outcomes

Following the initial decline in GFR (as half the donor's nephron mass is removed at the time of surgery), the rate of loss of renal function is no faster than expected with normal ageing, in fact, residual hyperfiltration leads to an increase in GFR to ~70% of pre-donation level.

There is a small increased risk of low-grade proteinuria (2° to hyperfiltration in the remaining kidney) and \uparrow BP. However, donation increases the absolute cumulative risk of ESRD by <1%.

There are data that suggest improved life expectancy for individuals who have donated, presumably reflecting their evident fitness at the time of donation and perhaps motivation to stay fit post-donation. However, this may not continue to hold true as more patients are accepted to donate and their long-term follow-up improves.

Assessment of GFR for live donation

In many countries (including the USA), GFR is estimated using creatinine clearance (CrCl) on a 24h urine collection. eGFR, using equations, such as MDRD, are not acceptable, as they are not sufficiently accurate when renal function is normal or near normal (□ p. 34).

GFR may also be measured using radioisotopes, such as $^{51}\text{Cr-EDTA}$ (recommended in the UK).

A suitable GFR for donation should be age-adjusted (see Fig. 5.16 and Table 5.5).

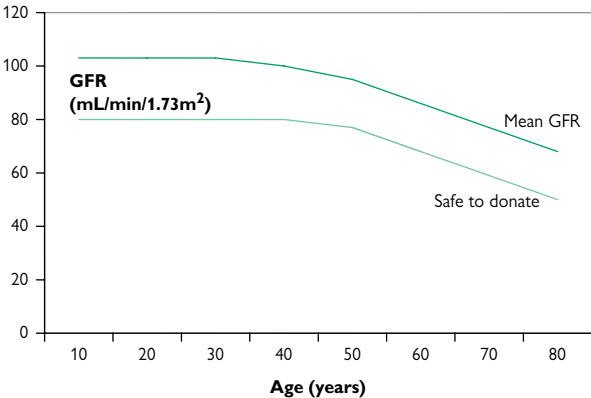


Fig. 5.16 Diagram showing the variation of GFR with age. The lower line shows the safety limit of $80\text{mL}/\text{min}/1.73\text{m}^2$ for adults up the age of 46 years, declining to $50\text{mL}/\text{min}/1.73\text{m}^2$ at age 80. For donors with a preoperative GFR above the lower line, the GFR of the remaining kidney will still be greater than $37.5\text{mL}/\text{min}/1.73\text{m}^2$ at age 80. The upper line is based on an analysis of ~425 living renal transplant donors who had $^{51}\text{Cr-EDTA}$ GFR measurements. Reproduced from the British Transplant Society *Guidelines for Living Donor Kidney Transplantation* (© www.bts.org.uk), with permission.

Table 5.5 Acceptable GFR by donor age prior to donation

Donor age	Acceptable corrected GFR prior to donation ($\text{mL}/\text{min}/1.73\text{m}^2$)
Up to 46	80
50	77
60	68
70	59
80	50

Reproduced, with permission, from the British Transplant Society *Guidelines for Living Donor Kidney Transplantation*.

Potential contraindications to live kidney donation

- Age <18 (except in exceptional circumstances).
- There is no upper age limit, but donors >60 will require particularly diligent assessment.
- Inadequately controlled ↑ BP (📖 p. 377).
- CV disease (including strong family history) (📖 p. 377).
- ↑ BMI (📖 p. 377).
- Diabetes mellitus or high risk of future diabetes (first-degree relative with T2DM + abnormal glucose tolerance, previous gestational DM).
- Other significant comorbidity, e.g. respiratory disease.
- Malignancy (localized skin malignancy is an exception). Ensure breast and cervical screening has been undertaken.
- Urinary tract infection.
- Structural urinary tract abnormalities.
- Nephrolithiasis.
- Renal disease. Any primary GN or other renal disease.
 - Proteinuria >150mg/24h precludes donation.
 - Microscopic haematuria: donation may still be possible (📖 p. 377).
 - If family history of renal disease, exclude in the donor, e.g. Alport syndrome.
- Thromboembolic disease.
- Transmissible infection (HIV, HBV, HCV, TB history, or recent contact).
- Previous extensive abdominal surgery.
- Smoking and alcohol excess.
- Recreational drug use or dependence on prescribed medication.
- Social issues: what will be the impact on employment, dependants, etc.
- Active mental health issues.

Common concerns during live donor work-up

- ↑ BP
 - Only a relative contraindication.
 - ↑ BP precludes donation if:
 - Evidence of target organ damage (📖 p. 462).
 - >2 antihypertensives are necessary to maintain BP <140/90mmHg.
 - 10-year CV risk <20% (📖 p. 470).
- CV disease:
 - CV assessment of potential donors is not always straightforward. As a general rule, there should be a low threshold for screening potential donors for CV disease.
 - Coronary artery disease is the most common concern, but valvular disease, cardiac dysfunction, and other vascular disease (e.g. peripheral, carotid) also require consideration.
 - Potential donors with exercise capacity >10 METs are at very low cardiac risk.
 - METs are metabolic equivalents—based on the resting oxygen consumption of a 70kg 40-year-old ♂ (3.5mL/kg/min or 1 MET). They can be calculated from activity scores, derived from questionnaire responses.
 - In the UK, it is suggested that potential donors with an exercise capacity of <4 METs (activities that require >4 METs include moderate cycling, skiing, tennis, and jogging) or who have >10% estimated risk of significant coronary disease (📖 p. 470) should undergo cardiological assessment (essentially dynamic stress testing of some type).
- Obesity:
 - A risk factor for perioperative complications, such as VTE, wound infection, chest infection.
 - Potential association with subsequent CKD, proteinuria, and T2DM.
 - Potential donors with a BMI >35 should be discouraged, but given lifestyle advice and, if appropriate, weight loss goals. Moderately obese patients (BMI 30–35kg/m²) should be counselled carefully concerning the additional perioperative and long-term risks and advised to lose weight prior to donation (and maintain this post-donation).
- Persistent microscopic haematuria:
 - A relatively common finding (~5%).
 - Requires urological assessment, with urinary tract imaging and cystoscopy.
 - 🏆 If urological investigations prove normal, many centres perform a renal biopsy to exclude significant (and potentially progressive) glomerular disease; for example, IgA nephropathy would be a contraindication to donation, whereas thin membrane disease (📖 p. 568), assuming appropriate assessment and counselling, might not.

Live donor nephrectomy

General issues

The most important early complications are bleeding, venous thromboembolism, renal impairment, chest infection/post-op atelectasis, and inadequate pain relief (see Box 5.3).

Ensure adequate hydration (e.g. IV crystalloid 1L over 6–8h, beginning pre-op), VTE prophylaxis (LMWH and compression stockings), adequate analgesia (see Box 5.3), early mobilization, and physiotherapy, as needed.

Live donor transplant recipients are often commenced on ciclosporin or tacrolimus a few days prior to the date of transplant, allowing therapeutic plasma levels to be reached and reducing the risk of early rejection.

Open vs laparoscopic nephrectomy

Laparoscopic donor nephrectomy is replacing open nephrectomy as the procedure of choice for live donor nephrectomy and has helped to increase donor rates. The kidney is usually removed through a 6cm Pfannenstiel or a lower midline incision. Open nephrectomy involves a larger, more painful wound (often requiring rib resection) and a longer recovery time.

Although overall complication rates are similar, laparoscopic nephrectomy is associated with less pain, a smaller wound (and several smaller scars), a shorter hospital stay, and swifter resumption of normal activities.

Disadvantages: laparoscopic techniques are more difficult to learn; there is less intraoperative control of bleeding, and warm ischaemic time is increased by a few minutes over open techniques.

There are several variations: total laparoscopic nephrectomy, hand-assisted laparoscopic nephrectomy (HALDN) and retroperitoneal donor nephrectomy (in the latter, the peritoneal cavity is not entered, so there is less risk of bowel injury and fewer subsequent adhesions).

Box 5.3 Pain relief in live donors

With post-operative attention often focused on the recipient, pain in the donor may be overlooked. Live donation is an unselfish act—it is inexcusable to leave a donor in pain because of insufficient analgesia.

- Consider a fentanyl PCA (to be set up in theatre), e.g. bolus 15 micrograms with a 5min lock-out and background infusion of 15 micrograms/h.
- On the ward:
 - Paracetamol 1g qds PO/IV (Δ if donor is <50kg, IV dose is 15mg/kg/dose).
 - NSAID, e.g. ibuprofen 400mg tds PO (unless patient intolerant/allergic). Ensure adequate hydration, and monitor renal function.
 - PPI, e.g. omeprazole 20mg od PO (to cover NSAID).
- Antiemetic:
 - Ondansetron 8mg tds PO/IV (regularly).
 - Cyclizine 50mg tds PO/IV prn.

If pain is inadequately controlled, ensure the PCA is set up correctly and being used appropriately. Then consider increasing bolus and background to 20 micrograms (ensure the patient is alert and respiratory rate is >12). Review regularly.

Depending on patient progress, the PCA will hopefully only be necessary for 24–48h. However, adequate step-down analgesia, based on preceding PCA use, is essential.

- If fentanyl use <400 micrograms in previous 24h, prescribe regular oxycodone 5mg qds as well as prn oxycodone 5–10mg 2-hourly.
- If fentanyl use >400micrograms in previous 24h, prescribe regular oxycodone 10mg qds and prn oxycodone 5–10mg 2-hourly.

Assess pain every 2h after step-down. If uncontrolled, consider restarting PCA.

Immunosuppression: overview

Introduction

Successful transplantation between non-identical individuals became possible with the combined use of corticosteroids and azathioprine in the 1960s. However, severe rejection, often with graft loss, remained common. Solid organ transplantation was transformed by the introduction of ciclosporin in the 1980s, with a significant reduction in acute rejection rates and improved long-term graft outcomes.

The number of immune suppressive agents has grown considerably over the last two decades. Randomized trials have attempted to define the ideal cocktail of drugs, but have generally been pharmaceutical company-driven, too short-term (often leading to the use of acute rejection, rather than graft outcomes as the primary endpoint), and too small to convincingly demonstrate any differences.

This means there is no universal regimen—each transplant centre will develop its own protocol, based on their interpretation of the available evidence, their local experience, and their local population.

General principles

- To match the amount of immune suppression with the perceived degree of immunological risk.
- To use higher doses in the early part of transplantation when the risk of rejection is highest (*induction*), with gradual reduction, even withdrawal, of some agents over time (*maintenance*).
- To try to tailor immune suppression to the individual where possible.
- The use of ciclosporin with corticosteroids and azathioprine became known as *triple therapy*. Similar such regimens are still the cornerstone of many protocols—modern triple therapy often comprises tacrolimus, corticosteroids, and MMF.
- Acute rejection is treated with an (immediate) escalation in immune suppression, often with a subsequent increase in maintenance therapy.
- Each immunosuppressive agent has a particular side effect profile. However, the entire group is associated with an increased risk of infection (bacterial, viral, and fungal) and malignancy.
- ► The more potent the immune suppression, the less chance of rejection and the greater chance of these side effects.
- As acute rejection rates have fallen and graft outcomes improved, both the short-term (Δ infection) and long-term (Δ CV disease, malignancy, nephrotoxicity) side effects of immune suppression have become increasingly familiar.
- Immune suppression is only effective if taken consistently and as prescribed. The stakes are high in non-compliant patients, but such non-adherence remains surprisingly common. It should be recognized that regimens are often burdensome, involving multiple tablets, with multiple side effects, taken at multiple times of day.

Key questions to ask of a transplant centre's immune suppression protocols

- Is immune suppression the same for each patient or modified, according to perceived immunological risk (see Box 5.4)?
- What antibody ('biological' agent), if any, is used at induction?
- If a depleting antibody is used, what are the protocols surrounding its safe administration?
- Is maintenance immune suppression based on ciclosporin or tacrolimus? What are the desired therapeutic ranges of these agents at each stage post-transplantation?
- Does maintenance immunosuppression include azathioprine or MMF?
- Are corticosteroids used from the outset? Under what circumstances are they withdrawn?
- What are the local policies concerning prophylaxis against infections, such as CMV and TB?
- What clinical trials are being undertaken at the centre? What protocols apply to these patients?
- What are the protocols for ABO- or HLA-incompatible transplantation if they are performed?
- How is T cell-mediated rejection treated?
- How is acute antibody-mediated rejection treated?

Box 5.4 Estimating immunological risk

- Many transplant centres aim to tailor immune suppression according to a stratification of immunological risk. Criteria vary but, as an example:
 - Low immunological risk:
 - Recipients without HLA antibodies, or
 - Recipients receiving a first transplant kidney from a HLA-identical sibling.
 - Standard immunological risk:
 - Recipients with HLA antibodies.
 - Any of the following groups, regardless of presence or absence of HLA antibodies:
 - Husband to wife, or child to mother.
 - Second or subsequent kidney transplant.
 - Black recipient.
 - High immunological risk:
 - Recipients who are FC-XM-negative but who have a current, or historic, antibody directed against the transplant organ (usually arises in a live donor transplant context, as such organs would not be allocated to a recipient via deceased donor schemes).
 - HLA-incompatible transplants require individualized immunosuppression regimens.

Immunosuppression: induction

Introduction

Induction therapy is an initial period of intense immune suppression, given at the time of transplantation, to reduce the incidence of early acute rejection. It has two components:

- Higher initial doses of agents that will subsequently be used for maintenance, e.g. pulsed IV and high-dose oral corticosteroids and ciclosporin or tacrolimus, with higher early target therapeutic levels.
- Antibody induction with a 'biological' agent; this will be with either a *depleting* or *non-depleting* antibody.
 - Depleting antibodies: ATG, OKT3, alemtuzumab.
 - Non-depleting antibodies: basiliximab.
- Antibody induction is used for >80% of transplants. In broad terms, depleting antibodies are favoured in the USA, whilst non-depleting antibodies are more widely used in the UK and Europe.
- While the evidence that antibody induction reduces acute rejection is good (depleting antibody > non-depleting antibody), the effects on long-term graft outcome are less clear.
- Other potential advantages (depleting antibody > non-depleting antibody): lower baseline maintenance immune suppression (esp. steroids), allows gradual introduction of CNI to assist recovery from DGF, facilitates higher immunological risk transplants (📖 p. 381).
- Potential disadvantages (depleting antibody >> non-depleting antibody): higher infection rates, greater long-term risk of malignancy.

Non-depleting antibodies

Basiliximab

- A monoclonal antibody directed against CD25, a component of the IL-2 receptor on activated T cells. Binding prevents IL-2-induced T cell proliferation and clonal expansion.
- Basiliximab is a chimeric mouse-human monoclonal antibody that does not evoke an immune response. It consequently has a long half-life.
- Used for transplant induction only, not the treatment of rejection (there are many other T cell mitogens besides IL-2, it is ineffective in this context).
- Demonstrably reduces acute rejection in the first year post-transplant (~33%).
- Basiliximab:
 - 20 mg IVI on day 0 and day 4.
- The first infusion is usually started immediately pre-theatre.
- SE: surprisingly few. Infusion reactions are rare. Does not appear to significantly increase the risk of infection or malignancy.

Depleting antibodies

Anti-thymocyte globulin (ATG)

- Polyclonal T cell-depleting antibodies are produced by immunizing animals with human thymic lymphocytes.
- Several are available, e.g. Thymoglobulin® (produced in rabbits).
- Among the polyclonal antibodies are antibodies specific for components of the TCR (CD3, CD4, CD8) and cytokine receptors (including CD25) as well as adhesion molecules.
- Numerous effects on T cells: cytokine release, ↓ proliferation, ↓ adherence, and ↑ clearance (→ lysis or reticuloendothelial uptake).
- ⚠ T cell depletion may persist for months (even years).
- They also have anti-B cell effects (↓ T cell help).
- SE:
 - ▶▶ Anaphylaxis.
 - Cytokine release syndrome (fever, rigors, pruritus, erythema, dyspnoea, ↑ HR, ↑ / ↓ BP). Generally limited to 1st or 2nd dose.
 - Serum sickness (2° to anti-rabbit antibodies and immune complex formation) after ~7 days' treatment. Features: fever, rash, arthralgia, myalgia. Requires treatment cessation.
 - ↓ WCC, ↓ Plt.
 - ↑ infections (PCP, adenovirus, invasive fungal infections, CMV, toxoplasma, HSV, VZV are all concerns during this therapy).
 - ↑ PTLD (risk × 2) (📖 p. 441).
- Used for both induction therapy and treatment of rejection (📖 p. 408).
- Anti-rabbit antibodies may develop and impair efficacy (especially with repeat courses).

Alemtuzumab

- Developed in the Cambridge Pathology Laboratories (hence Campath®). Licensed for the treatment of CLL but used extensively in transplantation.
- It is a humanized anti-CD52 antibody: CD52 is a highly expressed glycoprotein antigen on the surface of T and B cells (as well as thymocytes, monocytes, macrophages, and NK cells).
- Binding does not cause cell activation, instead cells are rapidly cleared from the circulation.
- Profound lymphopenia persists for 6 months (B cells reconstitute before T cells).
- Dose: 2 × 30mg doses administered by SC injection (can be IV) 24h apart (day 0 and day 1 post-transplant). Initial dose generally administered intraoperatively prior to organ reperfusion (if the patient is age >60, some centres administer only one dose).
- Infusion reactions (SC < IV) are less severe than other depleting antibodies (as not associated with cytokine release) but still occur.
- Premedication and prophylaxis as for thymoglobulin in Box 5.5.
- SE: ↓ Hb, ↓ Plt (⚠ weeks 2–4), ↓ WCC (⚠ weeks 4–8), ↑ infection; autoimmune phenomena, such as ITP and haemolytic anaemia, may be seen as lymphocytes reconstitute.
- ⚠ Beware late rejection, as T cells reconstitute at ~6 months.

- There are no randomized studies that directly compare against other agents for induction. It had been used to treat acute rejection, but experience and evidence are currently lacking.

Box 5.5 Administration of thymoglobulin

Dose

1.5mg/kg (ideal body weight), rounded up to nearest 25mg in 500mL normal saline or 5% glucose.

Premedication

Chlorphenamine 10mg IV and hydrocortisone 100mg IV 1h before each infusion. Antipyretic agents (e.g. paracetamol) may also increase tolerability.

If reactions occur, treat with additional steroid, antihistamine, nebulized salbutamol, and IV hydration.

Administration

- ⚠ ATG should be given via a central line.
- Administration through a 0.22 micron in-line filter is recommended.
- Administer first dose at 10mL/h for the first hour.
- If no adverse effects, ↑ infusion rate so that total duration is ≥6h.
- Subsequent infusions should be administered over ≥6h.
- Treatment with ATG should not usually exceed 14 days.
- Vials batch numbers should be recorded (it is a blood product).

Monitoring

CD3 monitoring

- ⚠ Not universally undertaken (or accepted).
- CD3 count should be measured before the first dose as a reference.
- Daily CD3 counts thereafter. Adjust daily doses according to result (reference range 1–30 cells/μL). Guide (local protocols will vary):
 - <10 cells/μL: no dose.
 - 10–20 cells/μL: half dose.
 - >20 cells/μL: full dose.

Other monitoring

- Monitor general appearance, BP, HR, and temp every 15min during initial hour of first infusion. Hourly monitoring for remainder of first and subsequent infusions.
- Check infusion rate regularly.
- Daily FBC.

Other considerations

Prophylaxis against opportunistic infections

- Oral candidiasis: nystatin 1mL qds. Continue 1 month after course.
- CMV (📖 p. 432), PCP (📖 p. 428), and TB prophylaxis (📖 p. 395).

Other immunosuppressive therapy

Stop MMF or azathioprine during therapy to reduce neutropenia risk. Restart 2–3 days before the end of the course.

OKT3

- OKT3 is a mouse mAb specific for CD3 (a component of the TCR on all T cells).
- On binding, CD3 +ve cells release cytokines, internalize the CD3-TCR complex, and are rapidly cleared from the circulation.
- T cell rebound is more rapid than for ATG.
- Premedication and prophylaxis as for thymoglobulin, except a larger dose of corticosteroid is often given, e.g. 250–500mg IV methylprednisolone.
- Given as a 5mg IV bolus (can be administered peripherally).
- Anaphylaxis is more common and cytokine release syndromes almost universal and more severe (particularly on repeat dosing).
- These serious (sometimes very serious: non-cardiogenic pulmonary oedema, aseptic meningitis, and encephalopathy) side effects mean that OKT3 is now generally reserved for the treatment of refractory rejection, rather than for induction therapy.
- ⚠ Do not administer to volume-overloaded patients (diurese or ultrafiltrate the patient, as necessary, first).
- ↑ infection and PTLD risk, as for other depleting agents.
- A 10-day course is usual. CD3 monitoring can be undertaken, as for thymoglobulin.
- Neutralizing antibodies may limit efficacy.

Rituximab

- A chimeric (mouse/human) mAb directed against CD20 (expressed on B cells but not plasma cells—so it rarely causes hypogammaglobulinaemia).
- Binding induces apoptosis and complement-dependent cytotoxicity.
- Causes rapid and sustained depletion (6–9 months) of both circulating and tissue-based B lymphocytes.
- Repeat administration of rituximab is sometimes based on measurement of circulating CD19 +ve B cells.
- Main role (in transplantation), to date, has been to prevent resynthesis of HLA or ABO antibodies, following plasma exchange in ABO- or HLA-incompatible transplants (see 📖 p. 444).
- Premedication and prophylaxis, as for thymoglobulin.
- Infusion reactions and cytokine release syndrome are well recognized.
- A single dose of 375mg/m² is given IV 2–4 weeks prior to transplantation (50–400mg/h).
- ⚠ Rituximab bound to B lymphocytes may lead to a false positive B cell cross-match.
- Role as induction therapy or in the treatment of antibody-mediated rejection remains to be defined.

Immunosuppression: maintenance

Introduction

Maintenance immune suppression is given for the lifetime of the graft to prevent rejection. These agents are administered orally, and regimens usually involve several agents. Standard 'triple therapy' consists of a calcineurin inhibitor (CNI), an antimetabolite and corticosteroids.

Calcineurin inhibitors: ciclosporin, tacrolimus

- The cornerstone of maintenance therapy over the last few decades.
- Ciclosporin (CIC) is a lipid-soluble peptide, derived from the fungus *Tolyplacadium inflatum*.
- Tacrolimus (TAC, previously known as FK506) is a macrolide antibiotic, isolated from the bacterium *Streptomyces tsukubaensis*.
- Both disrupt T cell signal 1 through binding intracytosolic immunophilins (cyclophilin or FKBP12). These complexes then bind calcineurin (a protein phosphatase), preventing its interaction with substrates, such as NFAT, and reducing the transcription of T cell activation genes (including IL-2 and IL-2R).
- Therapeutic drug monitoring is mandatory:
 - Both have a narrow therapeutic index: too little → inadequate immune suppression; too much → side effects (⚠ particularly nephrotoxicity).
 - There is also significant interpatient variation in drug metabolism.
- Drug concentrations are measured in whole blood, as much is red blood cell or plasma protein-bound.
- 12h 'trough' levels (C_0) are generally measured.
- The use of TAC is growing at the expense of CIC:
 - Head-to-head comparisons have generally been confounded by inadequate power and variable dosing regimens.
 - However, there has been a significant ↓ in acute rejection in many studies (including ↓ steroid-resistant rejection), and a large meta-analysis has suggested ↓ early graft loss.

Ciclosporin

- Neoral[®], a microemulsion preparation, has been the main CIC formulation over recent years, but several generic preparations are now available.
- ⚠ There are important differences in bioavailability between formulations, so it is crucial that the patient is consistently prescribed the same brand.
- Dose: 7mg/kg in two divided doses (PO), with subsequent adjustment, according to levels.
- Target ranges (12-hour trough). ⚠ Depends on local practice, immunological risk, and evidence of nephrotoxicity. For guidance:
 - 0–6 months: 200–250ng/mL.
 - 6–12 months: 150–200ng/mL.
 - >12 months: 75–150ng/mL.
- 📖 There has been much interest in using 2h post-dose levels (C_2) for therapeutic monitoring, as these provide a better estimate of drug

exposure (and have been associated with ↓ acute rejection in some studies). However, perhaps because it is a less practical, it has not been widely adopted.

- CIC is metabolized in the GI tract and liver by the cytochrome P450 system (CYP3A4)—with implications for drug interactions (see Table 5.6, Box 5.6).
- If required IV, administer 1/3 of the oral dose.

Tacrolimus

- Prograf[®] has been the main formulation over recent years. Advagraf[®] is a once-daily formulation.
- ⚠ Several generic preparations are now available, with potentially significant differences in bioavailability between brands.
- Dose: 0.1mg/kg in two divided doses (or as a single dose for once-daily formulations), with subsequent adjustment, according to level.
- Typical target ranges (12-hour trough). ⚠ Depends on immunological risk and evidence of nephrotoxicity. Check local protocols:
 - Low immunological risk: trough level 3–7 micrograms/L.
 - Standard immunological risk: trough level 10–12 micrograms/L for first 2 months, then 8–10 micrograms/L.
 - High immunological risk: trough level 10–12 micrograms/L for first 2 months, then 8–10 micrograms/L.
- C₀ (trough) levels correlate well with drug exposure (a significant advantage over CIC).
- Metabolized by the cytochrome P450 (CYP3A4) system—with implications for drug interactions (see Table 5.6, Box 5.6).
- If required IV, the dose is 0.03–0.05mg/kg as an infusion over 24h.

CNI side effects

- Nephrotoxicity: initially reversible renal vasoconstriction → ↓ GFR, but irreversible interstitial fibrosis supervenes. Some degree is common on transplant biopsies (and a particular problem in recipients of other solid organ transplants, with ~5% → ESRD after 10 years).
- ↑ BP.
- Headache (rarely, more severe neuropsychiatric issues).
- Tremor.
- Liver dysfunction.
- Post-transplant DM—NODAT (esp. TAC) (📖 p. 424).
- May potentiate DGF.
- ↑ K⁺ (similar to a type IV RTA) (📖 p. 825).
- ↑ urate (+ gout), ↓ Mg²⁺, ↓ PO₄⁻.
- Thrombotic microangiopathy (TMA) (📖 p. 412).
- Cosmetic: hirsutism (esp. dark-haired, darker-skinned patients), gum hypertrophy (CIC > TAC), hair loss (TAC > CIC).
- Dyslipidaemia (CIC > TAC).
- Diarrhoea (TAC > CIC).

⚠ Severe diarrhoea may significantly ↑ TAC levels (enterocytes that normally secrete TAC into the gut lumen via P-glycoprotein are destroyed, causing less TAC elimination via this route).

Table 5.6 Induction and inhibition of CYP3A4

↑ CNI levels	↓ CNI levels
Grapefruit juice	Rifampicin
Erythromycin	Caspofungin
Clarithromycin	Griseofulvin
Fluconazole	Phenobarbital
Ketoconazole	Phenytoin
Itraconazole	Carbamazepine
Verapamil	St John's wort
Diltiazem	
Lercanidipine	
Ritonavir	
Nelfinavir	

Box 5.6 CNI drug interactions

- Statin levels are significantly increased by CNIs (CIC > TAC).
 - May →↑ CK and rhabdomyolysis.
 - Statins should be introduced at low dose and titrated cautiously.
 - The co-prescription of simvastatin and CIC is contraindicated by the MHRA in the UK.
- CIC inhibits the enterohepatic recirculation of MPA, meaning that higher MMF doses are required in recipients treated with CIC.
- These drugs increase the nephrotoxicity of CNIs:
 - NSAIDs.
 - Aminoglycosides.
 - Amphotericin.
- These drugs increase the incidence of ↑ K⁺:
 - ACE-I/ARB.
 - K⁺-sparing diuretics.

Mycophenolic acid

- Mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) are the ester and sodium salt pro-drugs of the active compound mycophenolic acid (MPA).
- MPA is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a critical enzyme for *de novo* purine nucleotide synthesis.
- Lymphocytes are dependent on the *de novo* pathway (other cell types have a salvage pathway), so inhibition →↓ proliferation of activated T and B lymphocytes.
- MMF has been shown to ↓ acute rejection, more than azathioprine, as part of triple therapy with CIC. Limited evidence for additional benefit in TAC-based regimens. However, there has been a massive shift toward MMF, such that it is now the staple at most centres. Note that AZA may remain a good option in TAC-treated patients with MMF-related GI side effects.
- SE: gastrointestinal side effects can be problematic. Diarrhoea in ~30%, gastritis in ~20%, nausea, vomiting, constipation, dyspepsia. Bone marrow suppression is relatively common. Infective side effects (e.g. CMV) are more common than with AZA.
- Relatively few important drug interactions. CIC ↓ enterohepatic recirculation of MPA, so higher doses of MMF are required than with TAC.
- MPA sodium is available as an enteric-coated, slow-release formulation, designed to ↓ GI side effects (Myfortic®). This is not demonstrably the case in practice, although some patients seem to benefit from a change in tablet.
- Initial dose: MMF 1g bd (or 500mg qds)—some centres use 1.5g bd for black recipients; MPA 720mg bd. Subsequent dosing will depend on local protocols, CNI levels, and side effects (including bone marrow tolerability).
- ☞ There is very marked interpatient variability in plasma MPA levels. Therapeutic monitoring of MPA levels is available, but its role has not

yet been established. May be measured in those with severe GI side effects.

Azathioprine

- Metabolized to a purine analogue (6-thioguanine), which competitively inhibits purine synthesis (for RNA and DNA). This inhibits all cell replication, including ↓ T cell proliferation.
- An old friend: in use in transplantation for >40 years.
- Dose: usual starting dose is 1.5–2mg/kg once daily. Reduce if WCC $<4.0 \times 10^9/L$ and stop if $<2.0 \times 10^9/L$.
- SE: myelosuppression, hepatitis, cholestasis.
- Interactions: ⚠ *allopurinol* should be used with great caution with azathioprine, as AZA is also metabolized by xanthine oxidase (→ potentiates bone marrow toxicity). Consider transfer to MMF.
- Patients with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) metabolize AZA slowly, resulting in drug accumulation (and bone marrow suppression). If necessary, patients can be screened for TPMT levels (and the presence of the genetic abnormality).

Sirolimus (rapamycin)

- Derived from a macrolide antibiotic identified on Rapa Nui (Easter Island).
- Inhibits mammalian target of rapamycin (mTOR), a key regulatory kinase in cell division.
- Like TAC, it binds FKBP12, but the resulting complex binds and inhibits mTOR → ↓ lymphocyte proliferation in response to cytokines.
- A long half-life allows once-daily dosing.
- Dose: typical loading dose of 6mg for two doses, followed by maintenance dose of 2–4mg.
- Trough C_0 levels correlate well with overall drug exposure. Aim level 5–10ng/mL.
- SE: antiproliferative and anti-angiogenic (⚠ → impaired wound healing and lymphocele formation). Pneumonitis (can be severe: cough, breathlessness, infiltrates on CXR/CT. Exclude infection. Resolves on withdrawal.). Also mouth ulcers, ↑ lipids, bone marrow suppression, TMA, rashes. Appears to prolong DGF (↓ tubular regeneration). ↑ proteinuria.
- ⚠ Intolerance is very common. Many side effects are more pronounced in those not on steroids.
- Because of its propensity to impair healing, it is often introduced after 3 months in selected patients.
- Interactions: potentiates CIC nephrotoxicity.
- An additional mTOR inhibitor everolimus is available in some countries.
- May have a role when there is progressive loss of GFR from non-immune mechanisms (→ IF/TA); for example, if CNI nephrotoxicity is problematic >6 months post-transplant (📖 p. 416).
- 📖 Associated with less malignancy. Not a strong evidence base but studies ongoing (particularly in the context of skin cancer) (📖 p. 440).

Corticosteroids

- ↓ cytokine gene transcription → ↓ cytokine-regulated lymphocyte signalling, ↓ T cell activation (via ↓ NF-κB), and ↓ chemokine-driven lymphocyte homing to areas of inflammation.
- Familiar toxicity: insomnia, weight gain, ↑ BP, ↑ CV risk, impaired glucose tolerance and ↑ NODAT (📖 p. 424), dyslipidaemia, mood disturbance, poor wound healing, osteoporosis.
- Dose: huge centre variation. Typical: pulsed steroids at the time of transplantation, followed by 20mg prednisolone orally for at least 4 weeks, then phased reduction to maintenance 5mg.

Steroid withdrawal

- The problems associated with steroid use have made regimens involving their withdrawal popular, particularly in the USA.
- However, RCTs involving withdrawal at 3–4 months have shown significantly ↑ rejection (albeit with CIC-based regimens).
- Experience with TAC- and MMF-based regimens is more positive.
- However, the benefits of late steroid withdrawal from a maintenance dose are likely to be quite marginal. What are you trying to achieve in this situation? This risk/benefit ratio needs careful explanation to the patient.
- Early withdrawal (e.g. first week) or total avoidance is increasingly popular with antibody induction and TAC-/MMF-based regimens.

Newer immune suppressants

Belatacept

- A fusion protein comprising an immunoglobulin domain and modified CTLA4 (a T cell molecule, which forms part of the co-stimulatory signals required for T cell activation).
- It is designed to strongly bind the APC surface co-stimulatory ligands CD80 and CD86.
- Must be given IV every 4–6 weeks.
- Has been used in early studies to allow CNI avoidance.
- In addition, experimental studies have suggested that the interruption of co-stimulatory signals could lead to donor-specific graft tolerance.

Eculizumab

- A humanized monoclonal antibody that targets complement protein C5, inhibiting its cleavage to C5a and C5b ∴ preventing formation of the membrane attack complex (MAC).
- It has been primarily used to treat atypical HUS and antibody-mediated rejection (AMR).
- It may have a prophylactic role in transplants at high risk for these conditions.
- All patients should receive vaccination against *Neisseria meningitidis* prior to receiving eculizumab.
- Clinical trials, predominantly in antibody-incompatible renal transplantation, are ongoing to determine the optimal use.
- It is eye-wateringly expensive.

Perioperative care

Introduction

Patients listed for transplantation will have undergone comprehensive prior evaluation and have been deemed suitable (📖 p. 350). However, circumstances may have changed physically, psychologically, or socially and require brief reassessment to ensure the recipient is fit to proceed with urgent surgery.

The same is true of live donor, but this is *elective* surgery without the time pressure of attempting to minimize CIT.

Transplantation is major surgery, and a full general history and examination are required. Additional useful information may be gained from the full case notes (which may need to be couriered from another site, if not available electronically). In particular, you need to establish the following.

Is the patient fit for major vascular surgery today?

- Is the CV work-up complete, up to date, and satisfactory?
- Are there any new cardiorespiratory symptoms (or signs) which warrant further assessment?
- Any recent or present intercurrent illness?
- Are the vascular history and exam satisfactory? Document femoral and more distal pulses; look for signs of ischaemia, and ask about claudication.

Is the patient appropriate for immune suppression?

- Any recent or active infections?
- Any history of malignant disease and treatment?
- Any concerning symptoms or signs under, or requiring, assessment, e.g. unexplained weight loss, new or disproportionate anaemia, change in bowel habit?

What are the likely requirements for RRT perioperatively?


- Is the patient pre-emptive, HD or PD?
- What is the K²? (▶ urgently required)
- Any signs of fluid overload?
- Current weight vs target weight?
- When did they last dialyse?
- What is the current dialysis access, and how has it been functioning?
- Is DGF anticipated (e.g. DCD, ECD, long CIT, AKI at retrieval)?

What are the factors that need extra consideration for this patient?

- What is the underlying renal disease and residual urine output?
- Any comorbid disease that increases operative risk ± requires specific perioperative management, e.g. diabetes, ↑ BP, airways disease?
- History of difficult vascular access? Will central venous access be possible?
- Previous major abdominal surgery?
- Previous urological surgery? Anticipated bladder or bladder outflow dysfunction?
- What is the bleeding risk? Antiplatelets or anticoagulation?

- What is the immunological history? Previous biological therapy (ATG, OKT3, alemtuzumab)?
- Current or historical HLA antibodies/PRA, previous transplants, recent potential sensitizing events (esp. blood transfusion)?

Investigations

- All patients should have their donor-specific cross-matched bloods sent urgently to tissue typing, as this is a rate-limiting step.
- In selected patients (esp. with no historical antibodies or recent sensitizing events), a 'virtual cross-match' (see  p. 364) may be permitted.
- FBC, clotting, and G&S (\pm cross-matched blood).
- U&E, Ca^{2+} , PO_4 , LFT, glucose, CRP.
- ECG—compare to previous.
- CXR—if significant cardiorespiratory disease or symptoms/signs.
- MSU—unless anuric.
- HIV, HBV, HCV—screened 3-monthly in HD patients but may not have been performed recently in others.
- CMV, EBV, toxoplasma, VZV, and syphilis serology. These will have been performed during work-up. They only need repeating if IgG previously negative.
- Pregnancy test, if relevant. Although pregnancy is rare in advanced CKD/dialysis patients, it is a possibility and generally considered a contra-indication to transplantation. A urinary pregnancy test is reliable if the patient passes urine, serum beta-HCG if not.

Preoperative RRT

- It is important to ensure that patients are safe for the fluid loading, tissue injury, and transfusion ($\rightarrow \uparrow \text{K}^+$) that may occur during a long transplant operation.
- However, dialysis may delay the operation, potentially \uparrow DGF (especially if excess UF is performed), and \uparrow bleeding if heparin is used.

Dialysis is advisable if:

- $\text{K}^+ \geq 5.5 \text{ mmol/L}$.
- Signs of fluid overload (pulmonary oedema $>$ peripheral oedema).
- A long delay is anticipated before the organ arrives.

A suitable strategy would be a short session (2–3 hours is adequate for K^+ removal), minimal or zero heparin, and the minimum necessary UF (often leaving the patient $\sim 1 \text{ kg}$ above their target weight).

Pre-dialysis patients

It is unusual for these patients to require HD pre-op. Minor electrolyte/fluid disturbances may be managed conservatively, with blood sugar control, isotonic sodium bicarbonate, diuretics, etc., as appropriate.

If there is no pre-existing vascular access, the benefits of dialysis catheter insertion need to be weighed against the risks of time delay, DVT (femoral), pneumothorax (internal jugular), etc.

If DGF is anticipated, ask the anaesthetist to site an internal jugular dialysis catheter intraoperatively.

PD patients

Similar considerations as for pre-dialysis patients tend to apply. Additionally, rapid exchanges can be used preoperatively. PD may be used

post-operatively if the peritoneum has not been breached (talk to the operating surgeon).

Writing the drug chart

It is good practice for transplant units to have their own clear guidelines for perioperative transplant prescribing, including sample drug charts for the immunosuppression protocols used. The general principles include:

Diabetes medications

- Stop all regular medications, including oral hypoglycaemics and SC insulin. Commence an IV short-acting insulin 'sliding scale' unless diet-controlled only.
- Regular medications will need careful retitration post-operatively once eating normally—requirements may have changed due to improved renal function.

Antihypertensives

- Fluid shifts, general anaesthesia, and opiate analgesia can all contribute to ↓ BP post-op.
- ↑ BP is preferred to ↓ BP post-op, as autoregulation is impaired and graft perfusion is ∴ more BP-dependent. All antihypertensives are generally stopped preoperatively. ⚠ Exceptions are beta-blockers (reflex tachycardia/myocardial ischaemia) and other drugs used as anti-anginals or anti-arrhythmic, e.g. diltiazem, verapamil.

Antiplatelets and anticoagulants

- The antiplatelet effects of aspirin and clopidogrel last at least 7 days.
- Monotherapy is not considered a contraindication to transplantation, and many routinely initiate low-dose aspirin as prophylaxis against graft thrombosis.
- Dual antiplatelet therapy is generally considered a contraindication. As such, patients should not be transplant-listed until they have reverted to monotherapy (e.g. after 6–12 months for a drug-eluting stent).
- Warfarin:
 - The INR should be corrected to at least <1.5 prior to surgery (discuss with your surgeon).
 - For live donor recipients, this can be achieved by omitting it from 5 days pre-op.
 - The decision to admit for therapeutic IV heparin infusion pre-op depends on the indication (absolute, e.g. metallic MVR, recurrent VTE vs relative, e.g. AF).
 - Reversal depends on the time available. If >6h, give 2mg vitamin K IV, and recheck in 4h.
 - If surgery is imminent, reversal can reliably be achieved with concentrated vitamin K-dependent clotting factors (e.g. Beriplex® 20–50IU/kg, depending on INR; discuss with haematology) or FFP 15mL/kg. You should not need to recheck INR prior to proceeding. ⚠ Effects only last ~4–6h though.
 - The effect of warfarin can be prolonged—ensure adequate vitamin K loading, and recheck INR post-op, and then 12-hourly for 48h.

CKD-related drugs

Stop:

- Phosphate binders.
- Vitamin D analogues, e.g. alfacalcidol (unless previous parathyroidectomy).
- Cinacalcet. Rebound hypercalcaemia can occur, so monitor closely.
- Iron.
- ESA—often stopped. Should continue if DGF to reduce the potential need for transfusion.

Immunosuppression

- Prescribe accurately, according to local protocols.
- Induction agents are prescribed on the 'stat' side and not given until the cross-match is confirmed negative.
- Ensure the anaesthetist is aware of intraoperative drugs, e.g. methylprednisolone.


VTE prophylaxis

- VTE risks are present as with any major surgery.
- Use anti-embolism stockings (unless contraindication).
- Consider SC heparin or LMWH prophylaxis (discuss with your surgeon).

GI prophylaxis

- If on H₂ antagonist or PPI, then continue.
- If on neither, start ranitidine 150mg PO bd until steroids are weaned.

Anti-infective prophylaxis

- Infections are a common cause of morbidity and mortality in transplant recipients, especially in the first 6 months.
 - PCP: co-trimoxazole 480mg od (also covers UTI, toxoplasma). Alternatives include dapsone 50–100mg od or monthly pentamidine nebs.
 - Oropharyngeal candidiasis: nystatin 1mL PO qds or amphotericin lozenges.
- CMV: valganciclovir (unless CMV D-/R-), dose according to GFR (see  p. 432)
- TB: local guidelines vary.
 - Prophylaxis is essentially treatment of potential latent TB with isoniazid 300mg od (+ pyridoxine 25mg od to prevent neuropathy).
 - Indicated where the TB risk is deemed greater than the risk of severe isoniazid toxicity, e.g. hepatitis (278/100,000).
 - Risk factors include prior infection without evidence of cure, ethnic origin, or close contacts affected.
- General surgical prophylaxis is often given at induction, e.g. cefuroxime 1.5g IV and/or amikacin 500mg IV. For DD transplant, further regular prophylaxis may be continued until culture of the graft transport medium is available.

Analgesia

- Give paracetamol 1g qds regularly PO/PR/IV unless contraindicated (reduce IV dose if <50kg).

- Patients will require opiate/opioid analgesia initially for comfort and to help them take deep breaths and cough.
- Patient-controlled analgesia (PCA) is preferred immediately post-op.
 - Morphine (1mg bolus, 5min lock-out) is an option, but its metabolite morphine-6-glucuronide is active and renally excreted.
 - Fentanyl (10–15 micrograms bolus, 5min lock-out) does not accumulate. It has a shorter half-life so is more patient-responsive.
 - Once patients are ready for oral analgesia, a moderately strong opioid can be used, e.g. oxycodone 2.5–5mg qds or tramadol 50–100mg qds.
 - ⚠ Do not forget to prescribe laxatives in conjunction with opiate analgesia.

Post-operative assessment

It is good practice for the patient to have a detailed clinical assessment in recovery prior to transfer back to the ward to ensure they have recovered safely from anaesthesia, are haemodynamically stable, have appropriate fluids and analgesia, and show no signs of haemorrhage or graft thrombosis necessitating immediate re-exploration.

- Talk to the surgeon—the op note does not always tell the full story!
- Read the op note thoroughly—any complications? Special instructions?
- Examine the anaesthetic chart—stable haemodynamics? (look for vasopressor administration, e.g. metaraminol/ephedrine, and boluses of furosemide).
- What was the fluid balance? Patients can be very fluid-loaded. Was there immediate urine output? Estimated blood loss?
- Examine the drug chart—was all induction immunosuppression given as planned?
- Careful clinical examination—ideally, the patient should be:
 - Alert, orientated, and comfortable. Able to cough.
 - Well perfused—warm peripherally. Normal lactate.
 - Haemodynamically stable—not tachycardic, good BP (MAP >80mmHg).
 - On no, or minimal, supplemental O₂, with good air entry to the lung bases.
 - Passing urine—unless DGF is anticipated.
- Additionally examine:
 - Drain outputs and contents.
 - Distal lower limb pulses—compare to pre-op.
- Abdomen (some post-op tenderness to be expected—but is it proportionate?).
- Check that full post-op bloods have been sent, particularly Hb and K⁺.
- Review the CXR: CVC position? Pneumothorax? Pulmonary oedema?
- ► Doppler USS—this should ideally be performed in recovery. It helps to exclude an immediate technical complication. Additionally, baseline perfusion, resistive indices, and diastolic flow patterns are very helpful for future comparative scans.

Post-operative care

Attention to detail is key. Always consider: what am I expecting from this graft, in this patient, at this time? Any deviations require urgent assessment, investigation, and intervention.

Monitoring

- HR, BP, RR, O₂ saturation hourly for at least 24h, then 4h.
- Accurate fluid balance charts, including hourly urine and drain outputs for at least 48h, then 4h.
- Daily weights.
- Bloods:
 - FBC and U&E 6-hourly for 24h. Expect a modest fall in Hb (blood loss/haemodilution).
 - Daily FBC, U&E, CRP, glucose (bone and liver profile may be 3x/weekly).
 - ► Trough CNi levels: 3x/weekly, starting day 3 (unless live donor with pre-loading).

Managing fluid balance

There is a broad spectrum of outcomes from the graft immediately post-transplant—from a brisk diuresis >20L in 24 hours to complete anuria. Additionally, the recipient's native UO may range from normal to anuric.

- As a general rule, daily fluid balance should be ~+500mL (for insensible losses).
- This can be achieved by 100% replacement of the previous hour's losses + 40mL.
- This must be combined with regular careful clinical examination to detect hyper-/hypovolaemia and adjusted accordingly. If the patient is still polyuric after 48–72h, it may be being 'driven' by this regimen. Try reducing to 75% replacement, and monitor for signs of hypovolaemia.

Fluid choice

- Due to the electrolytes losses that can occur, it is best to use a balanced electrolyte solution, e.g. Hartmann's or Ringer's lactate (especially if polyuria).
- The risk of them contributing to ↑ K⁺ is low, as they only contain 4–5mmol/L.
- 0.9% NaCl should be avoided in high volume, as excess salt-loading and hyperchloraemic metabolic acidosis may develop.

Responding to low urine output

- Oliguria may be defined as UO <0.5mL/kg/h.
- Remember, what are you expecting? DGF and oliguria are unusual in live donor kidneys or a DBD kidney with a short CIT.
- ⚠ The most worrying sign is oliguria (or anuria!) developing in a patient previously passing good urine volumes. Causes include:
 - Hypovolaemia (beware inaccurate charts, undocumented loose stools, etc.).
 - Catheter problems (obstruction, bypassing).
 - Relative hypotension (esp. if the donor was hypertensive).

- Ureteric obstruction.
- Urinary leak (high drain volumes?).
- CNI toxicity.
- Arterial or venous thrombosis.
- Hyperacute rejection (graft pain, swelling, tenderness) is rare but should be checked for.

Action

- Unless there are definite signs of fluid overload, give a fluid challenge:
 - Rate of delivery is more important than choice of fluid.
 - Administer a rapid bolus of 250mL.
 - Use additional variables to assess response, e.g. HR, BP, JVP, CVP.
 - Do not give repeated fluid challenges for oliguria, unless there are signs of a positive impact, e.g. improved BP or low CVP rising to 8–12cmH₂O, otherwise there is a danger of pulmonary oedema.
- Flush the catheter, and replace, if necessary.
- Send a drain creatinine if volumes are high (📖 p. 402).
- Check/review CNI levels.
- Arrange an urgent Doppler USS to assess vascular patency and flow, RI, and signs of obstruction or collections.
- If all these factors are in order, the most likely diagnosis is DGF (📖 p. 404).
- If DGF persists to day 5–7 post-op, then a surveillance transplant biopsy is usually undertaken.
- There is no role for the use of furosemide or 'renal dose' dopamine to augment urine output.

RRT post-transplant

- Unless immediate graft function occurs, dialysis may be required.
- Patients should be reassured that this is not uncommon.
- ⚠ Haemodialysis post-transplant can actually increase/prolong DGF.
- Standard indications apply in the presence of oliguria:
 - Hyperkalaemia: >6.5mmol/L and/or ECG changes.
 - Pulmonary oedema.
 - Symptomatic uraemia.
- If patients are passing good volumes of urine, medical therapies may be more appropriate. Avoid calcium/K⁺ exchange resins.
- In addition, RRT may be required for:
 - Safe transfusion of blood products, e.g. if Hb <70g/L.
 - Reducing risk of uraemic bleeding for planned procedures, e.g. transplant biopsy.
- Aim to minimize UF, and avoid intradialytic hypotension as much as possible.
- PD may be used if the peritoneum has not been breached.

General measures

- Remove IV lines, including CVC, as soon as practical to avoid infection.
- Early oral intake, as advised by the surgical team.
- Encourage deep breathing exercises and early mobilization.
- Urinary catheter to stay until at least day 5 (protects the vesicoureteric anastomosis).

- Watch phosphate levels. Urinary phosphate excretion often precedes a falling creatinine. Frank hypophosphataemia is relatively common. Encourage high phosphate foods; may require oral or IV supplementation.
- Remove drains when volume <50mL/24h (with surgical approval).
- Watch blood sugars closely for the development of NODAT (📖 p. 424).
- Encourage self-administration of medications prior to discharge.
- Do not forget subsequent induction immune suppression doses, e.g. day 4 basiliximab.

The transplant operation

Organ retrieval

- Retrieval of multiple organs is the norm (i.e. heart–lung, liver, renal, pancreas), and several retrieval teams are often present.
- Both kidneys are harvested and may be sent to different centres.
- The kidneys are perfused with a cooled balanced physiological solution *in situ* (e.g. with Marshall's or University of Wisconsin solution) prior to removal.
- Along with the kidney, the renal artery (on a cuff of aorta), the renal vein(s) (with a cuff of IVC), and as much ureter as possible (with periureteral tissue—to preserve its vascular supply) are removed.
- The kidneys are placed on ice for transport. Machine perfusion techniques are an alternative—several types of apparatus are commercially available.
- Splenic tissue and mesenteric lymph nodes are also retrieved for cytotoxic cross-matching.

Recipient operation

- The kidney is carefully examined 'on the bench', paying particular attention to the arterial anatomy (accessory arteries cannot be sacrificed, as there is no collateral supply). Small veins may be more expendable, as there is some overlap in venous drainage. Vascular reconstruction may be necessary prior to implantation.
- The left renal vein is longer, making it easier to implant.
- Graft implantation is heterotopic, usually into the right iliac fossa (the right iliac vessels are generally more accessible), although some surgeons favour placing a right donor kidney on the left side and vice versa (as kidney orientation is easier). If a previous transplant remains *in situ*, the contralateral side will be favoured.
- An implantation biopsy may be taken (esp. if the donor is considered marginal) to help predict graft function in the post-operative period. Scoring systems are applied to these 'time zero' biopsies in an attempt to predict subsequent graft outcomes, e.g. the Karpinski score is based on summation of damage to glomerular, tubular, interstitial, and vascular compartments.
- An oblique incision is made from above the symphysis pubis towards the anterior superior iliac spine.
- The operation is largely extra-/retroperitoneal.
- Note: the native kidneys are not removed.
- Vascular anastomoses are usually end-to-side to the iliac vessels (preferably the external iliac artery—use of the internal may lead to erectile dysfunction in ♂).
- The ureter is joined to the recipient bladder. A submucosal tunnel (or oversew of bladder muscle) helps to prevent urine reflux.
- A JJ stent is usually placed to protect this anastomosis (removed cystoscopically at ~4 weeks). A urethral catheter is left *in situ* for 5 days.
- A drain is usually left in the perirenal space.

- Intraoperative CVP is maintained at $>10\text{cmH}_2\text{O}$ and MAP $>90\text{mmHg}$ using crystalloid (\pm albumin).
- Mannitol (or furosemide) may be administered as the vascular clamps are released.
- Methylprednisolone (0.5–1g) is also given intraoperatively.
- See Fig. 5.17.

Dual transplants

- Double transplants represent an attempt to increase the transplanted nephron mass.
- Dual transplants are increasing, as more ECD kidneys are accepted for transplantation.
- There are no universally agreed criteria: some centres will be guided by a pre-implant biopsy, some by donor characteristics alone, and some by both donor and recipient characteristics.
- Both kidneys are usually placed in the same iliac fossa, but one can be placed on each side in some circumstances.
- It is a significantly longer operation than a single kidney transplant, so intraoperative risks are higher.

En bloc transplantation refers to a technique wherein both kidneys are retrieved together, with donor aorta and IVC still attached. They are then transplanted en bloc into the recipient. This is usually performed in the context of paediatric donation (age <5): it increases the transplanted nephron mass and helps make the surgical anastomoses less technically demanding.

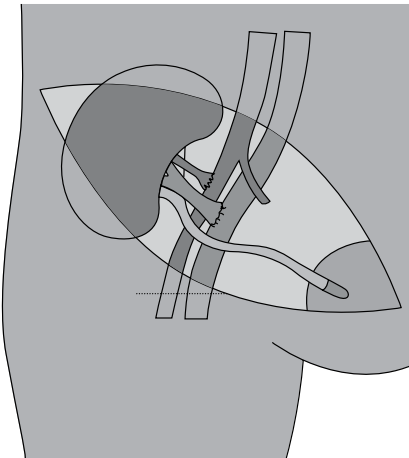


Fig. 5.17 Renal transplant surgery with an end-to-side anastomosis between the renal artery and external iliac artery. Reproduced from *Oxford Desk Nephrology*, Jonathan Barratt, Kevin Harris, and Peter Topham (2008), with permission of Oxford University Press.

Surgical complications

Early

Bleeding

Rarely from the vascular anastomoses (→ haemorrhagic shock), more likely from damage to a smaller vessel. May present with ↑ HR, ↓ BP, ↑ drain output, blood loss from the surgical wound, ↓ Hb. USS or CT may reveal a haematoma around the graft. Resuscitation, then urgent re-exploration is usually indicated.

Wound infection

The incidence has reduced with the use of perioperative antibiotics. Contributing factors include uraemia, steroids, sirolimus, diabetes mellitus, older age, and obesity. Causative organisms are usually Gram +ve.

Vascular thrombosis/occlusion

- Occurs in 0.5–5% of transplants.
- Risk factors: complex vascular anastomoses, ↓ BP, donor vascular disease, recipient thrombotic tendency (e.g. APS), recipient sickle cell disease (→ pre-transplant exchange transfusion to ↓ sickle Hb + warm graft prior to reperfusion).

Arterial

Arterial thrombosis is usually secondary to a technical error (either during retrieval or during transplantation—usually intimal injury). Usually presents with oliguria and deteriorating graft function (± pain). Requires urgent surgery, but graft loss is the usual outcome. Regular USS with Doppler is required to confirm perfusion in those with DGF.

Venous

Suspect if sudden ↓ UO, graft tenderness and swelling, macroscopic haematuria, pain (often severe). Doppler USS will show thrombosis and reversed diastolic arterial flow. Management: surgical exploration. The kidney will usually be removed (and reperfused) whilst the venous anastomosis is completely revised.

Urinary leak

Most commonly a technical problem with the vesicoureteric anastomosis or necrosis of the distal transplant ureter due to poor blood supply. Rarely, a complication of transplant biopsy. Often silent but may be painful (as the collection of irritant urine expands), scrotal/labial swelling, ↓ UO, ↑ SCr (resorbed urinary creatinine), ↑ drain volumes, wound leak, collection of fluid on imaging. *Investigation:* biochemical analysis of drain (or aspirate) will reveal a high Cr—higher than serum (lymphocele fluid has the same Cr as serum). Na⁺ and K⁺ are also high. Cystography/retrograde pyelography will demonstrate the source of the leak. *Management:* re-catheterize the bladder. If the ureteric stent has been removed, it may be reinserted (usually antegrade insertion) and left *in situ* until the leak has sealed (may take weeks to months). If this conservative approach fails, then surgery is necessary.

Lymphocele

Graft implantation interrupts the pelvic lymphatics. This may result in a collection of lymph around the transplant (~10% of transplants). Usually small and uncomplicated. May become large enough to obstruct the kidney or iliac veins (→ thrombosis). Can cause leg swelling and DVT and may become infected. More common in those treated with sirolimus (📖 p. 390). Diagnosis is on USS (or CT). Indications for intervention: discomfort, obstruction, or infection. Aspiration or drainage is usually carried out percutaneously. Recurrent lymphoceles may need fenestration to allow drainage into the peritoneal cavity.

Early obstruction

Early obstruction is usually caused by urethral catheter blockage by clots. Ureteral blockage from clot or oedema is rare if a JJ stent has been left *in situ* (⚠️ but suspect if ↑ SCr when it is removed). Extrinsic compression from a lymphocele may occur. USS will demonstrate hydronephrosis (but is often normal in early obstruction).

Late

Renal artery stenosis

Transplant renal artery stenosis may occur early (either a technical complication due to vessel injury or 2° to neointimal hyperplasia) or late (often atheromatous build-up at the transplant artery origin). Presents with ↑ SCr (± ACE-I/ARB-related transplant dysfunction), increasing BP, salt and water retention. Rarely, a transplant bruit. Should also be suspected if progressive transplant dysfunction with unexplained scarring on biopsy. *Investigation:* Doppler USS, CT angiography, MRA, formal angiography (according to local expertise). Percutaneous angioplasty can be undertaken, although recurrence is common (→ repeat angioplasty ± stenting). If required, surgical correction is technically challenging.

Ureteric stenosis

Occurs in 1–5% of transplants. Almost always in the distal ureter and 2° to ischaemia (the ureter is supplied by the transplant renal artery; ischaemia → fibrosis). Other causes include: lymphoceles, BK virus (📖 p. 436), urothelial tumours, and renal calculi. *Investigation:* USS will show hydronephrosis and allow nephrostomy placement. A nephrostogram will show the level of the obstruction. CT and cystoscopy may be needed to determine the cause in some cases. *Management:* JJ stenting. Small strictures may be amenable to endourological dilatation, but surgical re-implantation is often required. Occasionally, a native ureter is mobilized and anastomosed to transplant pelvis.

Bladder dysfunction

Transplantation may uncover pre-existing bladder outflow obstruction or bladder dysfunction. Examine for a palpable bladder, DRE, USS bladder pre-/post-voiding and consider urodynamic studies. Bladder training may be required in patients who have undergone long-term dialysis, as their bladders may have reduced capacity and muscle tone, resulting in significant urinary frequency.

Graft dysfunction

Introduction

Immune factors are important to both acute rejection and chronic allograft dysfunction, but there are many other potential causes (pp. 405, 414). Consideration of their timing post-transplant can help narrow the differential diagnosis (see Fig. 5.18).

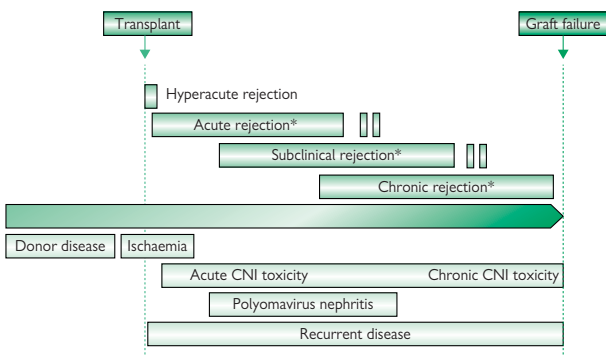


Fig. 5.18 Timing of graft dysfunction after renal transplantation. Reproduced from Chapman *et al. Kidney Int. Suppl.* **99**, S108–S112 (2005), with permission.

Immediate post-transplant period

Causes of graft dysfunction

- Delayed graft function (DGF).
- Vascular thrombosis.
- Ureteric leak or obstruction.
- Hyperacute rejection.
- Recurrent disease (► FSGS, HUS).

Delayed graft function (DGF)

Occurs in the immediate post-operative period and can effectively be considered as acute tubular injury or AKI following transplantation (it is caused by an ischaemia-reperfusion injury). The recipient will usually be oliguric, unless they had a significant urine output pre-transplant (e.g. a pre-emptive transplant). DGF is unusual with living donors (~3%) but affects ~20% of deceased donor grafts overall (~30% for ECD and ~40% for DCD kidneys).

DGF has numerous definitions but is usually described as the need for >1 dialysis post-transplantation. Of those patients with DGF: ~50% will recover by day 10; ~33% will recover between day 10 and 20; ~10–15% will recover subsequently, and ~2–15% will not recover at all (primary non-function).

DGF is associated with acute rejection (inflammation → HLA upregulation → enhanced graft immunogenicity). It is also associated with ↓ graft survival and ↑ mortality (see Table 5.7).

Table 5.7 Risk factors for DGF

Donor	Recipient
DCD or ECD donor	Black race
Inadequate perfusion/cold storage	Vascular disease
Long cold ischaemia time (>18h)	Intra-op/post-op ↓ BP
Pre-donation AKI	Highly sensitized (PRA >50)
↑ BP, vascular disease	Calcineurin inhibitors
Older donor (>60)	
High Karpinski score on time 0 biopsy (📖 p. 400)	

Management

- Regular USS and Doppler to ensure adequate perfusion (including immediately post-op).
- Maintain euvoemia to encourage recovery.
- Avoid ↓ BP during dialysis.
- Transplant biopsy (usually day 5–7) to confirm diagnosis (histology: acute tubular injury) and exclude acute rejection. Repeat every 5–7 days if no improvement.
- CNI-related vasoconstriction may aggravate DGF. If immunological risk allows, some centres will reduce (or even stop) CNIs—particularly if a depleting antibody has been used for induction.

Early graft dysfunction

Initial transplant function, but subsequent progressive ↑ SCr.

Causes

- Pre-transplant:
 - Volume depletion.
 - Vascular thrombosis (📖 p. 402).
 - Sepsis.
- Intrinsic transplant:
 - Acute rejection (📖 p. 408).
 - CNI nephrotoxicity (📖 p. 416).
 - Thrombotic microangiopathy (📖 p. 412).
 - Recurrent disease (📖 p. 418).
- Post-transplant:
 - Obstruction (📖 p. 403).
 - Urinary leak (📖 p. 402).
 - Urinary infection (📖 p. 438).

Assessment

- Clinical assessment:
 - Fluid balance; assess volume status.
 - Any new nephrotoxic drugs?
 - Urinary tract symptoms to suggest infection or outflow obstruction?
 - Any other evidence of infection, e.g. fever?
 - Pain over graft?
- Investigation
 - FBC, SCr, U&E, bone profile, clotting.
 - If ↓ Plt → LDH and blood film (TMA?).
 - Review recent CNI levels.
 - Urinalysis and MSU for M,C&S.
 - Urgent transplant USS (→ obstruction) and Doppler (→ perfusion).
 - Transplant biopsy.

Transplant biopsy

See native renal biopsy (📖 p. 81). The patient may no longer be an inpatient, in which case a day case biopsy can be considered. However, if SCr is rapidly rising, rejection is deemed likely, or the patient is high-risk for any other reason (e.g. Hb <80g/L; BP requires additional treatment), then an inpatient biopsy, with at least an overnight stay, may be desirable.

- Pre-biopsy:
 - USS: to exclude obstruction.
 - BP <160/90mmHg, preferably <140/90mmHg.
 - Hb ideally >80g/L.
 - Normal clotting (PT and APTT <1.2 × control). Platelet count >100 × 10⁹/L.
 - Send G&S.
 - Omit aspirin and prophylactic heparin on the day of biopsy and day after (preferably 5 days for aspirin if an elective biopsy).
 - Consider DDAVP if eGFR <25mL/min or urea >30mmol/L (~80mg/dL) (📖 p.80).
 - Sterile urine.
 - Informed consent.
 - If the patient has DGF, they should be well dialysed, preferably with their last dialysis the day before biopsy.
- Biopsy:
 - Performed under USS guidance.
 - Usually upper pole (further away from vasculature and ureter).
 - LA is infiltrated down to the transplant.
 - Disposable TruCut[®] needles or spring-loaded biopsy guns are generally used (e.g. 16 gauge—larger needles may ↑ complication rate). An initial stab incision at the skin can ease passage of the needle.
 - One core of tissue is usually adequate, although 2 are preferred (sampling of 10 glomeruli and 2 vessels is required for accurate Banff classification). Avoid >4 passes with the biopsy needle. Call for a more experienced operator after two unsuccessful passes.
 - Pressure can be applied to the biopsy site for 10min. The patient remains on bed rest with a good fluid intake for 6h. Pulse and BP are monitored regularly and urine inspected for haematuria.
- Complications:
 - Haematuria (macroscopic in ~5%).
 - Bleeding. Blood transfusion required in <2%.
 - If bleeding is severe or persistent (~1 in 1,500), then angiography with embolization can be undertaken. However, many centres would proceed directly to surgical exploration. A transplant nephrectomy is necessary in ~1 in 3,000.
 - Small AV fistulae complicate ~10% of transplant biopsies. These very rarely become large enough to cause problems or require embolization.

Acute rejection

► Treat suspected rejection immediately.

Introduction






Acute rejection is defined as a sudden deterioration in graft function, associated with specific immunopathological changes which are classified according to agreed international criteria (Banff classification, see Table 5.8).

Acute rejection is described as either predominantly T cell-mediated or predominantly antibody-mediated (humoral), although, in reality, there is almost certain to be a degree of pathophysiological overlap.

Key facts

- Modern immunosuppressive regimens have reduced the incidence of early acute rejection to ~10–20%.
- <10% of patients experience rejection after 1 year ('late' rejection is often associated with non-compliance).
- A single episode of rejection reduces 5-year graft survival by ~10%.
- The classical presentation of fever, painful graft, and oligo-anuria is now very rare. Rejection usually presents with an asymptomatic rise in SCr (or as a finding on a protocol or DGF transplant biopsy).

Risk factors (see also Box 5.4, p. 381)

- Delayed graft function ( p. 404).
- Sensitization with anti-HLA antibodies ( pp. 361–3).
- Repeat transplantation.
- HLA-mismatched graft ( p. 361).
- No induction immunosuppressive therapy ( p. 382).
- Non-TAC-/MMF-based immune suppression ( p. 386).
- Poor compliance or other cause of inadequate immune suppression (e.g. recent vomiting).
- Recent CMV infection (intentional reduction in immune suppression).
- Recent UTI (increased graft immunogenicity).

►► Hyperacute rejection

This catastrophic form of rejection occurs immediately on reperfusion of the transplanted kidney and is due to the presence of pre-formed antibodies (anti-ABO or anti-HLA). These antibodies bind to donor endothelial cells where they activate complement and clotting cascades → vascular thrombosis. Graft loss is inevitable.

Thankfully, it has been virtually eradicated by modern cross-matching techniques.

T cell-mediated rejection

- Most common form of rejection (~90%).
- Highest incidence in the first 3 months post-transplantation.


- T cell-mediated rejection may either be *tubulointerstitial* (more common—previously known as *cellular*) or *vascular* or both.
- Tubulitis is the characteristic lesion of tubulointerstitial T cell-mediated rejection: mononuclear cells infiltrate the walls and lumina of the tubules.
- Tubulitis is scored as mild, moderate, or severe, depending on the number of mononuclear cells within the tubular basement membrane (scored $t1-3$).
- In addition to T cells, infiltrates often contain macrophages, eosinophils, and plasma cells. There is usually associated interstitial oedema.
- Intimal arteritis or 'endothelialitis' is the characteristic lesion of vascular T cell-mediated rejection: mononuclear cells infiltrate the arterial endothelium.
- More severe vascular rejection will demonstrate transmural arteritis, fibrinoid change \pm stromal haemorrhage (scored $v1-3$).

Treatment

T cell-mediated rejection without vascular involvement

- Corticosteroids:
 - Methylprednisolone IV 500mg daily for 3 days.
 - Consider increasing oral prednisolone to 0.3mg/kg/day to a maximum 20mg, then taper by 5mg weekly to previous maintenance dose.
- Optimize maintenance immunosuppression:
 - Switch CIC to TAC. Target trough concentration 10–12 micrograms/L.
 - Optimize MMF dose. Target dose of 2g/day, if tolerated.
- Response expected within 5 days (~75% response rate). Re-biopsy if no improvement.

Refractory ('steroid-resistant') or vascular (Banff IIB, III) T cell-mediated rejection

- Add T cell-depleting antibody (e.g. ATG) (~90% response).
- For protocol, see  p. 384.
- If no response (~5%), consider IVIg 2g/kg single dose (or 0.4g/kg for five doses).

Humoral or antibody-mediated rejection

Antibody-mediated rejection (AMR) refers to rejection caused by antibodies directed against donor HLA, blood group antigens, or other endothelial cell antigens. The dominant mechanism of injury is antibody-dependent, with activation of the classical complement pathway.

Although antibody-mediated, T cells are vital for the initiation and maintenance of the B cell responses that lead to the generation of plasma cells and injurious antibody.

The diagnosis of AMR requires evidence of graft dysfunction and is supported by the presence of the following features:

- Morphologic evidence of acute tissue injury:
 - Acute tubular injury.
 - Neutrophils and/or mononuclear cells in peritubular capillaries (PTC) \pm glomeruli \pm capillary thrombosis.

- Fibrinoid necrosis/intramural or transmural inflammation in arteries.
- Immunopathological evidence of antibody action (often absent, so not essential to the diagnosis of AMR):
 - C4d \pm (rarely) immunoglobulin in PTC. C4d is a complement degradation product, derived from classical pathway activation).
 - Ig and complement in arterial fibrinoid necrosis.
- Serologic evidence of circulating antibodies to donor HLA (DSA) or other anti-donor endothelial antigen.

Cases that meet only two out of the three criteria are considered suspicious for AMR. Acute T cell-mediated rejection may also be present.

Treatment

☹ Unfortunately, the evidence base is poor and mostly derived from single centre experiences. However, the treatment of AMR is based on four concepts:

- Suppression of T cell responses (e.g. depleting antibody, escalation in maintenance immune suppression (MMF, CNI)).
- Elimination of circulating antibody using plasma exchange or other immunoadsorption technique.
- Inhibition of residual antibody (e.g. IV immunoglobulin).
- Suppression or depletion of B cells (e.g. rituximab or splenectomy).

In practice

- DSA level daily during treatment course.
- Optimize maintenance immunosuppression:
 - Switch CIC to TAC. Target trough concentration 10–12 micrograms/L.
 - Optimize MMF dose. Target dose of 2g/day, if tolerated.
- Corticosteroids:
 - Methylprednisolone IV 500mg daily for 3 days.
 - Increase oral prednisolone to 0.3mg/kg/day to a maximum 20mg, then taper by 5mg weekly to previous maintenance dose.
- EITHER: ATG if evidence of concomitant T cell-mediated rejection.
- OR: plasma exchange (📖 p. 950):
 - This should be given on alternate days or daily in severe cases (e.g. high DSA titre, anuric patient). Treatment should continue until there is clinical improvement \pm DSA titres become undetectable.
- After each PEX, give intravenous immunoglobulin (IVIg) 400mg/kg.
- Consider rituximab as part of initial therapy if severe histological change (or ongoing AMR despite PEX and IVIg).
- Repeat biopsy if no improvement in SCr in 7 days:
 - Ongoing AMR: continue PEX and IVIg \pm rituximab, if not already given. Consider eculizumab (📖 p. 391). Some centres would also contemplate a splenectomy.
 - Resolution of AMR: continue oral immunosuppression at doses above. Close monitoring with weekly DSA.

Table 5.8 Revised Banff classification (2007)

T cell-mediated rejection		Potential management
Borderline changes 'suspicious' for rejection	Tubulitis but no significant interstitial inflammation (or vice versa). No arteritis.	• None. Close surveillance
IA	Moderate tubulitis (>4 MC in >25% of sample)	Optimize immunosuppression levels Switch to more potent drugs (→ TAC, MMF)
IB	Severe tubulitis (>10 MC in >25% of sample)	Pulse corticosteroids If unresponsive, consider depleting antibody
IIA	Mild → moderate arteritis in one or more vessels (v1)	
IIB	Severe arteritis (>25% ↓ in luminal area) (v2)	
III	Transmural arteritis, with fibrinoid necrosis and perivascular inflammation (v3)	Switch to TAC Anti-lymphocyte therapy
Antibody-mediated rejection		Potential management
C4d +ve 'Indeterminate'	Circulating DSA, no evidence of active rejection but borderline changes or ATN	Low threshold for switching to tacrolimus or increasing target range. Likely to need interval biopsy
C4d +ve Acute antibody-mediated rejection	Circulating DSA, evidence of active rejection: I—ATN-like minimal inflammation II—capillary and/or glomerular inflammation III—arterial lesions	Switch to tacrolimus Consider IV immunoglobulin ± plasma exchange Anti-lymphocyte therapy

MC, mononuclear cells.

Thrombotic microangiopathy

Occurs in two contexts post-transplantation:

- Recurrent HUS (📖 p. 420).
- New TMA:
 - Usually associated with CNI use but associated with other drugs (particularly sirolimus).
 - Rejection: antibody-mediated rejection and severe T cell-mediated rejection.
 - Antiphospholipid syndrome (📖 p. 664).
 - Accelerated ↑ BP.
 - Unsuspected complement mutations (these should always be considered).
 - CMV disease.

Pathogenesis

Involves endothelial toxicity, ↓ prostacyclin synthesis, vasoconstriction, ↑ synthesis and release of large vWF multimers, ↑ leucocyte adhesion to vascular endothelium, platelet aggregation, thrombosis, and ischaemia.

Clinical features

May occur <1 week to >5 years post-transplant. Often, an unexpected finding on transplant biopsy, following ↑ SCr (graft dysfunction may be rapidly progressive). <50% have ↓ Plt, ↓ Hb, red cell fragmentation on blood film, ↑ LDH—but may be 'transplant-limited', with none of these apparent.

Consider investigation for complement mutations (usually H or I) in all patients.

Histology

Vessels: arteriolar wall thickening, swelling and detachment of endothelial cells, fibrinoid necrosis.

Glomeruli: capillary thrombi, attenuation of mesangial matrix and degeneration of mesangial cells ('mesangiolysis'), glomerular ischaemia.

📌 Management

- In less fulminant disease, more gradual changes to immune suppression can be undertaken—although the optimum regimen is unknown.
- ► Treat rejection.
- In more aggressive disease:
 - Stop CNI.
 - The role of PEX (with FFP) in CNI-associated TMA is uncertain but often undertaken anyway.
- Eculizumab (📖 p. 391) shows great promise, but its role awaits further clarification.

Chronic allograft dysfunction

Introduction

Both immunological and non-immunological factors play a role in progressive graft dysfunction and loss over time (see Table 5.9). Use of the previous descriptive term 'chronic allograft nephropathy' (CAN) is now discouraged, as a more pathologically specific diagnosis (or diagnoses) should always be sought. Chronic rejection implies an immune-mediated process, but optimum treatments are unknown.

Shared histological features are of interstitial fibrosis and tubular atrophy (IF/TA). At 2 years, ~70–90% of grafts will show features of IF/TA.

Table 5.9 Contributors to chronic allograft dysfunction

Alloantigen-dependent	Alloantigen-independent
Chronic rejection	CNI toxicity
Acute rejection episodes	Delayed graft function
HLA mismatches	Prolonged cold ischaemia
Prior sensitization	Reduced nephron number
Donor-specific antibodies	Donor factors (e.g. DCD or ECD donor, pre-existing donor disease, ↑ age, ↑ BP)
Inadequate immunosuppression	Recurrent recipient disease
Proteinuria (transplant glomerulopathy)	Recipient factors (e.g. ↑ BP, diabetes, CV disease, obesity)
	Recipient urinary tract infection or obstruction
	BK virus nephropathy
	Proteinuria

Assessment

The monitoring of graft function over time is one of the fundamental roles of a transplant follow-up clinic. Most patients will be asymptomatic. Key investigations include:

- SCr and eGFR.
 - It is important to consider changes in these over time in a similar manner to native kidney CKD.
- Therapeutic drug levels, especially CNI levels.
 - Again, these should be considered over time and in the context of an individual patient's progress.
 - What was their immunological risk? What were the donor characteristics of their graft? Have they had any rejection episodes? Have they developed any infections or other complications of immune suppression?
- Urinalysis and uPCR.
 - Proteinuria is a marker of renal injury, as well as risk of progressive transplant dysfunction, and overall CV morbidity and mortality. It may also identify recurrent native disease.

- It is a feature of transplant glomerulopathy, the glomerular manifestation of chronic antibody-mediated rejection (see below).
- MSU: if abnormal urinalysis, symptoms of UTI, unexplained loss of function, and pre-biopsy.
- HLA antibody screen (📖 p. 363).
 - Measure monthly for the first 3 months (weekly in selected cases), then 3-monthly for the first year, then annually.
- BK virus screening (📖 p. 436).
- Transplant USS (\pm renal artery Doppler).
- Transplant biopsy (the majority).
 - Some centres perform interval 'protocol biopsies', regardless of function (e.g. at 1, 3, 6, or 12 months), to assess overall graft health and individualize management, esp. immunosuppression.
 - 📌 The relevance of 'subclinical' rejection on such protocol biopsies is uncertain.
 - ► The interpretation of a transplant biopsy performed for chronic dysfunction is complex and requires careful clinical-histological correlation, considering all the factors in Table 5.9.

Histology

The Banff classification includes both 'immune' and 'non-immune' chronic damage.

- Chronic active antibody-mediated rejection.
 - Only accepted as a distinct entity in 2005 but now the focus of a considerable amount of attention.
 - Features: (i) circulating anti-HLA antibody (esp. DSA), (ii) peritubular capillary (PTC) C4d positivity (only present in ~50% cases), and (iii) evidence of chronic tissue damage (arterial intimal fibrosis without elastosis, duplication of the glomerular basement membrane ('double contours'), multilayering of the peritubular capillary basement membrane, IF/TA). The glomerular changes are referred to as *transplant glomerulopathy* and will eventually develop into glomerulosclerosis.
- Chronic active T cell-mediated rejection.
 - Chronic allograft arteriopathy is characterized by rejection-induced intimal thickening of arteries (\rightarrow arterial luminal occlusion and graft ischaemia).
 - Characterized by arterial intimal fibrosis with mononuclear cell infiltration in fibrosis and formation of neointima.
- IF/TA, with no evidence of specific aetiology.
 - I: mild IF/TA (<25% of cortical area).
 - II: moderate IF/TA (>25–50% of cortical area).
 - III: severe IF/TA (>50% of cortical area).

► The key structures that determine the destiny of a transplant are the vessels (mainly arteries). There is no collateral vasculature, so vessel narrowing and occlusion inevitably lead to downstream ischaemia, particularly in the interstitium.

Management: general measures

- BP control (📖 pp. 422–3).
- ACE-I/ARB if proteinuria.
- CV disease prevention (📖 p. 422).
- Avoid nephrotoxins.
- Maintain good fluid balance.

Management of chronic rejection**Chronic active T cell-mediated rejection**

Generally treated as for acute T cell-mediated rejection (📖 p. 408–9).

- **Chronic active antibody-mediated rejection**

Present in ~25% of those undergoing assessment for loss of graft function. Optimum treatment is unclear—studies are ongoing. Common strategies include optimizing general measures, switching from CIC to TAC, increasing MMF as tolerated. IVIg, PEX, and rituximab are used in some centres (as for acute antibody-mediated rejection), but benefit is unproven.

Management of CNI toxicity

The earliest functional change is vasoconstriction, but structural toxicity, with histological change in arterioles, glomeruli, and tubules eventually supervenes. Some degree of damage is inevitable in all patients taking a CNI (>50% within 12 months).

CNI-induced arteriolar changes include swelling of the medial smooth muscle cells and occasional endothelial or smooth muscle cell necrosis. The mature lesion demonstrates PAS-positive hyaline nodules in the media and adventitia of the afferent arteriole (similar to hypertensive damage). TMA may also be present, and FSGS can occur in the glomeruli as a 2° consequence of arteriolar injury. IF/TA is considered a non-specific secondary feature caused by nephron dropout. It is characteristically described as *striped fibrosis* in this context. Tubuloe epithelial cell vacuolization ± microcalcification may be evident.

CNI minimization

- Either:
 - Dose reduction to aim for a lower therapeutic level.
 - Complete withdrawal, usually with a switch to sirolimus. There is some evidence to suggest benefit from this manoeuvre if undertaken early enough in selected patients (⚠ not those with proteinuria).
 - Other agents, such as belatacept, may have a role in the future.

The failing transplant

It is very easy to forget the 'CKD basics' in a transplant patient with deteriorating graft function. These include:

- Explaining the situation to the patient, with appropriate psychosocial support.
- Management of the secondary complications of a falling GFR, including anaemia (with IV iron and an ESA, as necessary) and CKD-MBD.
- Ongoing control of BP and CV risk.
- Early discussion regarding future dialysis and possible retransplantation (ideally pre-emptively). The earlier this is undertaken, the greater chance the patient will be able to choose the most acceptable modality for them.
- Creation of dialysis access. In some cases, this may still be functioning from earlier in their RRT career.

⚠ Immune suppression should not be stopped suddenly. AZA/MMF are generally stopped first, followed by slow steroid withdrawal and progressive reduction of CNI (over ~3–6 months). Slow weaning will help to prevent inflammation in a remnant graft which can make the patient feel quite unwell and provoke the development of anti-HLA antibodies that might prejudice future transplantation.

Transplant nephrectomy is an operation with appreciable associated morbidity. Indications: the graft is a source of infection or inflammation (presenting as pain, general malaise, haematuria, ESA resistance).

Removal of the graft to prevent HLA sensitization is controversial—the patient may still become sensitized to antigens present in the vascular stump.

Recurrent disease

Introduction

Recurrence of original disease following transplantation affects ~10–20% of patients and accounts for ~8% of graft failures at 10 years. It is an important differential in the assessment of a recipient with graft dysfunction, particularly in the presence of proteinuria.

With the exception of primary FSGS and atypical HUS, which can recur immediately, recurrent glomerular disease tends to manifest months, or even years, after transplantation.

Even then, recurrent disease may run an incipient course; for example, although evidence of recurrent IgA is present on a significant number of transplant biopsies, it does not lead to graft dysfunction or loss in the majority (see Table 5.10).

Table 5.10 Recurrent disease post-transplantation

	Recurrence rate	Graft loss
1° FSGS	~40%	~50%
IgAN	~40%	~5–10%
Membranous	~20–30%	~20%
MCGN I	~20%	~33%
MCGN II	>90%	~25%
Diabetic nephropathy	~100%	<5%
HUS (D–)	~50%	>80%
Familial HUS (with complement gene mutation)	~80	>80%

Primary FSGS

Risk factors for recurrence include a short time between initial presentation and ESRD, recurrence in a previous transplant (→ recurrence >80% for subsequent transplant), younger patients (a particular problem in paediatric transplantation where FSGS is a common cause of ESRD), diffuse mesangial proliferation on native renal biopsy. Black patients appear to have a reduced risk. Familial FSGS is a different disease, and recurrence is rare. Potential recurrence is not an absolute contraindication to live donor transplantation but requires careful assessment and discussion, as recurrence appears more common in this context.

Presentation

May present immediately post-transplant, with oliguria and graft dysfunction from acute tubular injury. This can mimic DGF. Urine should be tested daily for proteinuria, and nephrotic range proteinuria may develop within days to weeks of transplantation (associated with a fall in serum albumin). Urinary protein excretion (e.g. uPCR) should be documented

pre-transplant for later comparison. Recurrence after 1 year is unusual. Early transplant biopsy is likely to be normal on light microscopy (besides ATN/ATI), as it takes several months for the typical FSGS lesions to develop. However, EM will be abnormal, with podocyte foot process effacement.

Treatment

- Difficult!
- Plasma exchange or immunoabsorption. Start as soon as proteinuria develops. Response in ~50% but relapse common (long-term 'maintenance' PEX is not an uncommon situation). PEX may be started pre-emptively in live donor and as cold ischaemic time allows in deceased donor transplantation.
- High-dose CIC (given IV in some protocols) is favoured.
- Steroids and cyclophosphamide (esp. children).
- Rituximab has been beneficial in some case series.
- ACE-I/ARB for proteinuria.

De novo FSGS post-transplantation

2° FSGS lesions are reported, with chronic allograft dysfunction from both immune (transplant glomerulopathy) and non-immune (e.g. hypertension) mechanisms. It may also be apparent with other recurrent diseases, e.g. IgAN. However, presentation with the nephrotic syndrome is unusual.

IgA nephropathy

Overall, long-term graft outcomes are the same as other recipients. Some series have suggested a recurrence in the majority (~60%) but clinically significant disease in a minority only. Younger patients appear at greatest risk, as do those with aggressive disease in their native kidneys—crescentic IgAN appears to carry a particularly high risk. No specific treatment, but BP control should be meticulous, with regimens including ACE-I/ARB.

Membranous GN

Recurrence risk of ~20–30% and also the commonest *de novo* form of GN post-transplant. It is not yet known if those with anti-PLA2 antibodies are at higher risk. Graft outcomes are relatively poor. In common with native disease, some patients will spontaneously remit, whilst others will have more progressive disease. Treatments have largely been extrapolated from native disease (where CNIs are commonly used!). A potential role for rituximab is under investigation.

MCGN

Bears more than a passing resemblance to transplant glomerulopathy, but clinical context, immunofluorescence, and EM should distinguish them. Younger age of onset and aggressive native disease appear to be more important risk factors for recurrent disease than histological subtype. Type I MCGN often has an underlying cause, so recurrence (and indeed the feasibility of transplantation) will be linked to this. Type II MCGN has a very high recurrence rate, a poor response to treatment, and a significant rate of graft loss.

Alport syndrome

Transplanted Alport's patients may rarely develop *de novo* anti-GBM antibodies and a rapidly progressive crescentic glomerulonephritis (donor $\alpha 5$ type IV collagen is recognized as non-self). This is extremely difficult to treat and has virtually 100% recurrence in subsequent transplants.

Diabetic nephropathy

Histological recurrence occurs eventually in 100% recipients (usually within 5 years)—unless simultaneous kidney–pancreas transplantation has been undertaken (📖 p. 446). A reported cause of graft loss in <2%. Has an important implication for CV disease progression and patient survival.

Transplantation in other systemic diseases, such as SLE, vasculitis, HBV, and HCV, is covered in the relevant section elsewhere in the book.

Haemolytic uraemic syndrome (HUS)

It is important to try and discriminate between *de novo* post-transplant HUS and recurrence of D+ HUS or D– HUS (a subset of the latter will be familial HUS, with a genetic basis).

The rate of recurrence of D+ HUS is <1%. D– HUS recurs in ~50%, usually within a month of transplantation. *De novo* HUS arises after transplantation and is discussed separately (📖 p. 412).

Presentation is usually with \uparrow SCr, \downarrow Plt, and microangiopathic haemolytic anaemia (MAHA).

Renal biopsy will reveal typical HUS changes of endothelial cell swelling, widened subendothelial spaces, and glomerular capillary fibrin deposits.

Risk factors for recurrence are mutation of complement regulatory proteins (e.g. causing factor H or factor I deficiency). Serum factor H and I concentration should be measured and a mutation analysis undertaken in all patients with HUS if transplantation is being contemplated. Previously, the risk of recurrence with almost inevitable graft loss, has been so high that transplantation, particularly live donor transplantation, has been relatively contraindicated.

Eculizumab shows great promise for protecting renal allografts from post-transplant HUS, although it is unclear how long treatment should continue (particularly important, given the cost of the drug).

Long-term transplant follow up

Introduction

The purpose of long-term follow-up is to maintain both graft and patient health. In most centres, this is undertaken in a dedicated multidisciplinary transplant clinic, but close communication with the patient's primary care provider is crucial. In general, after ~3 months the focus begins to shift from immunological factors and rejection risk towards more long term concerns such as CV risk.

Initial follow-up is intense; usually at least three clinic visits a week for the first 1–2 months, gradually reducing to ~1 visit monthly at 6–12 months, and eventually every 3–6 months.

Cardiovascular disease


- Cardiovascular disease (CVD) is the commonest cause of death with a functioning graft in renal transplant patients.
- Renal transplantation is considered cardioprotective—dialysis patients have ~10–20× increased risk of CVD mortality, and renal transplant patients have a 3–5× increased risk of CVD mortality, when compared to the general population.
- Pre-transplantation CVD management and screening are discussed in earlier sections.
- Immunosuppressive medications can exacerbate CV risk factors (see Table 5.11).
- The relationship between falling GFR and increasing CV risk holds true in patients with renal allograft dysfunction. Stroke and sudden cardiac death are the main CV associations.
- Addressing CV risk factors should be a focus of care within the long-term management of the renal transplant recipient. Achieving optimal graft function is one of the most effective ways to reduce CVD.

Table 5.11 Immune suppression and CV risk

CV risk	Corticosteroids	CNIs	MMF	mTOR inhibitor
Hypertension	++	++	↔	↔
Dyslipidaemia	++	+	↔	+++
NODAT	+	++	↔	↔
Proteinuria	↔	↔	↔	+++
↓ eGFR	↔	++	↔	↔

Hypertension


- The rationale for controlling hypertension in transplant recipients is twofold—and the same as in patients with CKD, i.e. reduce CV risk and slow progressive loss of GFR.

- ► Hypertension has been identified as a major predictor of graft survival in renal transplant recipients.
- BP targets for transplant patients have mostly been extrapolated from RCT studies in the CKD population (see  Chapter 3).
- Of note, there are no large-scale studies comparing different classes of antihypertensive drugs with a focus on reducing CV events in transplant recipients.

Hypertension is common after transplantation due to:

- Pre-existing hypertension (~90% of patients with ESRD have hypertension pre-transplantation).
- Established arterial stiffness (may improve over time but only slowly, if at all).
- Use of immunosuppressive drugs, particularly steroids (through ↑ Na⁺ retention) and CNIs (↑ vasoactive and nephrotoxic effect).
- May occur in the setting of transplant renal artery stenosis.

Approach to management

- Kidney Disease Improving Global Outcome (KDIGO) guidelines suggest a target BP of <130/80mmHg.
- Many centres aim for a target BP of <125/75mmHg if coexistent proteinuria (uPCR >50mg/mmol).
- Patients should be educated regarding the benefits of lifestyle interventions for BP control.
- Choice of drug class as per BHS/NICE guidelines ( p. 488). Of note:
 - Drugs that block the renin–angiotensin system may unmask a transplant renal artery stenosis.
 - Hyperkalaemia is common in patients on CNIs and ACE-I/ARBs (CNI → acidosis and distal tubule K⁺ retention).
 - Dihydropyridine calcium antagonists inhibit cytochrome P450 isoenzyme → ↑ CNI levels.
 - Calcium antagonists reduce blood pressure effectively and, theoretically, protect against the vasoconstrictor actions of CNIs.

Dyslipidaemia

- Dyslipidaemia often results in raised total cholesterol, LDL cholesterol, and triglycerides as well as increased levels of intermediate (atherogenic) lipoproteins.
- Studies have shown that this dyslipidaemia, in the context of transplantation, is modifiable by reduction of immune suppression and the use of conventional lipid-lowering drugs.
- ALERT is the only larger RCT of statin treatment in renal transplant recipients and demonstrated a significant reduction in non-fatal MI and cardiac death in the fluvastatin treatment group. SHARP was another landmark renal statin study and, although transplant patients were excluded, many patients received a transplant in the follow-up period.

Dyslipidaemia is common after transplantation due to:

- Pre-existing dyslipidaemia (>60% of patients with ESRD have dyslipidaemia pre-transplant).

- Use of immunosuppressive drugs, particularly steroids, CNIs and mTOR inhibitors (see Table 5.11).
- Change in dietary intake in the absence of restriction associated with ESRD.

Approach to management

- CV risk tables are not always helpful in this cohort of patients, but, in the UK, guidelines suggest any transplant patient with a 10-year CVD risk of >20% should take a statin. Treatment should be to a target TC <4mmol/L, LDL cholesterol <2mmol/L. However, KDIGO practice guidelines have recently moved away from such numeric targets, recommending statin treatment for all transplant recipients (p. 205).
- Patients should be educated regarding the benefits of lifestyle interventions for lipid control.
- Review immune suppression, and moderate where possible.
- Options regarding statin choice should take into consideration the following:
 - Simvastatin, lovastatin, and rosuvastatin are metabolized by microsomal enzyme cytochrome P450 3A4, which is inhibited by calcineurin inhibitors, particularly CIC. The resultant increased statin concentrations can cause adverse effects.
 - The prescription of simvastatin and CIC is contraindicated by the MHRA in the UK. The others should be started at lower doses and titrated carefully.
 - Drugs with alternative metabolism, such as pravastatin, fluvastatin, and atorvastatin, are reported to be safe and effective at standard doses, but should be introduced and titrated carefully under supervision.
- There are no data to support fibrates, and concerns regarding side effect profile in the presence of low eGFR, makes them a less favourable choice.

New-onset diabetes after transplantation



- New-onset diabetes after transplantation (NODAT) is due to both impairment of insulin secretion and increased insulin resistance.
- Incidence of new-onset diabetes is between 5 and 20% in the first year after transplantation.
- ► The presence of diabetes is an important risk factor for both poor patient and graft survival. This is in the context of both pre-existing diabetes and NODAT. NODAT is associated with a doubling in all-cause mortality and a tripling in CV events.
- Steroid avoidance regimens have reported that NODAT occurred less frequently—and, when it did, it was less severe. However, overall benefits were modest and associated with increased risk of acute rejection.

Risk factors for new-onset diabetes after transplantation are:


- Age >60.
- Use of certain immunosuppressive drugs, particularly steroids, CNIs, and mTOR inhibitors (impaired insulin secretion).
- Non-Caucasian ethnicity (particularly Afro-Caribbean and Indo-Asian patients).
- Deceased donor transplants.
- BMI >30kg/m².

- Family history of T2DM.
- History of diabetes in pregnancy.
- HCV +ve patients.
- Predisposing genetic markers (e.g. *TCF7L2* and *PPARG*).

Approach to management

- Use WHO criteria for diagnosis.
- Patients should be educated regarding the benefits of lifestyle interventions for diabetic control.
- Review medications—many would consider steroid withdrawal, although the evidence of benefit is slim (despite the well-recognized risk of late steroid withdrawal,  p. 391).
- In terms of hypoglycaemic agents:
 - Refer to local guidelines for oral hypoglycaemic use. Metformin is an option if eGFR >45mL/min (caution due to risk of lactic acidosis).  Exercise caution with thiazolidinediones, acarbose, and exenatide if eGFR <30mL/min.
 - Refer to local guidelines for insulin choice.
- Standard screening for diabetic complications apply for patients with NODAT, monitoring for neuropathy, retinopathy, and vigilant foot care (due to infection risk in patients on immune suppression).

Bone and mineral metabolism

- Transplant recipients are at increased risk of fracture. This risk is higher than in dialysis patients.
- Risk factors: steroid use, CNIs, previous renal osteodystrophy, persistent hyperparathyroidism, metabolic acidosis, hypophosphataemia, lack of physical activity, post-menopausal ♀, smoking.
- Almost all patients will enter transplantation with a degree of renal osteodystrophy—and this will persist post-transplant.
- Patients who have an impaired post-transplant function (e.g. eGFR <30mL/min) are best viewed using a CKD-MBD paradigm, i.e. they are more accurately described as having osteodystrophy than osteoporosis. This may explain why DEXA scanning does not accurately predict fracture risk in transplant recipients (even though BMD rapidly decreases in the first year).
- *Management*: control of serum phosphate and PTH, according to familiar CKD targets ( p. 244); correct nutritional vitamin D deficiency (e.g. if 25-OH vitamin D <30 micrograms/L).
 - Those with persistent tertiary hyperparathyroidism should be observed for a year to see if spontaneous involution occurs prior to proceeding with parathyroidectomy. Cinacalcet can be a useful means of ameliorating hypercalcaemia during this period.
- Those patients with a GFR >30mL/min can be generally be managed as osteoporosis.
 - *Management*: oral calcium and vitamin D preparations, correction of acidosis, oral bisphosphonates, steroid minimization.

Post-transplant infections

Introduction

Transplant recipients are susceptible to a wide variety of infectious pathogens (see Fig. 5.19). The general principles of management in this group are: (i) to prevent certain common infections (particularly in the first few months after transplantation or during periods of heavier immune suppression); (ii) to be aware of the spectrum of infectious disease to which recipients are vulnerable at particular times post-transplantation; and (iii) to rapidly assess and treat transplant patients presenting with suspected infectious disease.

Strategies for prevention might include:

- Perioperative broad-spectrum antibiotics.
- Co-trimoxazole (PCP, UTI).
- Isoniazid for TB in high-risk recipients (📖 p. 395).
- Valganciclovir for CMV in at-risk recipients (📖 p. 432).
- Screening of dialysis patients for MRSA (nose, throat, and perineal swabs), with eradication therapy if +ve.
- VZV vaccination for non-immune patients pre-transplantation (see Table 5.12).
- Pneumococcal and influenza vaccinations.
- HBV vaccination for all those with advanced CKD (see Table 5.12).

Timing of infection

Infections in the first month

- Standard post-operative infections related to the procedure itself—see Surgical complications (📖 p. 402). Including wound, chest, and infected haematomas or lymphoceles.
- Urinary tract infection: common. Anuric dialysis patients often have small-capacity dysfunctional bladders, and indwelling urinary catheters or ureteric stents further increase risk. If recurrent, USS transplant, and assess bladder emptying. Is there a relevant abnormality of the native kidneys that may be contributing? Ureteric stent may require early removal.
- Infected lines: remove all cannulae (central and peripheral) as quickly as possible. Are dialysis lines (or PD catheters) still *in situ*?
- *Clostridium difficile*: the most important cause of hospital-acquired diarrhoea. Incidence of 3.5–16% in transplant recipients. Antibiotic use is the most significant risk factor, but there are others, including ↑ age, ICU admission, ↑ length of stay.
- Graft → recipient bacterial infections. It is common practice to culture a sample of the preservation fluid that is used to transplant the organ and to treat according to the result.
- Rarely, a recipient bacterial infection will recrudescence in the recipient (usually *S. aureus* or Gram –ve organism).

1–6 months

- Viral infections (often reactivation of latent disease): CMV, HSV, VZV, EBV, BK virus.
- TB.
- Opportunistic infections: *Listeria*, *Aspergillus*, pneumocystis pneumonia.

Beyond 6 months

- Conventional community-acquired pathogens.
- Chronic viral infection: BK nephropathy, EBV-driven PTLD.

General management issues

► When treating:

- Appropriate dose reductions for ↓GFR: watch SCr carefully.
- Drug interactions, particularly antimicrobials, that may induce/inhibit cytochrome P450 and thus modify CNI levels: monitor CNI trough levels carefully (📖 p. 388).

The transplant patient with a fever

- Fever may represent:
 - Infection.
 - Acute rejection (less common with modern immune suppression).
 - Systemic inflammatory response.
 - May occur during treatment with biological agents (📖 pp. 383–5).
- Take a full history.
- Full examination:
 - Including palpation of transplant.
 - Look under all dressings!
 - What was the patient's dialysis modality and access?
- Investigations:
 - Urinalysis and MSU.
 - ↑ WCC (or neutropenia—stop myelosuppressive drugs: MMF/AZA/co-trimoxazole/valganciclovir).
 - ↑ CRP.
 - Blood cultures.
 - Culture wound discharge, if present, and drain fluids.
 - CXR.
 - USS transplant.
 - Imaging for collections in the post-op period (usually USS or CT abdomen and pelvis). Aspirate for fluid culture.
- Remove lines, catheters, and ureteric stents, if relevant.
- Consider broad-spectrum empiric treatment prior to results of the investigations.
- Seek microbiological input ASAP.
- Immune suppression may require reduction. Seek specialist advice.
- PO paracetamol to reduce fever.
- Fluid resuscitation.

Table 5.12 Vaccination in transplant recipients

Vaccines that are safe	⚠ Vaccines that are not safe
Influenza vaccine	Oral polio vaccine
Pneumococcal vaccine	MMR or MR vaccine
Inactivated polio vaccine	Mumps vaccine
Pertussis vaccine	Rubella vaccine
Adsorbed tetanus vaccine	BCG vaccine
Adsorbed diphtheria vaccine	Yellow fever vaccine
<i>Haemophilus influenzae</i> type B vaccine	Smallpox vaccine
Hep A vaccine	Oral typhoid vaccine
Hep B vaccine	
Cholera vaccine	
Meningococcal polysaccharide vaccine	
Meningococcal C conjugate vaccine	
Typhoid vaccine	

Pneumocystis pneumonia (PCP)

- *Pneumocystis jiroveci*, previously known as *Pneumocystis carinii*, is a significant opportunistic pathogen in organ transplantation.
- Before routine PCP prophylaxis, the overall incidence among kidney transplant recipients was 2–15%.
- Risk factors: more intense immune suppression, particularly corticosteroids and depleting antibodies. Also pre-existing or co-infection with CMV (an immunomodulatory virus).
- Clinical features: develops over several days. Dyspnoea and hypoxaemia out of proportion to physical and radiological findings.
- CXR: normal or bilateral pulmonary infiltrates.
- CT: more sensitive. Ground glass opacification (but multiple different appearances are described).
- Confirmation by demonstration of organisms in lung tissue or respiratory secretions. Usually requires induced sputum or bronchoscopy for BAL (stain with antibodies to PCP).
- Treatment: co-trimoxazole. Minimum 14 days (SE: bone marrow suppression, rash, hepatitis, interstitial nephritis). Second-line: pentamidine (SE: pancreatitis—avoid in kidney–pancreas recipients, disturbed glucose metabolism, bone marrow suppression, nephrotoxic).
- Adjunctive high-dose steroid if hypoxic (e.g. 40–60mg prednisolone bd for 5–7 days, then taper). Respiratory support, as necessary.
- Prophylaxis: co-trimoxazole for 6–12 months (also suppresses toxoplasma and *Listeria*). Dapsone (SE: haemolytic anaemia) and monthly nebulized pentamidine are alternatives, if intolerant.

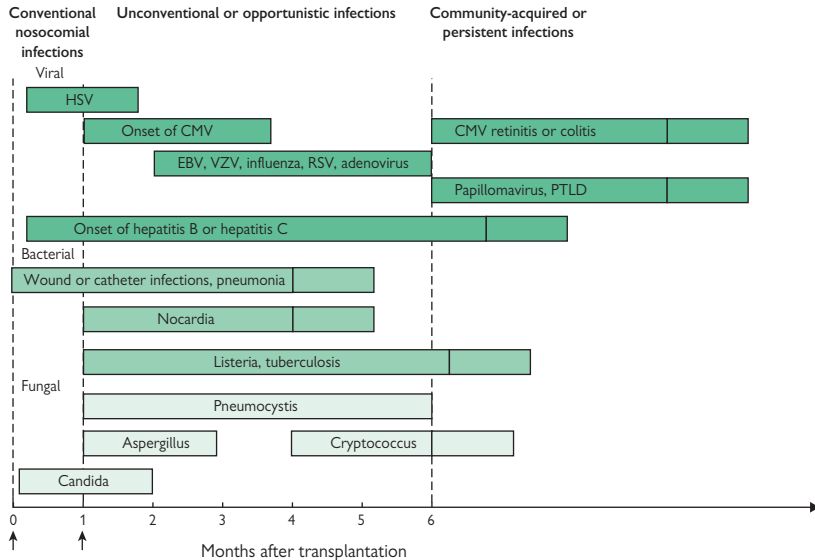


Fig. 5.19 Sequence of post-transplant infection. Adapted with permission from Davidson AMA, Cameron JS, Grunfeld J-P, et al. (eds) (2005). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford: Oxford University Press.

Cytomegalovirus (CMV)

Introduction

▶ The most important infectious complication of transplantation.

CMV is a DNA (herpes type) virus that infects ~50% of the normal population. Following 1° CMV infection (usually asymptomatic in immunocompetent individuals), CMV persists in the host, and reactivation usually results in asymptomatic viral shedding. The presence of CMV IgG in serum identifies past infection (~50% of adults). CMV is transmitted in saliva and other body fluids (including blood) as well as in transplanted organs (CMV infection via blood products is now rare, as leucocyte-depleted products are usually supplied).

CMV in transplant recipients

Immunosuppression promotes reactivation of latent CMV in the transplanted organ and/or tissues of the recipient. The resultant active CMV infection may be asymptomatic or result in CMV disease.

▶ Donor/recipient pre-transplant CMV serological status is important in determining the risk of CMV infection/disease (see Table 5.13).

Symptomatic CMV disease is largely confined to the first 6 months post-transplant but may present later, especially in high-risk recipients who cease prophylaxis.

CMV disease

CMV disease is manifested by fever ($>38^{\circ}\text{C}$ for 2 days over a 4-day period), \downarrow WCC, \downarrow Plt. Malaise, fatigue, fever, myalgia, and night sweats are also common. Δ CMV causes further host immunosuppression (predisposing to 2° invasion—esp. PCP and fungi).

CMV end-organ disease

- Hepatitis.
- Pneumonitis.
- GI: diarrhoea (colitis), abdominal pain, nausea, dysphagia.
- Transplant dysfunction:
 - Due to invasive CMV disease Δ OR due to rejection (CMV increases the expression of graft HLA antigens).
- CMV retinitis is unusual and occurs late (usually >6 months).

Table 5.13 Risk of CMV according to serological status

Donor CMV status	Recipient CMV status	Risk
-ve	-ve	Low
+ve	-ve	High
-ve	+ve	Medium
+ve	+ve	Medium
Either donor and/or recipient CMV +ve and treatment with depleting antibody		High

CMV presents the greatest threat to D+ R- transplant recipients and those requiring additional immunosuppressive therapy for rejection (e.g. following a depleting agent).

Antiviral prophylaxis is currently administered to those at greatest risk but does not guarantee protection (and may delay presentation) (see Fig. 5.20).

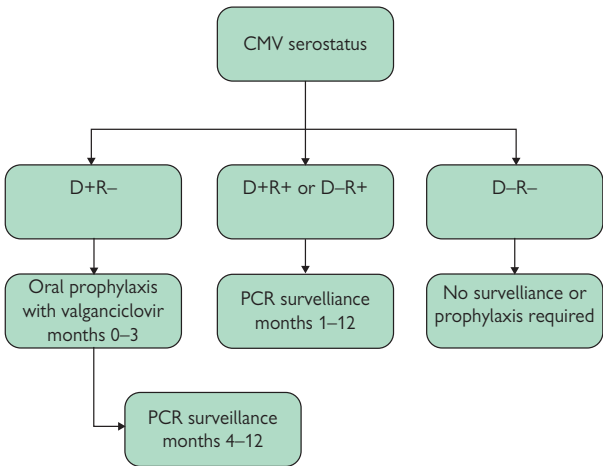


Fig. 5.20 CMV prophylaxis and surveillance strategy by CMV serostatus. Some centres give prophylaxis to all recipients, except D- R-.

Diagnosis and monitoring

- Ascertain CMV IgG status pre-transplantation: test prospective recipient at the time of listing. Recheck recipient CMV IgG on admission for transplant if previously seronegative.
- Donor status is provided with transplant organ.

CMV prophylaxis

- Indicated for CMV donor +ve/recipient -ve patients (D+ R-).
- Valganciclovir 900mg PO od, adjusted for renal function, for 90 days post-transplant (see Table 5.14).

Routine surveillance of asymptomatic patients

- CMV viral load is measured in whole blood by PCR.
- Routine surveillance should commence at 2 weeks post-transplant and continue for 12 months (weekly for the first 3 months and monthly thereafter).
- It is unnecessary to perform viral surveillance in D- R- patients or in D+ R- patients receiving prophylactic valganciclovir. Some centres issue prophylaxis to all, but D+ R-, recipients.

Interpretation of CMV viral load results

- Rapid increases in CMV viral load (the trend), rather than isolated results, are predictive of development of CMV disease.
- Routine surveillance forms the basis for pre-emptive therapy. The goal is to detect active CMV viraemia in order to facilitate prevention of symptomatic CMV infection/end-organ disease.
- Both international units (IU) and logs are often reported. A change of one log or more in the space of 3 or 4 days is likely to be significant.

Pre-emptive treatment

- This strategy includes both reduction of immunosuppression, where possible, and the institution of treatment doses of valganciclovir to prevent or ameliorate clinical CMV disease.
- Valganciclovir 900mg PO bd, adjusted for renal function, for a minimum of 2 weeks or until CMV viral load is undetectable (see Table 5.14).
- For patients who are CMV-negative pre-transplant, detection of CMV viraemia is consistent with primary CMV infection. The patient should be clinically reviewed ASAP.
- Immediate reduction of immunosuppression and initiation of pre-emptive antiviral therapy should be considered.
- If the patient was seropositive pre-transplant and is asymptomatic and the viral loads detected are low and not rapidly increasing, it may be appropriate to either retest in 1 week or to reduce immune suppression and then retest.
- In contrast, a rapidly increasing viral load, with or without symptoms, would suggest the need to commence antiviral therapy, with additional reduction of immunosuppression.

Management of CMV disease*Reduction of immunosuppression*

- Review immunosuppressive therapy, and stop/reduce one agent, usually MMF (or AZA).
- Do not recommence the discontinued drug for a minimum of 1 month, unless rejection occurs.

- CMV relapse is common, usually presenting 1–4 weeks after completion of treatment, and is more likely if immunosuppressive therapy is reinstated during this period.

Antiviral therapy

- Oral valganciclovir 900mg PO bd, adjusted for renal function. ► Note the higher dose frequency required for pre-emptive therapy and for treatment of CMV syndrome/disease vs prophylaxis.
- IV ganciclovir 5mg/kg IV bd, adjusted for renal function.
 - IV therapy is generally reserved for patients unable to tolerate oral treatment.
- Intravenous immunoglobulin (IVIg) is used as an adjunct for pneumonitis (IVIg 500mg/kg every other day for a total of 10 doses).

Duration of therapy

- Treatment should be given for a minimum of 2 weeks and continued until the CMV viral load in whole blood is undetectable on at least one occasion.
- Treatment of end-organ CMV disease should be continued for a minimum of 3 weeks and continued until the CMV viral load in whole blood is undetectable on at least one occasion.

Table 5.14 Dosing of valganciclovir in renal impairment (based on Cockcroft–Gault GFR)

CrCl (mL/min)	Prophylaxis dose	Treatment dose
>60	900mg once daily	900mg twice daily
40–59	450mg once daily	450mg twice daily
25–39	450mg every 48h	450mg once daily
10–24	450mg twice weekly	450mg every 48h
<10	100mg three times a week after dialysis*	200mg three times a week after dialysis*

* 50mg/mL oral suspension available for doses less than 450mg.

Herpes simplex virus infection

Herpes simplex virus seroprevalence is ~50% in the renal transplant population. Post-transplant infection may be primary, following reactivation, or secondary as a result of person-to-person contact or allograft transmission.

Clinical features

- Oral or genital mucocutaneous lesions are most common; however, patients may present with:
 - Pneumonitis.
 - Tracheobronchitis.
 - Oesophagitis.
 - Hepatitis.
 - Disseminated infection.
 - CNS infection.

Diagnosis

- Direct fluorescence antibody for HSV from vesicles.
- PCR—quantifying viral copy number from CSF, blood, etc.
- Serology is rarely helpful in distinguishing active infection.

Treatment

- Oral aciclovir for mucocutaneous manifestations.
- IV aciclovir for disseminated or solid organ infection.
- Ganciclovir and foscarnet are also effective.
- Renal function should be carefully monitored throughout treatment with antivirals.

BK virus nephropathy

Introduction

Polyomaviruses are ubiquitous but rarely cause clinical illness. Only two virus strains are known to be pathogenic in humans: *Polyomavirus hominis* 1 (BK) and *Polyomavirus hominis* 2 (JC) (named with the initials of the individuals from whom they were first isolated), and these only cause disease in immunocompromised patients.

BK virus causes viral nephropathy (polyomavirus-associated nephropathy, PVAN) as well as haemorrhagic cystitis and ureteric ulceration and stenosis (\pm obstruction). JC virus causes a viral encephalopathy.

Primary BK virus infection occurs in early life, resulting in almost universal seropositivity. The virus persists in the urinary tract (including latency in tubular cells), and viral shedding into the urine is relatively common (particularly older patients, patients with diabetes, HIV-infected and transplant patients). There are several genotypes, so, although a recipient may have acquired partial immunity to one genotype, the allograft may expose them to another.

Over the last 20 years, PVAN has emerged as an important cause of allograft dysfunction (perhaps reflecting the more potent immune suppression introduced during that era). Risk factors appear to include: donor seropositive and recipient seronegative (usually paediatric recipient), significant HLA mismatch, graft injury of other cause, acute rejection, and potency of immune suppression.

PVAN occurs in ~5% of kidney transplant recipients. Viraemia occurs in a greater proportion (~10%), and BK viraemia is even more common. The risk of graft failure is high, with 3- and 5-year graft survival rates of ~65% and ~55%, respectively.

Clinical features

Often an asymptomatic increase in SCr (~9–18 months after transplantation).

Diagnosis

- Urine cytology. Infected tubular cells are shed into the urine—these so-called ‘decoy cells’ (with ground glass intranuclear inclusions) are present in 90% of infected patients (>10 decoy cells/hpf suggests disease). This finding precedes viraemia by weeks and nephropathy by months.
- PCR quantification of virus in urine or blood is now widely available. These are very sensitive but less specific.
- Some advocate monitoring for BK viraemia (e.g. screen monthly for the post-transplant year) so that pre-emptive changes can be made to immune suppression before BK nephropathy supervenes.
- Renal biopsy is necessary to confirm the diagnosis (although PVAN is unlikely if blood and urine PCR are normal).
- Histology. The characteristic finding is tubulointerstitial nephritis with a mononuclear cell infiltrate, along with viral cytopathic changes, such as inclusions in tubular cells. Immunohistochemistry will confirm BK virus.
- ⚠ These findings are focal and easy to miss. They may also be confused with rejection.

Treatment

(See Fig. 5.21)

- ► Reduction of immunosuppression. There is no good evidence to guide this, but many protocols start with reduction or withdrawal of antiproliferative agents (MMF/AZA). Aim for lower CNI levels, e.g. TAC 3–6ng/mL.
- ⚠ The risk is precipitating rejection, the treatment of which, with concomitant PVAN, is extremely challenging. Many continue with immune suppression reduction and treat rejection with IV and oral steroids. IVIg is an alternative (e.g. 2g/kg), as it has the theoretical ability to ‘neutralize’ BK virus as well as having recognized anti-rejection efficacy.
- The anti-arthritic drug leflunomide has both immunosuppressive and antiviral properties (acts through inhibition of tyrosine kinase activity and depletion of pyrimidine). ⚠ SE: haemolytic anaemia, thrombocytopenia, and TMA.
- No clear evidence to support the use of antivirals. Cidofovir for 1–4 fortnightly doses has been the most popular (⚠ nephrotoxic).
- Quinolones, including ciprofloxacin, may be of some benefit (inhibit DNA topoisomerase and polyomavirus-associated helicase).

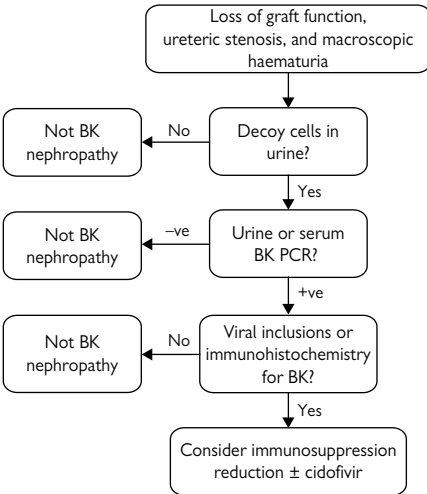


Fig. 5.21 BK investigation and treatment algorithm. Reproduced from Nicholas Torpey et al. (Oxford Specialist Handbook) *Renal Transplantation* (2010), with permission from Oxford University Press.

Post-transplant UTI

► UTI is the most common infection, following kidney transplantation, and has been reported in 42–70% of patient cohorts. This relates to urinary tract instrumentation, poor bladder function, other pre-existing urinary tract abnormalities, and immune suppression. It is most common in the first year and associated with higher rates of hospital admission. More common in ♀.

Prevention

Patients with recurrent UTIs should undergo urological investigation prior to transplantation. Those taking prophylactic antibiotics pre-transplant may need to continue them post-transplant—co-trimoxazole for PCP prophylaxis will provide some cover. Broad-spectrum antibiotic prophylaxis is administered preoperatively. Ensure timely removal of urinary catheter (usually 5 days) and ureteric stent (usually 4–6 weeks).

Clinical features

- Asymptomatic, with incidental detection on urinalysis/MSU more common in this group (and more likely to develop into a symptomatic infection).
- Irritative urinary tract symptoms—dysuria, frequency, nocturia.
- Graft pyelonephritis: fever, graft tenderness, often systemically unwell with graft dysfunction.
- Systemic inflammatory response syndrome → septic shock.
- ⚠ Note: UTI is a risk factor for rejection.

Diagnosis

- Urinalysis.
- MSU for M,C&S.
- Transplant (and native kidney) USS: exclude obstruction.

Microbiology

- *E. coli* is the most common pathogen.
- Others: enterococci, *Pseudomonas*, coagulase-negative staphylococci, and *Enterobacter*.

Treatment

- Empirical antibiotics should be started after an MSU has been obtained in symptomatic patients.
- Therapy should be guided by sensitivities (⚠ a significant proportion of infections will be resistant to first-line antibiotics, with increasing detection of extended-spectrum beta-lactamase organisms). Discuss complex cases with microbiology.
- Avoid nephrotoxic antibiotics, and adjust doses, according to renal function.
- Graft pyelonephritis: co-amoxiclav IV for 10–14 days (+ gentamicin IV). Convert to oral if clinically improving and afebrile for 24h. If penicillin-allergic, give 1–2 doses gentamicin, then review culture results.

Recurrent UTI

- Clarify previous infective episodes, duration of treatment, compliance, and whether negative urine culture was obtained following treatment.
- Ensure adequate bladder emptying (USS).
- Consider urodynamics.
- Late UTIs (>6 months) are associated with worse graft outcomes: consider DMSA for transplant scarring if deteriorating graft function.
- Consider cystoscopy, particularly if recurrent graft pyelonephritis.
- Consider prophylactic and rotational antibiotic therapy.

Post-transplant malignancy

Introduction

The frequency of malignancy is increased in the post-transplant population, with a risk of ~2.5–3.0× over an age-matched non-transplant population (as well as over age-matched dialysis patients). There is a huge variation between tumour types. Non-melanoma skin cancer (NMSC) has ~100× greater risk (~200× for squamous cell cancer); renal cell and urothelial cancer have ~10× risk, and breast cancer in ♀ has approximately equal risk. Cancer is recorded as the cause of death in ~10% of transplant recipients who die with a functioning graft (higher in some studies). Immune suppression is the most important risk factor, but others, including smoking, viral infections (e.g. EBV), and older age, are also relevant.

Although donors (both living and deceased) are screened for malignancy, there are rare reports of malignancy being transmitted from donor to recipient.

Mechanisms

- Increased risk is more a function of overall immune suppressant burden than of a particular immune suppressive agent.
- Most immune suppressants impair the cell cycle and cell growth across many different cell types.
- CNIs upregulate both TGF-β and VEGF, leading to increased angiogenesis and tumour spread in animal models.
- Azathioprine interrupts the repair of UV light-associated DNA damage in the skin. This may be aided by the viral-induced inhibition of the p53 tumour suppressor gene.
- PTLD is associated with EBV proliferation. Human herpes virus 8 (HHV-8) is associated with Kaposi's sarcoma.
- Sirolimus and other mTOR inhibitors reduce angiogenesis, so it is hoped they may be associated with less malignancy than other agents. Studies are ongoing.

Screening

Ensure access to national screening programmes, such as cervical screening, mammography, and FOB testing. ♦ PSA ± DRE in ♂ recipients aged >50 (or younger if family history of prostate cancer). Some advocate annual USS screening of native kidneys for renal cell cancer (particularly if known acquired cystic disease, i.e. cysts arising in atrophic ESRD kidneys).

Prevention

▶ Smoking cessation, self-examination, sun avoidance (appropriate clothing; sunblock; avoid sunburn), reporting of untoward symptoms.

Education should start in the pre-transplant phase and be continually reinforced during transplant follow-up.

Skin cancer

~50% of transplant recipients will develop a non-melanoma skin cancer (NMSC) after 20 years (SCC > BCC—a reversal of the incidence in the general population). Skin type (△ pale skin), human papilloma virus, and

sun exposure (∴ older age) all appear to be risk factors. Tumours are often multiple and metastasize more commonly (~5%).

► Advocate sun protection at all times, starting pre-transplant. Recommend regular self-surveillance and annual dermatological review (particularly if previous NMSC).

Treatment: local excision, topical therapy, e.g. imiquimod, 5-fluorouracil, podophyllin. Retinoids have been used for secondary prevention.

Consider reduction of immune suppression. Stop AZA/MMF, if possible.

● Conversion from a CNI to sirolimus may be advantageous (proven benefit in Kaposi's sarcoma). Studies are ongoing.

Malignant melanoma and Kaposi's sarcoma also occur more frequently in transplant recipients.

Post-transplant lymphoproliferative disorder

Second most common post-transplant malignancy after NMSC. PTLD encompasses a range of disorders, from an EBV-associated infectious mononucleosis syndrome early after transplantation through to non-EBV- (and often non-B cell-) associated malignant lymphoma, occurring late after transplantation (see Table 5.15).

EBV and PTLD

EBV is an overwhelming risk factor for PTLD. EBV is usually acquired in childhood. Most transplant recipients will be EBV-seropositive. However, EBV may be transmitted to an EBV-naive recipient from a donor kidney. EBV-related lymphomas occur mainly within the first year post-transplantation (>90%). Immune suppression disrupts CD8 +ve cytotoxic T cell EBV surveillance, allowing latently infected cells to undergo replication → eventual B cell transformation and immortalization.

► Recipient and donor EBV serological status should be known pre-transplant.

EBV infection post-transplant: fever, malaise, pharyngitis, lymphadenopathy, hepatosplenomegaly, and lymphocytosis. Other non-PTLD manifestations include: hepatitis, pneumonitis, bone marrow suppression.

PTLD risk factors

- EBV-seronegative recipient.
- Depleting antibodies and high levels of immune suppression.
- The development of a primary EBV infection.
- CMV infection
- For late PTLD: risk factors include older donor age and length of immune suppression.

Table 5.15 WHO classification of PTLD

Categories of PTLD			Comment
Early lesions		Plasmacytic hyperplasia Infectious mononucleosis-like lesion	Usually EBV +ve Early
Polymorphic PTLD			Most common Usually EBV positive
Monomorphic PTLD	B cell neoplasms	Diffuse large B cell lymphoma	High-grade malignancy
		Burkitt's lymphoma	Usually EBV -ve
		Plasma cell myeloma	Late
		Plasmacytoma-like lesion	
	T cell neoplasms	Peripheral T cell lymphoma Hepatosplenic T cell lymphoma Other rare types	
Classical Hodgkin's lymphoma-type PTLD			

Clinical presentation of PTLD

May be asymptomatic. Weight loss, fever, night sweats, sore throat, malaise, anorexia, GI symptoms, and headache.

Signs include: lymphadenopathy, hepatosplenomegaly, tonsillar enlargement, and focal neurological signs.

Disease may be nodal or extranodal, localized (more common) or disseminated. Localized disease may occur in the transplant kidney.

Investigations

- Anaemia, ↑ serum urate, ↑ LDH.
- High-risk individuals (children and seronegative adults) should undergo surveillance, using EBV-DNA PCR.
- If suspected, whole body CT is usually undertaken (or CT-PET).
- Histopathology to confirm diagnosis, and classify according to international criteria.
- Additional tests may include bone marrow examination and LP for CSF examination.

Management

- A multidisciplinary approach, involving transplant physicians, histopathologists, and haemato-oncologists is essential.
- Histological type is crucial to planning therapy.

- For EBV-associated PTLD, the mainstay is a stepwise reduction in immune suppression. Expect response in 2–4 weeks. ⚠ Rejection causing graft loss in <10%.
- This process can be tailored by measuring EBV-specific T cell subsets (their appearance with reduction of immunosuppression may herald regression of tumour).
- No evidence to support antiviral therapy.
- Rituximab (anti-CD20 antibody) is usually the next step and has made a significant difference to remission rates (B cell tumours are CD20 +ve).
- Treatment of late and T cell PTLD requires more conventional chemotherapy, e.g. CHOP.

Prognosis

- >80% of early EBV-associated polymorphic disease will enter remission with treatment, and relapse is rare.
- Worse prognosis with ↑ age, non-EBV-associated disease, monomorphic disease, high LDH that is slow to fall with treatment.

ABO- and HLA-incompatible transplantation

Introduction

Many patients have live donors come forward to donate, but the transplant cannot proceed, as they are not ABO-compatible or because they have a positive cross-match.

Transplanting across blood groups

Blood group O individuals are universal donors and AB universal recipients. Until fairly recently, transplantation was only carried out in blood group matched pairs or according to 'transfusion rules'. This is no longer necessarily the case.

Note: blood group A patients can be subgrouped as A1 and A2. Those with A2 express much lower amounts of A antigen on cell (including endothelial) surfaces and can \therefore be considered as blood group O if the recipients have no (or low) levels of circulating anti-A antibodies. This means that A2 to O transplants are relatively straightforward.

In addition, anti-blood group antibody removal to reduce anti-A and anti-B antibody titres to an acceptable range for transplantation (generally 1:8) is increasingly common.

Technique

Plasma exchange or immunoabsorption are used to remove anti-A and anti-B antibody. The number of treatments will depend on the initial antibody titre. Treatment is often continued post-transplant. New antibody production is prevented by administration of rituximab—usually ~1 month prior to transplantation (previously a splenectomy was necessary). Induction therapy (often with a repeat dose of rituximab) is usual. Maintenance immune suppression will be TAC- and MMF-based. Antibody titres are measured regularly post-transplant (often daily initially). Anti-A and anti-B antibody titres rise over time but do not injure the graft (thought to be an example of immune accommodation).

► It is imperative that anti-A and anti-B antibodies are not inadvertently transfused back to the recipient in a blood transfusion or FFP. This means that only blood group AB FFP or blood products should generally be used. Packed red cells of the recipient's type are safe to use. Discuss with your transfusion laboratory.

~10% incidence of antibody-mediated rejection (the majority of grafts are C4d +ve but with no other evidence of antibody-mediated rejection). Graft outcomes are excellent: 1- and 3-year graft survival 96% and 94%, respectively.

Transplanting across a positive cross-match

- The aim is to remove donor-specific anti-HLA antibodies prior to transplantation.
- This has proved more challenging than ABO-incompatible pairs.
- Meticulous assessment of the donor-specific cross-match is necessary.

- The goal is essentially to remove DSA until the CDC-XM becomes negative (pp. 363–4).
- Unfortunately, antibody removal is often a temporary phenomenon. There is likely to be a memory immune response with induction of, and concomitant, T cell reaction.
- Antibody removal protocols are often complex, involving PEX (\pm IVIg), rituximab, depleting antibody induction, steroids, TAC, and MMF.
- Serial DSAs are measured both pre- and post-transplantation.
- There is higher incidence of DGF and both antibody and T cell-mediated acute rejection (\sim 35%).
- Outcomes are generally comparable to deceased, rather than live, donor transplantation.
- 1-year graft survival \sim 80%. Long-term data, particularly with respect to the incidence of chronic antibody-mediated rejection and graft outcomes, are awaited.
- Most pairs should be offered the paired scheme (see below) before proceeding.

Live donor exchange schemes

If a patient has a live donor but, for ABO or immunological reasons, a direct transplant cannot go ahead, donors and recipients may agree to swap kidneys (see Fig. 5.22). This is coordinated centrally (e.g. by NHSBT in the UK). Very careful planning is required. Donor nephrectomies are carried out simultaneously in order to prevent a particular donor 'backing out' after their relative has received a kidney. A large pool is required for suitable exchanges to occur. Blood group O and highly sensitized patients are the least likely to be matched (as per the deceased donor list).

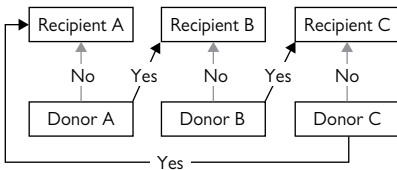


Fig. 5.22 Donor A is unable to donate to recipient A for immunological reasons. The same is true of the pairs B and C. Using an exchange scheme, donor A donates to recipient B, donor B to recipient C, and donor C to recipient A.

Kidney–pancreas transplantation

Introduction

Transplantation is the treatment of choice for diabetic patients with ESRD. In addition to kidney transplantation alone, options are:

- Simultaneous kidney–pancreas transplantation (SPK) (~80%).
- Pancreas (cadaveric) after kidney (usually living donor) transplantation (PAK) (~20%).
- Islet cell transplantation (see Box 5.7).

Benefits

- Pancreas transplantation corrects the glycaemic state (HbA1c falls to normal), leading to improved quality of life (freedom from both insulin and dialysis).
- Prevention of progression (and possibly partial reversal 📉) of diabetic complications.
- Comparable survival to live donor kidney transplant alone.

Selection criteria for SPK

- T1DM and ESRD (dialysis anticipated within 6 months).
- Usually have established diabetic complications.
- Recipient age <60.
- BMI <30.
- Adequate cardiovascular reserve (📖 pp. 352–6).
- Note: T2DM patients may also be eligible if insulin-requiring, BMI is close to or <25, and who fulfill the listed criteria.

Selection criteria for PAK

- Patients with stable function of a previous renal transplant (usually eGFR >40mL/min) who meet earlier listed criteria for SPK.

Selection criteria for pancreas transplant alone (PTA)

- Presence of T1DM.
- Life-threatening complications: hypoglycaemic unawareness, with frequent or severe episodes of hypoglycaemia.
- These patients do not have ESRD.

Selection criteria for islet cell transplantation

- In combination with renal transplantation in a patient with T1DM and ESRD.
- After successful live or deceased donor transplantation in a patient with T1DM and ESRD.
- Hypoglycaemic unawareness, with frequent or severe episodes of hypoglycaemia.
- Less commonly: poor metabolic control and progressive diabetic complications, despite intensive insulin therapy.

Box 5.7 Barriers to successful islet cell transplantation

Islet cell transplantation shows promise, but early excellent results have proved difficult to sustain. Supplemental insulin is required by many recipients within 1 year and >90% by 5 years. Reasons include:

- Immune-mediated destruction (highly immunogenic).
- Insufficient islet cell mass (more than one donor needed).
- Drug toxicity (CNIs and steroids are toxic to islet cells).
- Recurrent transplantation is often necessary.

Surgical technique for pancreas transplantation

Two options:

- Bladder drainage. Kidney is transplanted into the left iliac fossa and exocrine secretions of the pancreas routed into the bladder via a duodenal cystotomy. Metabolic complications:
 - Acidosis (HCO_3^- depletion) and Na^+ loss (\rightarrow relative \downarrow BP requiring oral sodium bicarbonate administration (e.g. 2g qds).
 - Calcium bladder stones (alkaline urine).
 - Chemical cystitis/urethritis.
 - Reflux pancreatitis.
- Enteric drainage (generally preferred): exocrine secretions drain into bowel. Fewer metabolic complications.
- Immunosuppression. Similar to kidney alone transplantation. Depleting antibodies more commonly used at induction. Steroid withdrawal often favoured, e.g. by 6 months.
- Graft thrombosis (rarely salvageable) is the commonest early cause of graft loss (prophylaxis with heparin \pm aspirin is usual).
- More morbidity in the first year (length of hospital stay doubles, compared to kidney alone).
- 20–30% chance of laparotomy during early post-transplant period (peripancreatic collections are common).
- Fungal infection more common than after kidney alone; prophylaxis is common practice.
- Rejection essentially causes pancreatitis, with \uparrow serum amylase and lipase. If bladder drained, urinary lipase and amylase will \downarrow during rejection. Δ Hyperglycaemia implies the majority of islet cells have been destroyed and is \therefore a worrying sign.
- Rejection in the pancreas is often diagnosed by biopsy of the kidney transplant (pancreas biopsies are possible but are technically challenging—there is a Banff classification of pancreas allograft rejection). However, asynchronous rejection (when one of the organs rejects without a simultaneous process in the other) may occur.
- 85% and 70% 1- and 5-year pancreas survival after SPK (higher kidney survival); 95% 1-year patient survival.
- Causes of post-transplant hyperglycaemia: graft dysfunction, NODAT (Δ steroids and CNI).

Indications for simultaneous liver and kidney transplantation

- Primary hyperoxaluria.
- Hereditary amyloidosis.
- HUS 2° to hereditary complement mutations.
- ADPKD: ESRD with large, symptomatic polycystic liver disease.
- Hepatorenal syndrome with irreversible renal failure.

Hypertension

- Hypertension facts and figures 450
- What is hypertension? 451
- Pathogenesis: general 452
- Pathogenesis: genetics, arterial stiffness, and SNS 454
- Pathogenesis: RAS and other factors 456
- BP measurement 458
- Clinical assessment 462
- Classification and treatment thresholds 464
- Cardiovascular risk assessment 470
- Lifestyle measures 472
- Secondary hypertension 474
- Primary hyperaldosteronism 476
- Specific causes of hyperaldosteronism 478
- Other 'hyperaldosteronism' syndromes 480
- Other causes of secondary hypertension 482
- Drug management of hypertension 484
- Guidelines for drug treatment 488
- BP treatment: special situations 490
- Clinical trials in hypertension 492
- Diuretics 1 498
- Diuretics 2 500
- β -blockers 502
- α -blockers 504
- Calcium channel blockers 506
- ACE inhibitors (ACE-I) 508
- A2 receptor blockers (ARB) 510
- Other antihypertensive agents 512
- Non-pharmacological strategies 514
- Resistant hypertension 516
- Hypertensive urgencies and emergencies 518
- Assessing urgencies and emergencies 520
- Management of urgencies and emergencies 522
- Orthostatic hypotension 526

Hypertension facts and figures

Epidemiology

The WHO identifies hypertension as the *single most important* preventable cause of premature death in developed countries. It is the most common indication for prescription drug therapy (in 2009, the NHS in the UK funded 140 million primary care prescriptions for antihypertensive drugs at a cost of £700 million).

- The 2010 Health Survey for England (sample size 12,000) found a prevalence of hypertension ($\geq 140/90$ or on antihypertensive medication) of 32% for ♂ and 27% for ♀. This increases to 73% ♂ and 64% ♀ in the >75 age group. In England, only 13.6% are registered on their GPs' hypertension register.
- It is often found in association with other CV risk factors, rather than in isolation.
- It is responsible for a significant burden to both individuals and society through coronary heart disease, stroke, and other vascular disease.
- Significant underdiagnosis and treatment remain common; the 'rule of halves' still applies:
 - 1/2 those with \uparrow BP have not been diagnosed.
 - 1/2 of those who have been diagnosed are not on treatment.
 - 1/2 of those receiving treatment do not have adequate control.

Classifying hypertension

- *Essential hypertension* is a heterogeneous genetic and environmental condition.
- *Secondary hypertension* implies \uparrow BP is 2° to an underlying disorder and accounts for 75–10% of cases (📖 p. 474).

Hypertension facts and figures

- Systolic BP (SBP) increases with age until the 8th decade.
- Diastolic BP (DBP) increases up to age 50, after which it plateaus or \uparrow slightly.
- DBP is the best indicator of CV risk <50 years. With \uparrow age, there is a shift to SBP as the principal risk predictor.
- Reduction in SBP of 20mmHg systolic or DBP of 10mmHg is associated with reductions in death from stroke and IHD of ~50% (slightly more in younger patients, slightly less in older). This is consistent down to 115/75mmHg in at least one large meta-analysis. 🌟 However, the question of 'how low to go?' remains an important one. It is unclear if there is a threshold below which further reduction in BP is no longer beneficial; the so-called 'J-curve' phenomenon (see 📖 p. 468).
- Non-pharmacological strategies (i.e. lifestyle measures) have been shown to \downarrow BP.
- Antihypertensive drug treatment not only \downarrow BP, but also \downarrow complications.
- Patient education is paramount: \uparrow BP is an asymptomatic condition, and benefits of treatment may not be immediately apparent to the patient.

What is hypertension?

BP variation in a given population follows a skewed normal distribution (see Fig. 6.1). Any cut-off point used to define abnormal will be arbitrary. Normal BP varies with race, sex, and age, so, even if an arbitrary definition of ↑ BP could be agreed, it would need to be adapted, according to the population in question.

► In addition, an individual whose BP is just below the defined cut-off has a virtually identical CV risk to one just above it.

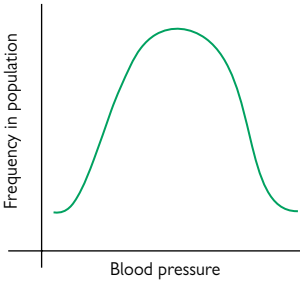


Fig. 6.1 Distribution of BP in any population: the cut-off for defining 'high' BP is arbitrary.

Definition

Perhaps the most useful definition is:

Hypertension is a level of blood pressure which places an individual at increased risk of cardiovascular events and, when treated, results in more benefit than harm.

SBP, pulse pressure, and CV risk

SBP

- Historically, DBP was thought the best predictor of CV disease.
- It is now clear that SBP has a continuous independent relationship with stroke and IHD risk.
- It can be difficult to get SBP to target, particularly in the elderly.

Pulse pressure (PP) and risk

- PP is SBP minus DBP.
- A wide PP more accurately predicts adverse CV outcome than SBP or DBP.
- PP appears to be a marker of arterial stiffness.
- PP may identify those with SBP at particularly high CV risk.
- At present, the majority of outcome data from clinical trials is for SBP and DBP, so the major guidelines are based on these, rather than on PP.

Pathogenesis: general

Introduction

The great apes do not get \uparrow BP, nor do present-day hunter-gatherer populations (with a similar diet and lifestyle to that of our ancestors). It appears that there are important factors within our *environment* and *diet* that predispose to hypertension. Genetic influences are important but insufficient in isolation.

The final common pathway in chronic \uparrow BP is \uparrow OH systemic vascular resistance (SVR). The earliest event in the development of \uparrow BP is usually a rise in cardiac output (CO). \uparrow CO causes an increase in wall:lumen ratio in resistance vessels (to normalize wall stress). This leads to a sustained rise in SVR and causes chronic \uparrow BP. CO is usually *normal* in those with *established* hypertension.

$$\text{BP} = \text{cardiac output (CO)} \times \text{systemic vascular resistance (SVR)}$$

Central role of the kidney

- Sodium excretion depends on renal perfusion pressure (the Guyton hypothesis). So \uparrow renal perfusion \rightarrow pressure natriuresis. In \uparrow BP, the curve describing this relationship is pushed to the right (see Fig. 6.2).
- In most people, the renal pressure natriuresis curve is steep (a small increase in BP \rightarrow large \uparrow in salt excretion). If this curve is shallower, BP will vary more widely with salt intake. This 'salt-sensitive' \uparrow BP occurs more commonly in black patients and in CKD.
- Monogenic forms of \uparrow BP (rare!) suggest tubular ion transport mechanisms are important mediators of blood pressure control.

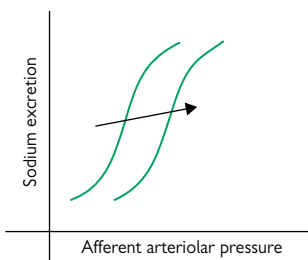


Fig. 6.2 In the normotensive individual, salt balance is maintained at a normal BP. The slope of the curve is very steep such that dietary salt loading does not significantly alter BP. In hypertensive individuals, the curve is shifted to the right, though it remains parallel. Thus, on a normal sodium diet, salt balance is maintained but at a higher BP. In salt-sensitive individuals, the rightward shift is accompanied by a depression of the slope (not shown). Thus, not only is the BP set point on a normal diet elevated, but the BP also increases in response to dietary salt loading.

Salt intake and blood pressure

- There is a large body of evidence supporting the role of high salt intake in the development of \uparrow BP.
- Genetic disorders associated with \uparrow BP often affect salt regulation.
- A high habitual salt intake is important for the development of the increase in BP with age.
- The effects of salt appear dose-dependent.
- A key study, the Intersalt study, found that populations with a low intake of dietary sodium have a low prevalence of \uparrow BP.
- \uparrow BP is seen mainly in societies with a salt intake >6 g per day. Modest reduction in salt intake for people on a typical western diet results in a BP drop of 5.3/3.7mmHg in hypertensive patients and 1.9/1.1mmHg in normotensives.
- Were salt intake to be reduced over many years, the population benefits would be substantial.
- The recommended intake is <6 g/day salt.
- The UK has led the way in reducing the salt content of food through public health programmes and engagement with food manufacturers.
- The major challenge for consumers is to be aware of the amount of 'hidden' salt in food. New labelling will hopefully go some way to help them to identify healthier food options.

Endothelial dysfunction and nitric oxide

\uparrow BP is associated with impaired endothelium-dependent relaxation of the vessel wall. A number of factors influence endothelial function:

- Nitric oxide (NO):
 - NO \rightarrow relaxation of vascular smooth muscle. Released by endothelium in response to shear stress (i.e. blood flow).
 - Endogenous NO synthase (eNOS) \rightarrow continuous normal basal release. Inducible iNOS \rightarrow high concentrations of NO in response to inflammatory cytokines.
 - \downarrow NO has been reported in hypertensive patients (+ their offspring).
- Oxidative stress: free radicals scavenge NO, forming potentially toxic by-products. Radicals themselves (such as superoxide, O_2^-) are potent vasoconstrictors.
- Prostaglandins: prostacyclin (PGI_2) is released by endothelial cells in response to shear stress and has a synergistic effect on tone with NO.
- Angiotensin II: a vasoconstrictor, also contributes to free radical generation and to endothelin release.
- Endothelins: potent vasoconstrictors, opposing the actions of NO. Also cause renal Na^+ retention, \uparrow aldosterone, vascular smooth muscle cell proliferation, cardiac hypertrophy, and fibrosis. Their role in the pathogenesis of \uparrow BP is unclear.

Pathogenesis: genetics, arterial stiffness, and SNS

Genetics

Inheritance is not Mendelian. No one gene is responsible. Larger collaborative studies are providing information on susceptibility genes.

Blood pressure levels are similar amongst close relatives (even those with 'normal' range BP), suggesting alleles on several different genes may have an effect on BP.

Rare monogenic causes of \uparrow BP have been identified, using linkage analysis in affected families (see Box 6.1). Defects in these genes may also be important in essential hypertension (gene defects coding the β and γ subunits of the epithelial Na^+ channel (linked to Liddle's syndrome) are associated with BP variations in the general population).

Research focus has been on likely culprit genes (esp. the angiotensinogen gene) and is now looking at genome-wide associations.

Genes that have been associated with essential \uparrow BP include:

- ACE polymorphisms (I/I and I/D phenotypes associate with salt-sensitive hypertension).
- α -adducin polymorphisms—a cytoskeletal protein which regulates ion transport in the renal tubule. Polymorphisms may relate to salt sensitivity, diuretic sensitivity, and essential hypertension.
- 11 β -hydroxysteroid dehydrogenase (GG phenotype correlates with salt sensitivity).
- AT-1 receptor gene—in experimental studies, AT-1a +/+ mice have higher blood pressures than -/- mice. Clinical relevance unknown.

Box 6.1 Rare single-gene causes of hypertension

- *Liddle's syndrome*: mutations affect the epithelial sodium channel (ENaC). Autosomal dominant, with \uparrow BP characterized by \downarrow renin, \downarrow aldosterone, and \downarrow K^+ (📖 p. 801).
- *Glucocorticoid-remediable aldosteronism* (📖 p. 478).
- *Syndrome of apparent mineralocorticoid excess* (📖 p. 480).
- *Pregnancy-associated hypertension*: a gene defect \rightarrow partial activation of the mineralocorticoid receptor by progesterone (rare).
- *Phaeochromocytoma*: may occur with one of the following:
 - Multiple endocrine neoplasia type 2A: mutations in the RET proto-oncogene. Autosomal dominant. Phaeochromocytoma, medullary thyroid carcinoma, and hyperparathyroidism.
 - von Hippel–Lindau disease (📖 p. 745).
 - Neurofibromatosis type 1: mutations in the NF1 tumour suppressor gene, autosomal dominant. Presents with phaeochromocytomas, multiple neurofibromas, café-au-lait spots, Lisch nodules of the iris.

Arterial stiffness

Arterial pressure depends in part on the compliance of conduit arteries. Stiff arteries are less able to dampen a surge in pressure during systole, so systolic pressure is higher. A stiffer artery will also conduct a pulse wave more rapidly. Normally, the pulse wave is reflected back from the small vessels, arriving back at the heart during diastole. If conducted more rapidly, the reflected pulse wave may reach the heart during systole, further ↑ systolic pressure and ↓ diastolic pressure. Coronary artery perfusion, which occurs predominantly during diastole, may be affected.

Commoner causes of reduced compliance (or ↑ stiffness) include:

- Ageing: loss of elastin, calcification of arterial walls, lipid deposition, and defective endothelial function all contribute.
- Diabetes: ↑ arterial stiffness is accelerated (even if ↑ BP is absent) 2° to non-enzymatic glycosylation of connective tissue, high insulin levels ± activation of the sympathetic nervous system.
- CKD, esp. ESRD: oxidant stress, impaired endothelial function, abnormal lipid profile, calcification of the arterial wall (exacerbated by disordered mineral metabolism), and a variety of putative uraemic toxins all contribute (📖 p. 212).

⚠ Increased arterial stiffness and pulse wave velocity are *independent predictors* of all-cause mortality and CV morbidity and mortality in patients with ↑ BP.

Sympathetic nervous system (SNS)

There has been considerable recent interest in the role of the SNS in ↑ BP, with the development of techniques to reduce sympathetic activity. These include renal denervation with radiofrequency energy and baroreceptor activation therapy (📖 p. 514).

Activation of the SNS is clearly linked with acute ↑ BP—chronic activation may have a role in the genesis of long-term ↑ BP in those with a genetic predisposition.

SNS activation causes:

- ↑ in stroke volume (via α -1 and -2 receptors).
- ↑ in heart rate (via β -1 receptors).
- ↑ in systemic vascular resistance (via α -1 receptors).
- Activation of the RAS (via β -1 receptor-mediated renin release).

Pathogenesis: RAS and other factors

The renin–angiotensin system (RAS)

Plays a central role in salt and water homeostasis, and \therefore BP control. An important therapeutic target (ACE-I, ARBs, renin inhibitors) (📖 pp. 508–511).

Granular cells in the juxtaglomerular apparatus synthesize and release renin. Renin converts inactive angiotensinogen into angiotensin I, which, in turn, is converted by ACE in the lungs to active angiotensin II (A2). A2 binds two receptors AT-1 and -2 (📖 p. 510).

Renin release is mediated by:

- ↓ afferent arteriolar (i.e. renal perfusion) pressure of any cause.
- Sympathetic nervous system activation (granular cell β -1 receptors).
- ↓ Na^+ delivery to the distal tubule (sensed by the macula densa).
- Prostacyclin, ACTH.

Causes of ↑ renin

- Sympathetic stimulation.
 - Renal artery stenosis.
 - Renal cell carcinoma.
 - Benign reninoma (very rare).
 - Other renin-secreting malignancies (also very rare).
 - Many antihypertensives, including CCBs and diuretics.
- ▶ Many patients with essential hypertension have ↑ plasma renin levels not related to any of the listed causes, nor of any therapeutic relevance.

Angiotensin

Circulating

A2 binds vascular receptors, but *locally released* A2 works at tissue level in a paracrine fashion. Tissue concentrations do not correlate with systemic levels but may correlate better with disease pathogenesis.

Actions of angiotensin II

- Arteriolar vasoconstriction (and venular constriction to a lesser extent).
- Efferent renal arteriolar vasoconstriction.
- Aldosterone secretion.
- Adrenaline (epinephrine) release.
- Smooth muscle hypertrophy.
- Increased reabsorption of sodium in PCT.
- Inhibits renin release (negative feedback loop).
- Renal mesangial cell growth and matrix expansion.
- Myocardial growth and matrix expansion.
- Stimulates thirst and ADH release.

Most effects are mediated by the angiotensin type 1 (AT-1) receptor.

The role of AT-2 receptors remains unclear, but ligand binding may regulate vasodilator, proliferative, and apoptotic effects of A2.

Aldosterone

Aldosterone synthesis occurs mainly in the zona glomerulosa of the adrenal cortex and is tightly regulated by the RAS and electrolyte homeostasis ($\uparrow K^+$ or $\downarrow Na^+$ intake \rightarrow aldosterone synthesis).

Aldosterone acts at the collecting duct to promote Na^+ retention and K^+ excretion (📖 p. 930). Cortisol also activates the mineralocorticoid receptor—so aldosterone-sensitive tissues contain high levels of 11β -hydroxysteroid dehydrogenase type 2 (converts cortisol \rightarrow cortisone, which is incapable of activating the receptor), protecting the mineralocorticoid receptor from states of high circulating cortisol.

Extrarenal actions of aldosterone

- Paracrine action in non-epithelial tissues (brain, heart, epithelium).
- Associated with vascular inflammation and cardiac fibrosis. The same may be true in non-vascular tissues.
- Activates pro-fibrotic and growth factors in several tissues (including the kidney).

Other factors

- There is much redundancy in the control of BP. Many neuroendocrine systems contribute to it in overlapping and interlocking ways—and any (or all) of these may lead to abnormal BP.
- Insulin resistance has a clear relationship with \uparrow BP:
 - Fasting insulin and glucose levels correlate with BP in insulin-resistant patients.
 - Relatives of those with \uparrow BP are more likely to have insulin resistance.
 - Insulin resistance predicts the subsequent development of \uparrow BP.
 - Mechanisms may include SNS activation and Na^+ retention.
- Natriuretic peptides, including:
 - ANP (atrial natriuretic peptide). Released by atrial tissue in response to stretch, i.e. volume overload.
 - BNP (brain natriuretic peptide). First discovered in the brain but synthesized and secreted by ventricular myocardium.
 - CNP (C-type) and DNP (Dendroaspis). More recently discovered. Relevance not yet clear (DNP was first discovered in the venom of the green mamba snake. Its subsequent detection in the plasma of humans is of uncertain significance. It may play a part in the diuresis associated with subarachnoid haemorrhage).
 - Urodilatin. Similar structure to ANP but confined to the kidney. Synthesized in distal tubular cells, causing natriuresis.

The natriuretic peptides are secreted in response to volume overload, leading to a compensatory natriuretic effect. Other effects include vasodilation, modulation of vascular smooth muscle function, and control of the RAS system. Their role in the pathogenesis of \uparrow BP is less clear. In experimental studies, defects in natriuretic peptide production appear to cause salt-sensitive \uparrow BP.

BP measurement

Clinic readings

- Gold standard is mercury sphygmomanometer. However, environmental concerns about mercury contamination have led to its gradual disappearance from clinical practice.
- Substitutes (aneroid sphygmomanometers or oscillometric automated devices) are now preferred.
- Semi-automated devices may not measure BP accurately in some clinical conditions, e.g. atrial fibrillation. Palpate the radial/brachial pulse before measuring, and, if irregular, measure BP, using a manual device.
- Validation and maintenance are vital: for a list of approved apparatus, see <http://www.bhsoc.org> for British Hypertension Society or <http://www.heart.org> for American Heart Association.

Examiner's technique is vital

⚠ Even a relatively small error in BP measurement could result in inappropriate under- or overtreatment.

- Standing BP should be recorded, esp. during the initial assessment of elderly or diabetic patients.
- Measure in both arms. If there is a significant difference ($>20\text{mmHg}$), then repeat. Measure subsequently in the arm with the higher value.
- Place cuff 1–2cm above the antecubital fossa.
- Select appropriate cuff size. Cuff bladder width should be 40% and length 80% of arm. The standard adult bladder is $12 \times 26\text{cm}$ (although some consider $12 \times 35\text{cm}$ standard).
 - Cuff too large → underestimation.
 - Cuff too small → overestimation.
- Inflate cuff whilst palpating the radial artery to estimate SBP. Inflate cuff to 30mmHg above estimated SBP.
- Deflate at 2mmHg/s , listening to Korotkoff phase I (appearance) for SBP and phase V (disappearance) for DBP. If phase V goes to zero, use phase IV (muffling).
- Take two measurements 1–2min apart, and read to the nearest 2mmHg (round off upwards).
- Document the time of measurement in relation to tablets.
- Do not round up or down to preconceived values (observer's prejudice).

Ambulatory BP monitoring (ABPM)

Now recommended in the UK by the National Institute for Health and Care Excellence (NICE) for the diagnosis of \uparrow BP (daytime). Daytime ambulatory BP correlates better with target organ damage (TOD) than clinic BP and provides a more accurate diagnosis of \uparrow BP. Day, night, and 24-hour BP measurements are recorded and are usually lower than clinic measurements (see Table 6.1 and Fig. 6.3). The patient should refrain from strenuous exercise and straightening their arm during measurement (tricky if driving) and should keep a concomitant diary, e.g. sleep times. For an accurate result, two measurements per hour during the day, with a

minimum of 14 measurements, are required. Several limitations, including cost, lack of outcome data for patients already on treatment, and acceptability to patients, still limit use.

Indications for ABPM

- If clinic BP is $>140/90$ mmHg or higher.
- Possible white coat effect or white coat hypertension.
- Resistant \uparrow BP.
- When BP unusually variable.
- To identify nocturnal hypertension.
- Symptoms suggestive of hypotension.
- Diagnosis and treatment of hypertension in pregnancy.

ABPM readings and interpretation

Table 6.1 ABPM readings at differing periods

	Normal	Abnormal
Daytime	$<135/85$	$>140/90$
Night-time	$<120/70$	$>125/75$
24 hours	$<130/80$	$>135/85$

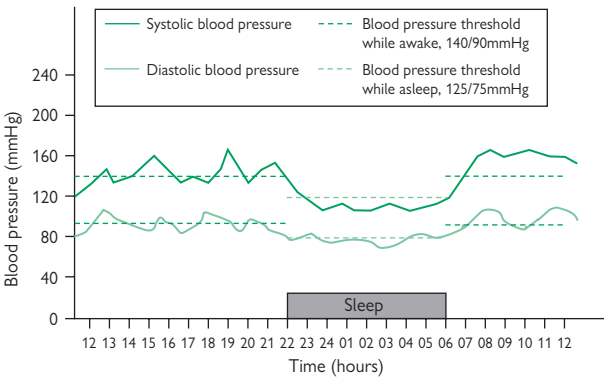


Fig. 6.3 Example of variation in daytime and night-time BP.

Look for the following characteristics:

- Nocturnal dipping: mean wake systolic BP falls by at least 10% during sleep. 'Super' dipping (20–30%) is associated with neurological sequelae. Non-dipping, or reverse dipping, is associated with increased CV mortality and TOD.
- Masked \uparrow BP: normal clinic BP but elevated ABPM. Associated with higher prevalence of TOD.

- White coat hypertension: elevated clinic BP, with normal ABPM and no evidence of TOD. Increased prevalence with ↑ age, milder hypertension (10–30% grade 1, <10% grades 2 and 3). Associated with increased CV risk. In hypertensive patients, known as ‘white coat effect’. Target ABPM for treated patients is <135/85 aged under 80, <145/85 aged over 80.

Home

Can be used as an alternative to ABPM for the diagnosis of ↑ BP.

When confirming hypertension using home BP

- Take two consecutive measurements for each BP recording, at least 1min apart.
- Record BP twice daily (morning and evening).
- Take readings for at least 4 days (ideally, 7 days).
- Discard the first day’s measurements.
- Use the average value of all the remaining measurements.

When treating hypertension using home BP

- Management of BP, according to home measurements, in individuals already receiving treatment is not backed by robust evidence.
- Home BP monitors are often inaccurate. The British Hypertension Society has a list of validated machines on their website (🔗 <http://www.bhsoc.org>).
- Patients are more likely to reach target BP with home BP monitoring but will need the same number of tablets to do so.
- It can be very helpful to involve patients in their own management.
- Helpful in those with white coat effect where the target BP is:
 - Aged below 80 <135/85mmHg.
 - Aged over 80 <145/85mmHg.

Blood pressure variability

- A recent series of analyses have recently been published, showing that excessive variability in BP is an independent risk factor for CVD.
- Variability in SBP is a strong predictor of stroke (independent of mean SBP).
- In treated ↑ BP, this variability is associated with a higher risk of vascular events.
- BP variability is measured as the standard deviation of mean BP.
- Not clear if causation, or marker, of vascular disease.
- The different classes of antihypertensive agent vary in their capacity to influence this BP variability.
- CCBs and thiazide-like diuretics are the most effective at reducing variability.
- Older and black patients are more likely to have ↑ SBP variability.

Clinical assessment

There are four fundamental questions to consider:

- Is this sustained hypertension?
- Is this primary or secondary hypertension?
- Are there other cardiovascular risk factors?
- Is there target organ disease?

Management of an individual patient will depend on these factors.

History and examination

- Duration of elevated BP. Previous monitoring, treatment, and control.
- Previous drug treatment and side effects.
- Contraindications to specific drugs, e.g. bronchospasm.
- Family history: ↑ BP, stroke, diabetes, ↑ lipids, renal disease, premature IHD.
- Previous history of pre-eclampsia or hypertension during pregnancy?
- Is this primary or secondary hypertension (📖 p. 474)? The following may suggest a secondary cause:
 - Young age (<30 years, esp. if no FH and Caucasian).
 - Sudden-onset hypertension.
 - Presents as malignant hypertension (📖 p. 518).
 - Acute rise with previously stable BP control.
 - Severe or 'resistant' (≥ 3 drugs) hypertension.
 - Other diagnostic clues (📖 p. 475)?
- Other contributory factors? Other cardiovascular risk factors?
 - Drugs (NSAIDs, decongestants, cocaine, amphetamines).
 - Obesity.
 - Excess alcohol.
 - Salt intake.
 - Lack of exercise.
 - Environmental stress.
 - Smoking.
 - Cholesterol.

Is there target organ damage?

- ▶ Think Brain, Eyes, Heart, Arteries, Kidneys.
- Stroke, TIA, cognitive decline.
- Fundi: hypertensive retinopathy. Grades 1 and 2 (silver wiring and AV nicking) are common. Grades 3 and 4 (haemorrhage, exudates, papilloedema) carry a significantly increased risk of stroke, CV disease, and CCF and require urgent treatment (📖 p. 522).
- LVH, IHD, cardiomegaly, CCF.
- Peripheral vascular disease: look for bruits—carotid, femoral, renal.
- Renal impairment, proteinuria, microscopic haematuria.
- Sexual dysfunction.

Investigations

Routine

- Urinalysis (? protein \pm blood).
- SCr, eGFR, U&E, Ca^{2+} .
- Blood glucose—preferably fasting.
- Lipid profile—preferably fasting.
- ECG for LVH (\uparrow LV strain \rightarrow higher risk) and/or evidence of IHD.

For selected patients

- Echocardiogram.
- Urine protein evaluation: uACR or uPCR (if dipstick proteinuria).
- Hb and Hct (polycythaemia).
- Bicarbonate (hypokalaemic alkalosis?).
- Thyroid function.
- Ferritin (haemochromatosis).
- ESR and CRP.
- Uric acid (\uparrow in metabolic syndrome).
- Plasma renin and aldosterone.
- Plasma and urine metanephrines.
- 24h urinary sodium.
- BP in lower limbs: hypertensive aged <40 ; older patient ? PVD.
- Research investigations: vascular USS, pulse wave velocity, assessment of endothelial function.

Major cardiovascular risk factors

- Hypertension.
- Smoking.
- Obesity (BMI ≥ 30).
- Physical inactivity.
- Dyslipidaemia.
- Diabetes mellitus.
- Albuminuria or GFR $<60\text{mL/min}$.
- Age (♂ >55 years, ♀ >65 years).
- Family history of premature CV disease (♂ <55 years, ♀ <65 years).

Classification and treatment thresholds

There are many different classifications and guidelines, but all use similar BP targets (themselves based on evidence regarding CV outcomes). The most important are those provided by:

- The British Hypertension Society (BHS) and National Institute for Health and Care Excellence (NICE)—a collaborative UK guideline.
- The European Society of Hypertension-European Society of Cardiology (ESH-ESC).
- The Joint National Committee (JNC) (USA).
- Kidney Disease Improving Global Outcomes (KDIGO) (↑ BP in the context of renal disease).

All draw on the results of large randomized controlled trials and meta-analyses to formulate their recommendations.

BHS/NICE guideline

The 2011 guidelines from BHS/NICE classify BP into stage 1, stage 2 and severe. They were also the first to use ambulatory (ABPM) and home BP (HBPM) measurements.

NICE/BHS primary hypertension targets (2011)

Clinic BP

- <140/90mmHg in people aged <80 years.
- <150/90mmHg in people aged ≥80 years.

Daytime average ABPM or average HBPM during waking hours


- <135/85mmHg in people aged <80 years.
- <145/85mmHg in people aged ≥80 years.

Overview

Offer lifestyle interventions and patient education to all.

Stage 1 hypertension

Clinic BP ≥140/90 mmHg and subsequent ABPM daytime average or HBPM average BP ≥135/85 mmHg.

- Offer antihypertensive drug treatment if:
 - TOD.
 - Established CV disease.
 - 10-year CV risk ≥20% (see  p. 470).
 - DM.
 - CKD.
- Annual review.
- If aged <40 years, consider more detailed evaluation of TOD and specialist referral (traditional CV risk calculators may underestimate lifetime risk).

Stage 2 hypertension

Clinic blood pressure $\geq 160/100$ mmHg and subsequent ABPM daytime average or HBPM average BP is $\geq 150/95$ mmHg.

- Offer antihypertensive drug treatment.
- Offer lifestyle interventions and patient education.
- Annual review.

Severe hypertension

Clinic systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg.

- Start hypertensive drug immediately. Do not wait for ABPM.
- Refer for specialist care immediately if:
 - Accelerated hypertension (grade 3 or 4 hypertensive retinopathy).
 - Cardiovascular complications.
 - New renal impairment, haemoproteinuria.
 - Suspected pheochromocytoma (📖 p. 482).

If hypertension is not diagnostic

Clinic blood pressure is $\geq 140/90$ mmHg or higher but subsequent ABPM or HBPM average BP is $\leq 135/85$ mmHg.

- Measure BP at least every 5 years.
- If TOD, look for alternative causes.

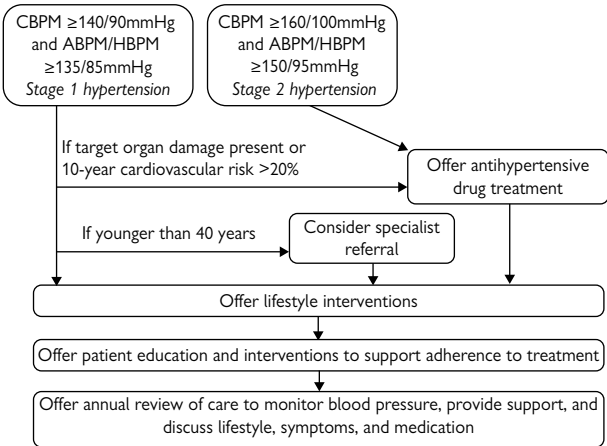


Fig. 6.4 Care pathways in hypertension. Used with kind permission of NICE. CBPM, clinic BP monitoring; ABPM, ambulatory BP monitoring; HBPM, home BP monitoring.

The European Society of Hypertension-European Society of Cardiology (ESH-ESC)

The latest ESH-ESC guideline was published in 2013. The full guideline is available at <http://eurheartj.oxfordjournals.org/content/34/28/2159>

The following summary is adapted with permission.

Table 6.2 ESH-ESC classification

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	<130	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension (mild)	140–159	and/or	90–99
Grade 2 hypertension (moderate)	160–179	and/or	100–109
Grade 3 hypertension (severe)	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and/or	<90

Table 6.3 ESH-ESC definitions of ↑ BP by office and 'out of office' BP measurement

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Office BP	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake)	≥135	and/or	≥85
Nighttime (or asleep)	≥120	and/or	≥70
24-h	≥130	and/or	≥80
Home BP	≥135	and/or	≥85

Summary of ESH-ESC treatment guidelines 2013

- Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 ↑ BP with any level of CV risk, a few weeks after (or simultaneous to) initiation of lifestyle changes.
- Lowering BP with drugs is recommended when total CV risk is high because of TOD, DM, CVD or CKD, even for grade 1 ↑ BP
- Initiation of drug treatment should also be considered for grade 1 patients at low to moderate risk when BP is within this range at several repeated visits, or elevated by ambulatory BP criteria - and remains within this range despite a reasonable period of lifestyle measures.

- Drug treatment is recommended in elderly patients (age >60) when SBP is ≥ 160 mmHg. However, treatment should also be considered in this group (esp. if age <80) if SBP is in the 150–160 mmHg range, provided that it is well tolerated. This recommendation in the elderly is an important change from previous ESH-ESC guidelines.
- A high normal BP should not be treated with antihypertensive drug therapy.
- Young individuals with isolated elevation of brachial SBP should not be treated (due to a lack of evidence), but should be followed closely with appropriate lifestyle recommendations.
- Treatment should target a BP <140/90 mmHg. A lower target of <130/80 mmHg in patients with CKD, diabetes or a CV disease is no longer recommended as it is not adequately supported by evidence from RCTs.


Table 6.4 Summary of ESH-ESC BP treatment goals (2013)

Recommendations	Class ^a	Level ^b
A SBP goal <140 mmHg		
a) is recommended in patients at low-moderate CV risk;	I	B
b) is recommended in patients with diabetes;	I	A
c) should be considered in patients with previous stroke or TIA	IIa	B
d) should be considered in patients with CHD;	IIa	B
e) should be considered in patients or non-diabetic CKD.	IIa	B
In elderly hypertensives less than 80 years old with SBP ≥ 160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.	I	A
In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability.	IIb	C
In individuals older than 80 years old with initial SBP ≥ 160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental condition.	I	B
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated.	I	A

^aClass of recommendation; ^blevel of evidence

Joint National Committee (JNC) guideline

The latest iteration of this influential guideline has been delayed by an unprecedented degree of prerelease stakeholder scrutiny. However, it is expected that JNC 8 (or JNC 'late' as it has been dubbed) may, like ESH-ESC, offer a more stringent interpretation of available data—retaining a goal of 140/90mmHg for the majority, but suggesting higher targets may be acceptable for many patients age >60 (and particularly age >80). JNC 8 may also echo ESH-ESC by offering a more circumspect view of lower treatment targets (<130/80mmHg) in the presence of comorbidities such as diabetes and CKD.

The current status is available at:  <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc8/>

KDIGO

- Recommend a BP target <140/90mmHg for non-diabetic, non-proteinuric CKD patients
- Target <130/80mmHg if proteinuria (>30mg/24h) whether diabetic or not.
- Tailor treatment regimes for individual elderly patients by carefully considering age, co-morbidities and other therapies. Escalate treatment carefully under appropriate supervision.

The J-curve phenomenon

The question 'how low to go?' remains both valid and important. It is possible that there may be a threshold below which additional BP reduction is no longer beneficial. This could be explained by the maintenance of physiological autoregulation within organ vascular beds, particularly in the presence of CV disease.

The data supporting a 'lower the better' approach have come from meta-analyses of multiple trials, rather than from studies specifically designed to scrutinize different target ranges. Indeed, some trials, such as ACCORD, have shown no consistent reduction in CV events, even when lower average SBPs are achieved. Furthermore, it has been inferred from some studies; e.g. ONTARGET that lower BP targets may actually be associated with additional coronary events.

Many interpret the J-curve relationship to mean that BP reduction to lower levels, even if not harmful, is certainly less meaningful than a reduction to more moderate values.

These issues are reflected in the latest iterations of the guidelines discussed above, which have become more guarded in their recommendation of lower targets, even in high-risk groups.

Overall, current evidence suggests that, even if escalating therapy to achieve the lowest possible BP is not clearly detrimental, neither is it clearly advantageous—it may not \therefore be cost effective, with patients unnecessarily exposed to side effects that influence their overall compliance.

Suggested indications for specialist referral

- Urgent (inpatient) treatment needed:
 - Accelerated hypertension (severe ↑ BP, with grades III–IV retinopathy).
 - Particularly severe hypertension (>220/120mmHg).
 - Hypertensive emergency (e.g. encephalopathy, eclampsia, aortic dissection).
 - Impending complications (e.g. LVF, TIA).
- Possible 2° hypertension.
- Resistance to treatment (≥3 drugs).
- Multiple drug intolerances.
- Multiple drug contraindications.
- Persistent non-adherence or non-compliance.
- Other situations:
 - Unusual blood pressure variability.
 - Possible white coat hypertension.
 - Hypertension in pregnancy.

Cardiovascular risk assessment

Formal assessment of CV risk is the starting point for treatment decisions and discussions between clinicians and patients. The ultimate goal of the treatment of hypertension is prevention of CV disease.

- The absolute risk of a CV event varies widely according to age, sex, severity of BP, and presence or absence of additional risk factors. The relative risk reduction of interventions is constant. Overprediction → overtreatment, underprediction → missed opportunity.
- Estimation of risk is straightforward in many patients; e.g. those with established CV disease, diabetes, CKD or a significantly elevated single risk factor. In these situations CV risk is high and aggressive intervention highly desirable.
- Many patients, however, do not belong to such high-risk groups and estimation of risk requires the use of risk-prediction models.
- Many computerized models have been developed. None are perfect. They aim to identify patients for intervention and calculate potential risk reduction.
- Many are based on Framingham data*. However, Framingham studied a Caucasian, middle class population on no treatment (i.e. no aspirin, statins etc.) and is several decades old. See www.framinghamheartstudy.org/risk
- Framingham-based scoring tends to overestimate CV risk in low and medium risk groups and underestimate CV risk in renal disease, diabetes, certain ethnic groups, those with LVH and those with FH of premature CHD. It has ∴ been suggested that the risk score should be adjusted by a factor of $\times 1.5$ if there is one relative with premature CVD and by $\times 1.4$ if the individual is a male of South Asian origin.
- Many models refer to 10-year risk of CV mortality. High risk refers to 10-year CV mortality of $\geq 20\%$.
- The Systematic Coronary Risk Evaluation (SCORE) model has been developed from large European cohort studies. It allows calibration for several different countries and is recommended by ESH-ESC. An interactive version of SCORE is available through www.heartscore.org.
- ASSIGN (www.assign-score.com) is based on Scottish data and takes FH and social deprivation into account.
- There is a move toward estimations of lifetime rather than 10-year risk. For example, the QRISK lifetime risk calculator identifies younger patients with high lifetime risk (defined as $>50\%$) who would not be identified using 10-year risk estimates. (www.qrisk.org).
- The prediction of lifetime risk is recommended by the Joint British Societies (see <http://www.jbs3risk.com>).
- Risk calculators may not be appropriate when individuals are at higher CV risk because of underlying medical conditions/treatments (e.g. HIV, autoimmune disease).
- Clinical judgement is important when making decisions in certain circumstances (e.g. obesity, taking statins, already on BP treatment, recently stopped smoking).

* The Framingham Heart Study: a cohort of over 5,000 men and women, aged 30–62, from Framingham, Massachusetts, followed up from 1971 to assess the determinants of CV disease.

When you *don't* need a risk calculator:

Assume the following groups of people are at high risk (10-year CVD risk $\geq 20\%$), rather than use risk calculators:

- Pre-existing CVD.
- DM.
- CKD.
- Familial hypercholesterolaemia.

Lifestyle measures

Lifestyle changes can ↓ BP, reduce drug requirements, and improve CV risk (see Table 6.5). The effects are synergistic. Clear advice, including culturally appropriate written and audiovisual material, should be provided to all patients as well as to those with a high normal (pre-hypertensive) BP or positive family history.

Low-sodium diet


Reduces BP in normotensive and hypertensive populations. Enhances response to ACE-I/ARB treatment. Usual Na⁺ intake is in the range 150–200mmol/day (8–12g/day). Reduce by as much as possible; at least <100mmol/day (~2.3g of Na⁺ or 6g NaCl). The majority (80%) of salt is 'hidden' (breads, stock cubes, 'ready meals', breakfast cereals, sauces). Avoid salt in cooking and on the table. Cook using natural ingredients. Dietary sodium can be estimated by 24h urine Na (aim <100mmol/24h). If necessary, refer to a dietitian. Note: 1g of Na⁺ contains 44meq, 1g of NaCl contains 17meq of Na⁺; 5g of NaCl ~1 teaspoon. Patients should be advised that, with time, their taste sensitivity to salt will increase if they undertake a restriction.

⚠ Low Na⁺ salt substitutes often contain K⁺ as KCl and can cause dangerous hyperkalaemia in patients with CKD and those taking K⁺-sparing diuretics.

Weight loss

Obesity (BMI ≥30) is fuelling the increasing incidence of ↑ BP and T2DM. Weight reduction improves BP, even without dietary Na⁺ restriction, and has beneficial effects on insulin resistance, lipids, LVH, and diabetic control.

Healthy eating

Advise a diet high in fruit and vegetables (five portions/day), low in saturated fats, low in total and saturated fats. The 'Dietary Approach to Hypertension Trial' (DASH) demonstrated impressive reductions in BP. The DASH eating plan can be downloaded at:  <http://www.nhlbi.nih.gov/health/public/heart/hbp/dash>. K⁺, Mg²⁺, and Ca²⁺ supplementation is not recommended.

Exercise

Exercise has been shown to reduce the risk of DM and decrease BP by up to 10mmHg.

► Think 'FITT' (Frequency (5x/week), Intensity (moderate, mildly SOB), Time (at least 30min), Type (any aerobic). Isometric and strenuous exercise tends to ↑ BP and is best avoided until BP is under control.

Alcohol

There is a linear relationship between C₂H₅OH consumption and BP, with the incidence of ↑ BP increasing ~1.5–2.0x at >2 drinks/day. It is also associated with drug resistance. Patients will, no doubt, remind you of the apparent paradox that moderate alcohol intake reduces overall CV risk;

however, recommended daily amounts should not be exceeded (♂: <21 units/week; ♀: <14 units/week). The effect of C_2H_5OH is reversible; ↓ alcohol intake by 3 units/day → ↓ need for medication (in ~1–6 weeks).

Caffeine

Caffeine is an adenosine receptor antagonist (→ vasoconstriction). >5 cups coffee/day is undesirable. It causes an immediate increase in SBP by ~10–15mmHg for several hours. Caffeine is also present in tea and cola drinks, although coffee only has been studied. Recommend decaffeinated alternatives.

Stress management

Modest effect, e.g. meditation, cognitive therapy, biofeedback, muscle relaxation, etc. If patients are keen, cognitive behavioural therapy is most likely to have a significant impact.

Table 6.5 Lifestyle interventions for BP reduction

Intervention	Recommendation	Expected SBP reduction (range)
Weight reduction	Maintain ideal BMI (20–25kg/m ²)	5–10mmHg per 10kg weight loss
Diet	Consume diet rich in fruit, vegetables, low-fat dairy products with reduced content of saturated and total fat	8–14mmHg
Dietary sodium restriction	↓ dietary sodium intake to <100mmol/day (<2.3g sodium or <6g sodium chloride)	2–8mmHg
Physical activity	Undertake regular aerobic activity, e.g. brisk walking for ≥30min most days	4–9mmHg
Alcohol	♂ <21 units/week ♀ <14 units/week	2–4mmHg

Additional lifestyle measures that ↓ CV risk

- Stop smoking. Does not ↓ BP but will improve overall CV risk. Quitting before middle age returns life expectancy to near that of lifelong non-smokers.
- Reduce total fat intake.
- Replace dietary saturated fats with monounsaturated fats.
- Increase consumption of oily fish.

Secondary hypertension

An identifiable cause is found in ~5–10% of all cases of ↑ BP, though true prevalence of secondary hypertension remains unknown. It is more common in the subgroup of ‘resistant’ hypertension (📖 p. 516).

History, examination, routine investigation (plus a high index of suspicion) should identify those in need of more specialist assessment. The diagnosis of secondary hypertension is important to make, as curative treatment may be available.

Diagnostic clues are shown in Table 6.6.

Classification

- *Renal disorders* (for ↑ BP in CKD, see 📖 p. 203–4):
 - Virtually any renal parenchymal disease: acute or chronic GN, tubulointerstitial disease, APKD, obstructive nephropathy.
 - Renovascular disease (📖 p. 586).
 - Renin-producing tumours (📖 p. 479).
 - Genetic diseases affecting tubular transport (Liddle’s syndrome, 📖 p. 800). Very rare.
- *Endocrine disorders*:
 - Mineralocorticoid excess (📖 p. 476): 1° aldosteronism, apparent mineralocorticoid excess, congenital adrenal hyperplasia, liquorice ingestion, ectopic ACTH secretion, exogenous mineralocorticoids (e.g. fludrocortisone), pseudohyperaldosteronism.
 - Others, including phaeochromocytoma, Cushing’s syndrome, hypothyroidism, hyperthyroidism (↑ SBP), hyperparathyroidism, acromegaly, or carcinoid syndrome.
- *Drugs*:
 - Prescribed: oestrogen-containing contraceptives, sympathomimetic agents (cold cures), glucocorticoids, NSAIDs (and COX-2 inhibitors), ciclosporin, monoamine oxidase inhibitors, sodium bicarbonate.
 - Over the counter: sympathomimetic agents, NSAIDs.
 - Illicit: amphetamines, cocaine.
- *Pregnancy* (📖 p. 846):
 - Pregnancy-induced hypertension, pre-eclampsia, and eclampsia.
- *Miscellaneous*:
 - Obstructive sleep apnoea.
 - Coarctation of the aorta (↓ renal perfusion).
 - Increased intracranial pressure or spinal cord injury.
 - Acute LVF and intravascular volume overload (IV fluids!).
 - Acute intermittent porphyria.
 - Alcohol withdrawal.
 - Haemochromatosis.
 - Hyperdynamic circulation (systolic hypertension): anaemia, fever, thyrotoxicosis, aortic regurgitation, AV fistulae.

Table 6.6 Diagnosis of secondary hypertension

Condition	Diagnostic clue	Further investigation
Primary renal disease	↑ SCr Proteinuria ± haematuria	Renal USS (?APKD) Renal biopsy
Renovascular hypertension	↑ SCr Acute ↑ SCr post-ACE-I/ARB Renal asymmetry on imaging Flash pulmonary oedema Abdominal bruit (sensitivity: 65%; specificity 90%)	CT angiogram MRA Duplex USS Formal angiography
Primary aldosteronism	Hypokalaemia (rarely → muscle weakness, polyuria, arrhythmias). May be unmasked following the introduction of a thiazide diuretic	Plasma aldosterone/renin ratio Urinary aldosterone excretion (post-salt load)
Apparent mineralocorticoid excess	Mainly children ↑ BP, ↓ K ⁺ , ↓ renin Aldosterone not ↑	↑ ratio of THF to THE in urine (see Other 'hyperaldosteronism' syndrome; Box 6.4)
Phaeochromocytoma	Paroxysmal symptoms (headache, palpitations sweating)	Urinary catecholamines
Thyroid disease	Both hypo- and hyper- are associated	Thyroid function
Hyperparathyroidism	↑ serum Ca ²⁺	Serum PTH
Cushing's syndrome	Corticosteroid therapy Cushingoid appearance (central obesity, striae bruising, etc.), muscle weakness, hyperglycaemia, oligomenorrhoea	Urinary cortisol excretion Dexamethasone suppression tests
Coarctation of the aorta	Midsystolic murmur (precordium → back) Weak femoral pulses Radiofemoral delay BP in arms ↑, BP in legs ↓	CT or MRA Aortography
Obstructive sleep apnoea	Snoring, daytime somnolence, morning headache, obesity (large collar size)	Sleep observation with pulse oximetry Formal polysomnography
Acromegaly	↑ sweating, headaches, fatigue, arthralgia, change in shoe/ring size, change in appearance, hyperglycaemia	↑ IGF-1 Failure to suppress GH to <2mU/L post-75g oral glucose load

Primary hyperaldosteronism

Introduction

Aldosterone acts on the distal tubule to \uparrow renal Na^+ retention (with \uparrow urinary K^+ and H^+ loss), \uparrow total body Na^+ content ($\rightarrow \uparrow$ BP). Disorders of autonomous aldosterone secretion with suppressed renin account for $\sim 0.1\%$ of the hypertensive population (possibly an underestimate, some say 1–5%) and is the most common endocrine disorder leading to 2° hypertension. It is also associated with \uparrow CV risk beyond that expected by the level of BP alone.

Clinical and biochemical findings vary widely. Often asymptomatic but may present with \downarrow K^+ , metabolic alkalosis, and mild \uparrow Na^+ (helps distinguish from essential BP treated with diuretics where Na^+ is usually low normal). However, $\downarrow \downarrow$ K^+ with diuretics ($< 3.0 \text{ mmol/L}$) remains suspicious.

Severe \downarrow $\text{K}^+ \rightarrow$ tetany, myopathy, and nephrogenic diabetes insipidus (polyuria and nocturia).

Causes

- Conn's syndrome (aldosterone-producing adrenal adenoma) $\sim 70\%$.
- Bilateral adrenal hyperplasia $\sim 30\%$.
- Aldosterone-producing adrenal carcinoma ($\uparrow \uparrow$ aldosterone and $\downarrow \downarrow$ K^+ —may also produce cortisol and sex steroids).
- Primary (unilateral) adrenal hyperplasia.
- Glucocorticoid-remediable aldosteronism.

Diagnosis

- \downarrow K^+ is only present in 50–80% early on (leading to underdiagnosis).
- Renal K^+ wasting (urinary $\text{K}^+ > 30 \text{ mmol/day}$).
- Aldosterone–renin ratio (ARR):
 - Commonly used diagnostic test (see Box 6.2).
 - Unregulated aldosterone secretion \rightarrow suppressed renin production and \uparrow ARR.
- Note \uparrow BP in the malignant phase often has electrolyte abnormalities similar to primary hyperaldosteronism, i.e. \downarrow K^+ , \uparrow HCO_3^- . ARR is not interpretable at this stage so should not be done in this acute setting.

There is no gold standard test for 1° hyperaldosteronism. Confirmatory tests include:

- Oral or IV salt loading:
 - High Na^+ diet for 3 days (200mmol/day—ask your dietitian) or IV normal saline (2L over 4h).
 - Verify with urinary $\text{Na}^+ > 250 \text{ mmol/24h}$.
 - Measure 24h urinary aldosterone. Normal response: suppressed aldosterone secretion (\rightarrow lack of suppression confirms diagnosis).
 - \triangle May precipitate \downarrow K^+ ; supplement with slow-release KCl.
- Fludrocortisone suppression test: 4-day administration of fludrocortisone further suppresses plasma renin activity without suppressing plasma aldosterone below a threshold value.

- A captopril challenge test fails to suppress aldosterone >30% in primary hyperaldosteronism.
- Adrenal CT and MRI are used to localize tumours (>1.5cm).
- ⚠ Never order imaging before confirming secretion.
- Never assume a radiologically apparent adrenal adenoma confirms the laterality of secretions if planning adrenalectomy.
- Adrenal venous sampling is occasionally necessary—the distinction between a discrete adenoma and diffuse hyperplasia is important because of the potential role of surgery in the former.

General principles of treatment

Spironolactone (a competitive antagonist of the mineralocorticoid receptor, [p. 501](#)), initially 50–100mg (SE: gynaecomastia, impotence, menstrual irregularities, GI upset). Eplerenone is an alternative but less effective. Add amiloride 5–20mg if ↓ K⁺ persists or gynaecomastia. Other antihypertensive agents may also be required. Surgical resection if adenoma: 70% normotensive at 1 year (● results less good in some series—esp. if BP long-standing). Some argue for a trial of spironolactone in all cases of resistant hypertension ([p. 516](#)).

Box 6.2 ARR: the nuts and bolts

- Correct hypokalaemia (↓ K⁺ suppresses aldosterone). Encourage liberal sodium intake.
- Tubes: liaise with your biochemistry lab—usually one plain tube or lithium tube for aldosterone and one EDTA tube for renin. They will definitely want to know that the samples are coming. Now generally NOT placed on ice (promotes conversion of inactive → active renin).
- Withdraw agents that markedly affect ARR for at least 4 weeks (spironolactone, eplerenone, amiloride, triamterene, potassium-wasting diuretics). This can be difficult.
- If it is possible to control BP with other medications, withdraw drugs that may affect the ARR for at least 2 weeks (β-blockers, ACE-I, ARB, diuretics). This can also be difficult.
- The ‘cleanest’ drugs are α-blockers, e.g. doxazosin. Hydralazine and verapamil also have minimal effects of ARR.
- Establish oral contraceptive and HRT status.
- Conditions for collection blood:
 - Time: 07.00–09.00.
 - Posture: upright (for at least 2h).
 - Maintain sample at room temperature.
 - Result: aldosterone (pmol/L)/plasma renin activity (ng/mL/h) >750 or aldosterone (ng/dL)/plasma renin activity (ng/mL/h) >30–50. The higher the ratio, the more likely the diagnosis.
 - Refer equivocal cases to a specialist centre.

Specific causes of hyperaldosteronism

Primary hyperaldosteronism

Glucocorticoid-remediable aldosteronism (GRA)

Very rare. Autosomal dominant. A chimeric aldosterone synthase/11 β -hydroxylase is ectopically expressed in the adrenal fasciculata. ACTH \rightarrow stimulates enzyme activity \rightarrow normal cortisol production + aldosterone excess (\rightarrow volume expansion and \uparrow BP). Presents with \uparrow BP at a young age, with a family history (early haemorrhagic stroke in some pedigrees). Diagnosis (see Fig. 6.5) now confirmed with genetic testing. Dexamethasone \rightarrow suppresses ACTH secretion \rightarrow \downarrow enzyme activity \rightarrow \downarrow aldosterone production.

Congenital adrenal hyperplasia (CAH)

Inherited enzymatic defects (autosomal recessive) in cortisol production. Clinical features depend on the enzyme affected but result from: (i) \downarrow cortisol synthesis, (ii) \uparrow ACTH-driven steroid production. Two forms (of six) are associated with mineralocorticoid excess and \therefore \uparrow BP:

- 11 β -hydroxylase (CYP11B1) deficiency, presenting in childhood; ♀ are virilized, and ♂ are sexually precocious.
- 17 α -hydroxylase (CYP17) deficiency. Extremely rare. Presents with \uparrow BP, \downarrow K⁺, and hypogonadism—often at puberty.

Secondary hyperaldosteronism

- Occurs when aldosterone hypersecretion results from \uparrow circulating renin levels—often in response to renal hypoperfusion.
- \uparrow renin \rightarrow \uparrow circulating A2, \uparrow peripheral resistance, and \uparrow BP (often severe).
- Associated 2° hyperaldosteronism \rightarrow \uparrow tubular Na⁺ reabsorption (\therefore \downarrow K⁺).
- Causes include:
 - Renal artery stenosis.
 - Renal infarction, e.g. atheroemboli.
 - Cirrhosis (vasodilatation \rightarrow \downarrow effective circulating volume).
 - CCF (falling CO \rightarrow \downarrow effective circulating volume).
 - Nephrotic syndrome.
 - Renal trauma (so-called ‘Page kidney’) (📖 p. 84).
 - Renin-secreting tumours (see Box 6.3).

Box 6.3 Renin-secreting tumours

- Very rare.
- Renin-secreting tumour of the juxtaglomerular cells → angiotensin-induced ↑ BP.
- Presents with severe ↑ BP, ↓ K⁺ (↑ urinary K⁺ excretion), ↑ renin, ↑ angiotensin II, and ↑ aldosterone.
- Diagnosis: MRA, angiography (tumour blush).
- Treatment: ACE-I and ARBs effectively ↓ BP.
- Surgery may be curative.

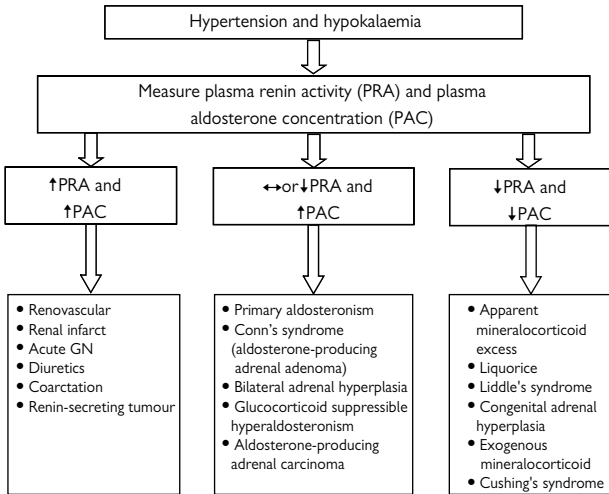


Fig. 6.5 Diagnostic algorithm for hyperaldosteronism.

Other 'hyperaldosteronism' syndromes

Other mineralocorticoids can cause a clinical syndrome very similar to that seen with \uparrow aldosterone—with \uparrow BP, \downarrow K^+ , and alkalosis. Crucially, both renin and aldosterone are suppressed.

- Causes include:
 - Apparent mineralocorticoid excess.
 - Congenital adrenal hyperplasia.
 - Liquorice ingestion.
 - Ectopic ACTH secretion.
 - Exogenous mineralocorticoids, e.g. fludrocortisone.

Apparent mineralocorticoid excess

<1% hypertensives. Autosomal recessive, presenting in childhood. Inactivating mutation in 11β -hydroxysteroid dehydrogenase 2 (11β HSD2). The mineralocorticoid receptor (which has an equal affinity for cortisol and aldosterone) is protected from ongoing cortisol stimulation by 11β HSD2, which metabolizes cortisol \rightarrow cortisone (relatively inactive). As cortisol is present at 100-fold concentrations, compared to aldosterone, absence/inhibition of this enzyme allows cortisol to flood the receptor \rightarrow chronic activation.

Diagnosis

\uparrow ratio of urinary tetrahydrocortisol (THF + 5α THF) (metabolite of cortisol) to tetrahydrocortisone (THE) (metabolite of cortisone).

Management

Block the mineralocorticoid receptor (spironolactone) or suppress ACTH secretion (dexamethasone suppresses endogenous cortisol synthesis but does not activate the mineralocorticoid receptor).

Liquorice contains glycyrrhizic acid, which can bind the 11β HSD2 enzyme, creating a state of apparent mineralocorticoid excess. Most commercial liquorice preparations in the UK do not contain large amounts, but continental or 'traditional' preparations are stronger (and often are combined with salt!). Also look out for it in herbal preparations.

'Pseudoaldosteronism'

Caused by abnormalities of renal tubular transport, rather than elevated renin or aldosterone. The electrolyte abnormalities mimic those seen with \uparrow aldosterone, hence the name (📖 p. 800). Causes include:

- Liddle's syndrome.
- Bartter's syndrome (normotensive).
- Gitelman's syndrome (normotensive).

Other causes of secondary hypertension

Cushing's syndrome

Prevalence in hypertensive populations estimated at 0.5–1%. ↑ BP is very common, affecting ~80%. Look for typical phenotype, and exclude exogenous glucocorticoids. 24h urinary cortisol excretion is a reliable diagnostic test (>110nmol/day is highly suggestive). Diagnosis confirmed by a 2-day low-dose dexamethasone suppression test (0.5mg every 6h for eight doses; a cortisol drawn 4–6h after the last dose should be <140nmol/L) or an overnight suppression test (1mg at 23.00; cortisol should suppress to <50nmol/L). Measurement of serum ACTH concentrations, a long dexamethasone suppression test ± corticotrophin-releasing hormone (CRH) stimulation test and adrenal/pituitary imaging will help to distinguish different forms of the syndrome (Cushing's disease most common: pituitary overproduction of ACTH).

Phaeochromocytoma

Adenoma (rarely carcinoma) of adrenal medulla → oversecretion of catecholamines (adrenaline → ↑ HR and contractility; noradrenaline → ↑ SVR). Can also arise in extra-adrenal chromaffin tissue (e.g. para-aortic ganglia). Very rare (<0.1% hypertensives). Consider if:

- Severe sustained and/or paroxysmal ↑ BP refractory to therapy.
- Large postural drop.
- ↑ BP + symptoms of catecholamine excess (headache, palpitations, sweating, angina, anxiety, etc.)
- ↑ BP triggered by β-blockade (2° to unopposed α stimulation. Avoid if suspected).
- Previous phaeochromocytoma (risk of recurrence).

Associated with multiple endocrine neoplasia (MEN) 2A or 2B, von Hippel–Lindau disease, von Recklinghausen's neurofibromatosis.

Best tested during, or immediately after, episodes. The sensitivity and specificity of various screening tests are shown in Table 6.7. Confirm biochemically before imaging, usually 24h urine catecholamines × 3 (acidified container). CT/MRI identifies most tumours. MIBG scanning localizes tumours or multiple tumours/metastases (~10% malignant). Treatment: α- and β-blockade prior to surgery.

Table 6.7 Sensitivity and specificity of screening tests for phaeochromocytoma

	Sensitivity (%)	Specificity (%)
Plasma metanephrines	99	89
Plasma catecholamines	85	80
Urinary catecholamines	83	88
Urinary metanephrines	76	94
Urinary vanillylmandelic acid	63	94

Reproduced with permission from Pacak K (2001). Recent advances in genetics, diagnosis, localisation and treatment of phaeochromocytoma. *Ann Internal Medicine*, 134, 315–29.

Coarctation of the aorta

A rare cause of 2° ↑ BP in children and young adults. ♂ > ♀. Represents <1% of congenital heart disease. Medial and neointimal thickening causes a shelf-like structure to extend into the aortic lumen just distal to the left subclavian artery. Often asymptomatic, may be diagnosed after CV examination; midsystolic murmur, radiofemoral delay, ↑ BP (arms > legs), or CXR (aortic '3 sign' from pre- and post-stenotic dilatation and posterior rib notching). If undetected in childhood, presents with cardiac failure in middle age and with a worse prognosis. *Diagnosis:* CT, MRA, or aortography.

Treatment: surgical. BP correction is age-dependent (>90% in childhood).

Drug-induced hypertension

See  p. 474.

Obstructive sleep apnoea (OSA)

The number of diagnosed and treated patients with OSA is rising rapidly. ↑ BP is commonly associated. Often treatment-resistant and associated with a lack of nocturnal dipping on ABPM. Assess for daytime somnolence (see Box 6.4).

Rx: treatment of the OSA improves BP. Weight reduction, alcohol avoidance, correction of airway obstruction, oral prosthetic devices, overnight non-invasive ventilation, CPAP, uvulopalatopharyngoplasty.

Box 6.4 Epworth sleepiness score

How likely are you to fall asleep in the following situations, in contrast to just feeling tired?

- 1 = slight chance of dozing
- 2 = moderate chance of dozing
- 3 = high chance of dozing

1–6 points: normal; 7–8 points: average; 9–24 points: abnormal (? pathological).

SITUATION

- Sitting and reading
- Watching TV
- Sitting inactive in public place
- As a passenger in a car for an hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking to someone
- Sitting quietly after lunch without alcohol
- In a car while stopped for a few minutes in traffic

Thyroid disease

- Hypothyroidism leads to ↑ DBP, ↓ cardiac output, ↓ renin levels, and narrow pulse pressure. It is salt-sensitive form of hypertension.
- Hyperthyroidism leads to ↑ SVR and stimulates ↑ renin synthesis and secretion, RAS activation, ↑ blood volume, and ↑ preload with a wide pulse pressure.

Drug management of hypertension

Introduction

- The 1° goal of treatment is to achieve a reduction in long-term CV morbidity and mortality risk.
- There is much debate on which medication to start when initiating therapy. In practice, most will require ≥ 2 drugs to attain target.
- There is increasing popularity in Europe and the USA for using combination therapy (\rightarrow synergistic effect + better compliance). UK physicians prescribe fewer combination pills than anywhere else in Europe.
- Compliance improved by once-a-day formulations and by clearly explaining the benefits and potential side effects of drug treatment.
- Although marked interindividual variation in drug responses reflects the heterogeneity of the pathogenesis of \uparrow BP, profiling patients, according to their hypertensive phenotype with a view to individualizing drug therapy, has proved difficult (exceptions: the elderly and ethnic groups).
- Drug withdrawal might be possible if other lifestyle interventions are undertaken and prove successful.
- The patient may benefit from joining local or national forums (e.g. <http://www.bpassoc.org.uk>).
- Once BP is adequately controlled, provide at least an annual review for monitoring.
- The major drug groups are equally well tolerated. They are prescribed in \sim equal amounts in primary care:
 - Thiazide diuretics (📖 p. 498).
 - ACE-I and ARBs (📖 p. 508–511).
 - Calcium channel blockers (CCBs) (📖 p. 506).
 - β -blockers (📖 p. 502). In the UK, β -blockers have been 'downgraded' and are not recommended as first-line therapy. However, it largely depends on which guideline you follow.
 - α -blockers are not recommended as first line (📖 p. 504).
- 🎯 The optimal cardiovascular outcome is most consistently linked with the level of BP control, rather than the class of drug used to achieve it.
- In general, the lower the BP, the better. Patients will be accruing benefit, even if they do not achieve target BP.
- There are now generic versions of key medications, which has reduced the cost of choosing many drugs.
- It is helpful to consider *compelling indications* and *compelling contraindications* (see Table 6.8). There are also other less definite pros and cons that will be assigned different importance by different prescribers.
- Timing of therapy may be important. If more than one agent is used, then having at least one dose at bedtime may improve circadian BP, CV outcomes, and daytime BP control (this has been demonstrated for both non-CKD and CKD populations in recent RCTs).

Aspirin and statins

Consider prescribing other drugs that modify CV risk.

- Aspirin 75mg od:
 - 1° prevention in hypertensives aged >50 and 10-year CV risk >20% and BP <150/90mmHg, with no contraindication.
 - 2° prevention of CV disease.
- Statin therapy:
 - 1° prevention in hypertensives with 10-year CV risk >20%.
 - 2° prevention in all with overt CV disease, irrespective of baseline total cholesterol or LDL. Targets: ↓ total cholesterol by 25% or LDL cholesterol by 30%, or achieve a total cholesterol of <4.0mmol/L or LDL cholesterol of <2.0mmol/L (whichever is the greatest reduction).

Table 6.8 Compelling and possible indications, contraindications, and cautions for the major classes of antihypertensive drugs

Class of drug	Compelling indications	Possible indications	Caution	Compelling contraindications
Alpha-blockers	Benign prostatic hypertrophy		Postural hypotension, heart failure ^a	Urinary incontinence
ACE inhibitors	Heart failure, LV dysfunction, post-MI or established CHD, type I diabetic nephropathy, 2 ^o stroke prevention ^c	Chronic renal disease, ^b type II diabetic nephropathy, proteinuric renal disease	Renal impairment, ^b PVC ^c	Pregnancy, renovascular disease ^d
ARBs	ACE inhibitor intolerance, type II diabetic nephropathy, hypertension with LVH, heart failure in ACE-intolerant patients, post-MI	LV dysfunction post-MI, intolerance of other antihypertensive drugs, proteinuric renal disease, chronic renal disease, heart failure ^c	Renal impairment, ^b PVD ^c	Pregnancy, renovascular disease ^d
Beta-blockers	MI, angina	Heart failure	Heart failure, ^c PVD, diabetes (except with CHD)	Asthma/possibly COPD, heart block
CCBs (dihydropyridine)	Elderly, ISH	Elderly, angina	–	–
CCBs (rate-limiting)	Angina	MI	Combination with beta-blockade	Heart block, heart failure
Thiazide/thiazide-like diuretics	Elderly, ISH, heart failure, 2 ^o stroke prevention			Gout ^f

COPD, chronic obstructive pulmonary disease; ISH, isolated systolic hypertension; PVD, peripheral vascular disease.

^a HF when used as monotherapy.

^b ACE inhibitors or ARBs may be beneficial in chronic renal failure but should only be used with caution, close supervision, and specialist advice when there is established and significant renal impairment.

^c Caution with ACE inhibitors and ARBs in peripheral vascular disease because of association with renovascular disease.

^d ACE inhibitors and ARBs are sometimes used in patients with renovascular disease under specialist supervision.

^e Beta-blockers are increasingly used to treat stable heart failure. However, beta-blockers may worsen heart failure.

^f Thiazide/thiazide-like diuretics may sometimes be necessary to control BP in people with a history of gout, ideally used in combination with allopurinol.

(From BHS guidelines. Used with permission.)

Guidelines for drug treatment

Algorithms

Guidelines have become increasingly didactic, as previous less specific recommendations generally proved ineffective.

The British Hypertensive Society and NICE

Two key UK advisory bodies published updated guidelines in 2011 on the treatment of hypertension (see Fig. 6.6). In the 2006 guidelines, β -blockers were downgraded in response to evidence suggesting they may be less effective at \downarrow major CV events (particularly stroke) than other drug classes and that they have a higher diabetes risk than ACE-I or CCBs (particularly in patients also taking a thiazide diuretic (📖 p. 502)). In this recent update, there has been a change in the priority of medications in people >55 years, with CCB as the first-line choice, based on event reduction and cost effectiveness. Thiazide-like diuretics (e.g. indapamide) are suggested in those with heart failure or very elderly who are intolerant of a CCB.

β -blockers can still be used as possible first-line therapy in ♀ of child-bearing potential and patients with evidence of \uparrow sympathetic drive.

Renin profiling demonstrates that younger people (<55 years) and Caucasians have higher renin levels, reflecting an active RAS, relative to elderly and black patients. Since ACE-I and ARBs act through RAS suppression, they are recommended as initial therapy in younger Caucasian patients.

Recommendations (see algorithm in Fig. 6.6)

- Step 1:
 - People aged <55 : initial therapy with an ACE-I/low-cost ARB.
 - People aged >55 : initial therapy with a CCB.
 - Black patients (any age): CCB (does not include mixed race, subcontinental Indian, or Chinese patients).
- Step 2:
 - Add ACE-I (or low-cost ARB) to CCB (or vice versa).
- Step 3:
 - Before considering step 3 treatment, ensure step 2 treatment is at optimal, or best tolerated, dose.

Compelling indications/contraindications should be taken into account (📖 p. 486).

Recommendations in other guidelines

The ESH-ESC guideline advocates the initiation of a drug combination in high-risk patients or in those with a significantly elevated presenting BP. It is thought that JNC 8 will take a similar view. In these circumstances, combined therapy should offer a greater potential for achieving target BP reduction and with fewer side effects than when maximizing the dose of a single agent (see Fig. 6.7).

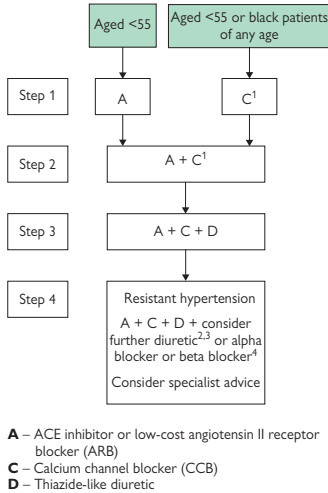
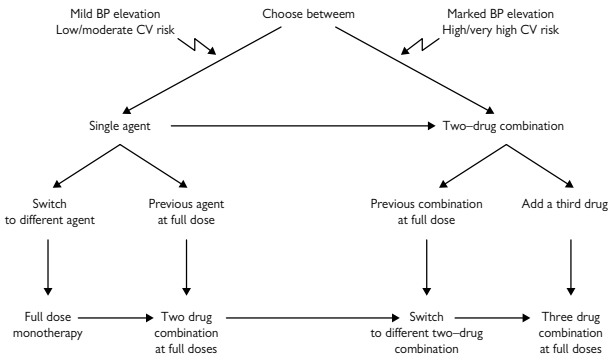


Fig. 6.6 2011 BHS/NICE recommendations for the drug treatment of hypertension. Used with kind permission of NICE.¹ A CCB is preferred, but consider a thiazide-like diuretic, if not tolerated, oedema, evidence/high risk of heart failure.² Consider a low dose of spironolactone or higher doses of a thiazide-like diuretic.³ At the time of publication (August 2011), spironolactone did not have a UK marketing authorization for this indication. Informed consent should be obtained and documented.⁴ Consider an α - or β -blocker if further diuretic therapy is not tolerated or is contraindicated or ineffective.



BP = blood pressure; CV = cardiovascular.

Fig. 6.7 Monotherapy vs. drug combination strategies to achieve target BP. Moving from a less intensive to a more intensive therapeutic strategy should be done whenever BP target is not achieved. Reproduced from 2013 ESH/ESC Guidelines for the management of arterial hypertension, *Eur. Heart. Jour.* 34: 28, 2159–2219 (2013), with permission of Oxford University Press.

BP treatment: special situations

Hypertension in black patients

The prevalence of \uparrow BP and related complications, such as CHD, stroke and renal disease, is higher in African Americans than other ethnic groups. This holds true in the UK, with mortality data for England and Wales showing mortality $3.5 \times$ the national average. British Asians have a mortality rate $1.5 \times$ the national average.

There is evidence of differential BP-lowering efficacy of particular drugs within ethnic groups, although the variability is greater within the groups than between them. The recommendation of CCB in this group is based on greater treatment effects, compared to ACE-I/ARB. If not tolerated, diuretic therapy is useful, as there is a higher prevalence of salt-sensitive \uparrow BP and increased salt and water retention likely to contribute to the increased \uparrow BP. Black patients, in general, have a lower renin, and so agents (ACE-I, ARB, and β -blockers) that suppress renin production may not be as effective, especially when used as monotherapy. The International Society of Hypertension in black people (\int <http://www.ishib.org>) has made recommendations for treatment and favour the initiation of combination therapy in individuals with more significant hypertension.

Hypertension in the elderly

CHD and stroke remain the major killers in those aged >65 , with BP the commonest treatable risk factor.

SBP increases with age. DBP increases to age 60, plateaus, and then falls. This leads to an age-related increase in pulse pressure and isolated SBP.

BP variability also increases \therefore more measurements are desirable prior to treatment. Using a relatively conservative definition of \uparrow BP ($\geq 160/95$ mmHg), it is estimated that $>15\%$ of the 12 million people aged >60 in the UK are hypertensive ($>70\%$ aged ≥ 80). \uparrow BP in the elderly is \therefore a major public health issue.

Clinical trials have shown that older people benefit just as much, if not more, from intervention as younger patients. A study of those ≥ 80 years (Hypertension in the Very Elderly (HYVET), with target BP 150/80 mmHg, showed overwhelming CV benefits from treatment.

\triangle This needs to be balanced against the risk of orthostatic hypertension (\rightarrow falls \rightarrow fractures). You may need to titrate treatment to the standing BP value, and DBP should not be reduced to <65 mmHg.

Low renin hypertension is the norm, so begin treatment with a thiazide or CCB. For second line, ACE-I/ARBs are demonstrably more effective than β -blockers.

Other lifestyle interventions still apply.

Hypertension in diabetes mellitus

(See \int p. 612.)

Hypertension in CKD

(See \int pp. 203–4.)

Hypertension in pregnancy

(See \int p. 846.)

Oral contraceptives, HRT, and BP

Oral contraceptives

- The combined oral contraceptive (COC) modestly ↑ BP in a minority of women (~1%). Occasionally, elevations may be severe. The rise in BP may not become apparent for several months, or even years, after COC introduction. The mechanism(s) of ↑ BP remain uncertain, and it has proved difficult to identify women at particular risk. COC use is also associated with increased stroke and MI risk.
- BP should be measured prior to COC use and at least every 6 months thereafter.
- Progestogen-only pills have not been associated with ↑ BP and are recommended for women with both COC-induced ↑ BP and pre-existing ↑ BP. In those women wishing to remain on the COC, antihypertensive medication should be given early consideration.
- For older women (aged >35) with higher CV risk (e.g. smokers), non-hormonal forms of contraception are preferable.

Hormone replacement therapy (HRT)

- HRT use is not associated with ↑ BP, and its use is not contraindicated in pre-existing hypertensives.
- Several large randomized trials have established that the CV protection afforded by HRT has been overplayed previously and should not be used as the motivation for their prescription.

Clinical trials in hypertension

The benefits of BP lowering are supported by one of the most authoritative evidence bases in clinical medicine. The foundation of this evidence base is the prospective randomized clinical trial.


Trial designs

- Duration rarely >5 years.
- Endpoints:
 - All-cause mortality.
 - Cause specific morbidity and mortality (usually CHD \pm stroke; more recently, CCF).
 - The 'composite 1^o endpoint' has emerged (i.e. a combination of events) because trials seldom have sufficient power to examine specific outcomes.
- Early trials compared active therapy with placebo, often among patients with severe \uparrow BP. Consequently, they had high power and could be conducted on a relatively small scale. Such trials became unethical, as the benefits of BP lowering became apparent.
- Modern 'head-to-head' trials tend to assess whether drug classes offer advantages over others (drug companies are desperate to demonstrate benefits 'beyond BP lowering').
- BP differences between treatment arms now tend to be minimal, \therefore \downarrow study power and necessitating \uparrow patient numbers.
- Contemporary treatment objectives also influence trial design—most patients now require multiple drugs to achieve target.
- The majority of patients at high CV risk will be receiving concomitant treatment with aspirin \pm a statin, further diminishing study power.
- Trials are hugely expensive.
- The data from clinical trials are often pooled for meta-analysis. This can provide increased power to examine drug-specific effects.
- See Table 6.9 for recent major trials.

Controversies

- Do specific classes of drugs offer benefits for CV disease prevention beyond the expected benefits of BP lowering?
 - There are marked drug-specific differences in their effect on CV structure and function as well as metabolic endpoints. The relevance of these effects on longer-term outcomes remains unknown.
 - Could certain classes of drugs be potentially harmful with regard to specific outcomes?
- With regard to study design, can treatment be solely measured in terms of CV events or is the real aim to prevent the evolution of a destructive disease process?
- Clinical trials rarely run for more than 5 years, while life expectancy in middle-aged hypertensives is 20–30 years.

Meta-analysis of BP-lowering trials: the BPLTTC

The Blood Pressure Lowering Treatment Trialists Collaborative (BPLTTC) was formed over 10 years ago and is an international alliance of the principal investigators of the largest trials of antihypertensive regimens. The project is based at the George Institute for International Health, a department of the University of Sydney ( <http://www.georgeinstitute.org/projects/blood-pressure-lowering-treatment-trialists-collaboration-bplttc>).

Its objective is to address questions concerning safety and outcome with specific drug classes. To achieve this, data from recent trials are pooled and subjected to meta-analysis (∴ providing the necessary statistical power to examine drug-specific effects).

Analysis includes differential drug effects in diabetes, between the sexes, and for the risk of major CV effects.

Analysis published in 2003,* incorporated data from 29 randomized controlled trials involving ~160,000 patients, with a mean duration of follow-up of 2.0–8.0 years (>70,000 patient years). The mean age was 65 years (52% ♂, 48% ♀).

Conclusions

- Treatment with any of the commonly used regimens ↓ the total risk of major CV events.
- Larger reductions in BP produce larger reductions in risk.
- ACE-I and diuretics ±β-blockers are more effective at preventing heart failure than regimens based on CCBs. Other differences in regimens 'beyond BP lowering' are less certain (including for stroke).

*Turubull F et al. (2003) *Lancet* 362: 1527–1535.

Table 6.9 Major trials in hypertension

Study acronym	Full name	Purpose
AASK	African American Study of Kidney Disease and Hypertension <i>JAMA</i> (2002); 288 : 2421–31	To determine whether lowering BP below recommended CV goals or particular agents slowed the progression of hypertensive renal disease (GFR 20–65mL/min). Patients received ramipril or amlodipine, with both compared to metoprolol.
ALLHAT	The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial <i>JAMA</i> (2002); 288 : 2981–97	The largest double-blind, randomized trial of hypertensive patients (n = 42,418). Hypothesis: fatal CHD and non-fatal MI would be lower in patients randomized to 'new' drugs (ACE-I and CCBs), as compared to those taking a thiazide.
ASCOT	The Anglo-Scandinavian Outcomes Trial <i>Lancet</i> (2005); 366 : 895–906	To compare the effects on CHD of a β -blocker \pm diuretic ('old-fashioned') vs a CCB \pm ACE-I ('modern') in patients with \uparrow BP. A second arm (<i>Lancet</i> (2003); 361 : 1149–58) compared atorvastatin with placebo for \uparrow lipids in hypertensive patients.
HOPE	Heart Outcomes Prevention Evaluation Study <i>NEJM</i> (2000); 342 :145–53	To compare ramipril to placebo for the prevention of CV events in patients with evidence of atherosclerotic CV disease taking standard therapy (~50% non-hypertensive).
HOT	Hypertension Optimal Treatment Study <i>Lancet</i> (1988); 351 : 1755–62	To assess the relationship of major CV events with three target DBPs (≤ 90 , ≤ 85 , or ≤ 80 mmHg). Also whether low dose aspirin, in addition to \downarrow BP therapy, \downarrow CV events.

Table 6.9 (Continued)

Result	Comment
Ramipril was superior in ↓ rate of decline. The amlodipine arm was stopped early because of worse outcomes.	Showed (surprisingly) that the level of BP attained did not affect the rate of decline of renal function.
A doxazosin arm was stopped early (median 3.3 years' follow-up) after interim data suggested an ↑ risk of combined CHD events. Main finding was that thiazides, CCBs, and ACE-I all provide similar protection from CHD. Thiazides appeared superior to CCBs and ACE-Is in preventing some adverse CV outcomes. CCBs not associated with excess CV deaths—a concern in previous studies.	General conclusion: thiazide diuretics are unsurpassed in preventing the major complications of ↑ BP. They are also well tolerated and inexpensive. They became the initial drug of choice in many guidelines. Criticisms: (i) designed in an era of monotherapy, (ii) many conclusions drawn on the basis of 2° endpoints, (iii) randomization deprived some patients with CCF of their diuretic, (iv) old-fashioned treatments were used for step-up (e.g. clonidine, reserpine).
Stopped early (median follow-up 5.4 years) because of superior results in the CCB/ACE-I arm for several 2° endpoints, including all-cause mortality and new-onset DM (1° endpoints were non-fatal MI and fatal CHD). Substudy with atorvastatin treatment resulted in a significant ↓ in the incidence of stroke.	Unique in its focus on combination therapy. Good press for CCBs after a lot of (unjustified) bad press. Reignited concerns regarding new-onset DM with diuretics + β-blocker. Led to early review of guidelines.
Ramipril decreased the combined relative risk of MI, stroke, or CV death by 22%.	Provided considerable impetus to the 'beyond BP lowering' hypothesis. There were important BP differences between the groups that probably accounted for the results (and led cynics to dub it the 'HYPE' trial).
Achieved BPs were 144/85, 141/83, and 140/81. The lowest incidence of CV events occurred at DBP 83mmHg. The benefit of progressive BP reduction was most marked in patients with DM. Aspirin caused a further significant ↓ in CV events (due entirely to a ↓ in MIs).	Defined a new optimal BP target (DBP 83mmHg), Further reductions did not ↓ CV events (i.e. did not support the 'J curve' hypothesis).

(Continued)

Table 6.9 (Continued)

Study acronym	Full name	Purpose
HYVET	Hypertension in the Very Elderly Trial <i>NEJM</i> (2008); 358 : 1887–98	To compare outcomes in 3,845 very elderly patients (aged ≥ 80) for placebo and a diuretic (indapamide) \pm ACE-I (perindopril).
INSIGHT	Intervention as a Goal in Hypertension Treatment <i>Lancet</i> (2000); 356 : 366–72	To compare CV events in high-risk hypertensive patients treated with nifedipine or amiloride + hydrochlorothiazide.
LIFE	Losartan Intervention for Endpoint Reduction in Hypertension <i>Lancet</i> (2002); 359 : 995–1003	To compare the long-term effects of losartan with atenolol on CV mortality and morbidity in hypertensive patients with LVH.
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial <i>NEJM</i> (2008); 358 : 1547–59	To investigate if dual therapy with ACE-I and ARB would offer additional cardiovascular and renal protection.
PROGRESS	Perindopril Protection against Recurrent Stroke Study <i>Lancet</i> (2001); 358 : 1033–40	To investigate whether perindopril alone, or in combination with indapamide, influenced stroke recurrence (~50% patients non-hypertensive).
STOP-2	The Swedish Trial in Old Patients with Hypertension-2 <i>Lancet</i> (1999); 354 : 1751–6	Patients aged 70–84 were assigned to either an ACE-I, a dihydropyridine CCB, or a 'conventional' therapy (β -blocker \pm diuretic).
SYST-EUR	Systolic Hypertension—Europe <i>Lancet</i> (1997); 354 : 757–64	To investigate whether antihypertensive treatment in elderly patients with isolated SBP could \downarrow CV events (primarily stroke). Participants received placebo or nitrendipine (with enalapril and hydrochlorothiazide added, if needed).
VALUE	Valsartan Antihypertensive Long-term Use Evaluation <i>Lancet</i> (2004); 363 : 2022–31	To investigate whether, for the same level of BP control, valsartan is more effective than amlodipine in \downarrow CV events.

Table 6.9 (Continued)

Result	Comment
Stopped early because of superior results in treatment arm for overall mortality and stroke. Final results showed additional ↓ in CV events as well as fatal and non-fatal heart failure.	Demonstrated effective treatment in age 80 years or older is beneficial, extending the patient group in whom prevention should be considered.
Both regimens resulted in equivalent BP control and outcomes.	The diuretic group needed significantly more add-on antihypertensive medications. Less new-onset DM was seen in the CCB group.
BP control was identical between the two groups. 1° events were fewer, the incidence of new-onset DM lower, and LVH regression greater for losartan than for the β-blocker.	One interpretation: the benefits of losartan extend beyond its BP-lowering effects. Another: apparent benefits of losartan actually due to negative effects of atenolol.
No differences in composite 1° outcome between ACE-I/ARB or combination but increased incidence of ESRD and renal impairment with combination therapy	Combination therapy was associated with more adverse events without increased benefit. This changed practice with respect to dual therapy.
Those on perindopril had a significant ↓ in recurrent stroke.	Often cited as evidence for the 'beyond BP lowering' hypothesis' for ACE-I, but the improved stroke outcome was probably driven by the more pronounced ↓ in BP in the combined perindopril + diuretic arm.
No difference in 1° endpoints among the three arms. ACE-I was associated with a lower risk of MI and CCF than those treated with a CCB.	Suggested newer and older drugs are generally equivalent.
Stopped early because of a 42% ↓ in stroke in the active arm. Cardiac events were also reduced but not significantly.	Also suggested CCBs may have a protective role in vascular dementia.
There were no differences between treatment groups in CV morbidity or mortality.	Good BP control in groups underscored the importance of achieving target BP, whatever the agent(s) used.

Diuretics 1

Introduction (see also p. 792)

Diuretics act by directly inhibiting the Na^+ transporters/channels mediating renal Na^+ reabsorption.

Efficacy depends on active secretion of the diuretic into the proximal nephron so that high concentrations are achieved at sites of action along the tubule. Renal insufficiency impairs proximal secretion \rightarrow relative diuretic resistance. Higher doses may still be effective but risk \uparrow toxicity.

The Na^+ and volume loss associated with diuretics is initially accompanied by the activation of vasoconstrictor mechanisms (including RAS). This is one of the reasons that diuretics and ACE-I/ARBs are a good combination (see Fig. 6.8).

Thiazide-type diuretic


Examples

- Thiazides: bendroflumethiazide, hydrochlorothiazide.
- Thiazide-like: chlortalidone, indapamide.

Mechanism

- Compete with both Na^+ and Cl^- to block the Na^+-Cl^- co-transporter in the DCT (normally responsible for 5–7% of filtered Na^+ reabsorption).
- \uparrow Na^+ delivery to distal nephron \rightarrow \uparrow Na^+/K^+ exchange and, indirectly, \uparrow H^+ excretion. Hypokalaemic metabolic alkalosis often results.
- Blocking the Na^+-Cl^- co-transporter \rightarrow \uparrow Ca^{2+} reabsorption. There are a number of potential mechanisms for this, but the relative contributions are unknown. It is most likely that chronic volume depletion leads to more proximal reabsorption. Thiazides \therefore have a role in prevention of renal stone disease and exert a protective effect in osteoporosis.
- Thiazide-like agents differ in several of their actions, including duration of action, channel-blocking activity, and inhibitory influence on carbonic anhydrase.

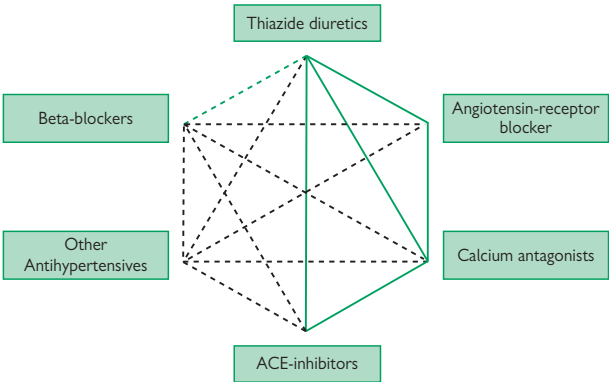
Role

- Effective, good evidence base, and inexpensive.
- Introduced in 1957 and still the first line in several guidelines.
- Evidence for bendroflumethiazide comes from studies with higher doses than those used in clinical practice now. For this reason, thiazide-like agents are now considered first choice over thiazides.
- \uparrow plasma half-life and sustained renal actions make them preferable to loop diuretics as antihypertensives (except in special situations,  p. 500).

Problems

- Hypokalaemia (dose-dependent).
- Impaired glucose tolerance (especially when used with a β -blocker).
- Small \uparrow in LDL cholesterol and triglycerides.
- Small \uparrow serum urate.

- Erectile dysfunction.
- Efficacy ↓ in those taking NSAIDs.
- Avoid if history of gout
- Avoid if taking lithium (↑ risk of lithium toxicity).



ACE = angiotensin-converting enzyme.

Fig. 6.8 Possible combinations of different classes of antihypertensive agents. The preferred combinations in hypertensive populations are represented as thick lines. The frames indicate agents proven to be beneficial in interventional studies. Reproduced from 2013 ESH/ESC Guidelines for the management of arterial hypertension, *Eur. Heart. Jour.* 34: 28, (2159–2219 (2013), with permission of Oxford University Press.

Diuretics 2

Loop diuretics

Examples

Furosemide, bumetanide.

Mechanism

- Block the type 2 $\text{Na}^+\text{K}^+2\text{Cl}^-$ (NKCC2) co-transporter in the thick ascending limb of the loop of Henle (usually responsible for 15–20% of filtered Na^+ reabsorption).
- Tubuloglomerular feedback would normally act to compensate by a \downarrow in GFR, but this is dependent on an identical (\therefore inhibited) co-transporter in the macula densa.
- Like thiazide diuretics, may cause hypokalaemic metabolic alkalosis.
- Initial Na^+ and volume loss may be compensated for by Na^+ retention during the latter part of the dosing interval, with amelioration of BP-lowering efficacy. So, more frequent dosing (at least twice daily) is necessary when used for treatment of hypertension.

Role

More potent natriuretics than thiazide-type diuretics but less effective BP-lowering agents. Their place in the management of \uparrow BP is limited to patients with CCF (with volume overload), renal impairment (with volume overload), and other oedematous states (e.g. cirrhosis).

Sequential nephron blockade

This is a strategy to overcome diuretic resistance in oedematous states that involves combination therapy with loop and thiazide (or thiazide-like) diuretics.

Potassium-sparing diuretics

Examples

Amiloride, triamterene.

Mechanism

- Block the epithelial Na^+ channel (ENaC) expressed in the late DCT and collecting duct.
 - ENaC plays a central role in the control of urinary Na^+ reabsorption, ECF volume homeostasis, and BP regulation.
 - Several hormones, including aldosterone, vasopressin, angiotensin II, insulin, and endothelin, regulate ENaC activity.
- K^+ absorption is tightly coupled with ENaC Na^+ absorption. Drugs blocking ENaC \therefore cause K^+ retention. Also has Mg^{2+} -sparing effects.

Role

Not first-line.

- Useful adjuncts to limit \downarrow K^+ and \downarrow Mg^{2+} with other diuretics. \downarrow K^+ may actually \uparrow BP and is associated with insulin resistance, DM, arrhythmias, and sudden death.

- Amiloride may be used to prevent \downarrow K^+ and \uparrow BP associated with excess glucocorticoids or mineralocorticoids (📖 p. 477) and in Liddle's syndrome (caused by activating mutation(s) in ENaC) (📖 p. 801).
- Can be useful in black patients where ENaC may play a more prominent role.
- Can be useful in patients with suspected hyperaldosteronism who are avoiding spironolactone/eplerenone before ARR testing.

Problems

⚠️ Hyperkalaemia! Cautions: renal impairment (especially in DM), combination with β -blockers, ACE-I/ARB, or spironolactone. The incidence of \uparrow K^+ when amiloride is co-prescribed with a thiazide or loop diuretic is very low.

Mineralocorticoid antagonists

Increasingly recommended as the fourth-line agent for resistant hypertension. Why is this?

- Aldosterone activates mineralocorticoid receptors in the heart, vasculature, and brain. Adverse consequences of activation include endothelial dysfunction, myocardial fibrosis, myocyte hypertrophy, vascular injury, and centrally mediated elevations in BP.
- RAS activation is associated with worse outcomes in patients with CCF and \uparrow BP.
- Although ACE-I and ARBs \downarrow aldosterone production, levels return toward normal with chronic use.
- Plasma aldosterone levels correlate with LVH in hypertensive patients.
- Patients with 1° hyperaldosteronism have worse CV outcomes.
- Pharmacological blockade of mineralocorticoid receptors \downarrow LVH and microalbuminuria in hypertensive patients.
- Experience in severe CCF is positive, with a \downarrow in mortality (RALES study).
- Spironolactone has long been used in the treatment of conditions associated with 2° hyperaldosteronism and volume expansion, such as cirrhotic ascites.

Spironolactone and eplerenone are the mineralocorticoid receptor antagonists in clinical use.

- Spironolactone is recommended as first line on efficacy and cost grounds. Highly effective. It can be used in combination with thiazide-like diuretics. Not actually licensed for use in hypertension in the UK (licence withdrawn in the 1980s due to concerns re malignancy in rodents. This has not been borne out in humans, but patients should be informed of the off-licence use).
- Eplerenone is a selective mineralocorticoid receptor with 20 \times affinity for mineralocorticoid receptor but just 75% potency of spironolactone. However, less affinity for androgen and progesterone receptors \rightarrow fewer SE.

Adverse effects: gynaecomastia (common), GI upset, impotence, \uparrow K^+ (⚠️ caution with ACE-I and ARB, especially if renal impairment).

β -blockers

Competitive inhibitors of catecholamines at β -adrenergic receptors. Many are available, with marked interdrug differences in pharmacodynamic and pharmacokinetic properties. In general, these characteristics influence clearance and side effect profile, rather than efficacy.

Examples

See Table 6.10.

Mechanism

Remains a matter of debate. Potentially:

- ↓ cardiac output.
- ↓ renin release.
- ↓ plasma volume.
- ↓ vasomotor tone.
- ↓ peripheral vascular resistance.
- Improved vascular compliance.
- Resetting of baroreceptor levels.
- Effects on prejunctional β receptors: ↓ noradrenaline release.
- ↓ pressor response to catecholamines with exercise and stress.
- Direct CNS effect.

Role

Downgraded in BHS/NICE in the UK and not first choice in JNC-7 although still useful if concomitant angina, post-MI (↓ mortality risk), arrhythmias, or hyperdynamic circulation. Consider in younger people and if resistant ↑ BP. Carvedilol, metoprolol, and bisoprolol have been shown to ↓ morbidity and mortality in patients with stable CCF. Labetalol is useful in pregnancy (📖 p. 849) and for parenteral treatment (📖 p. 522).

Problems

- Avoid in marked bradycardia, AV node disease.
- Avoid abrupt withdrawal, as rebound tachycardia can cause myocardial ischaemia in susceptible individuals.
- 🗣️ Many patients with obstructive airways disease have compelling indications for β -blocker therapy (IHD/CCF/arrhythmias). β_1 selective agents (atenolol or metoprolol) appear to be safe and may actually reduce exacerbations and mortality.
- Can cause lethargy, impaired concentration and memory, vivid dreams, hallucinations, depression (CNS effects may be more prominent with lipid-soluble agents), deterioration in peripheral vascular disease (nebivolol has some peripheral vasodilating properties and may well be tolerated in patients with claudication), and Raynaud's symptoms.
- Metabolic effects:
 - ↓ HDL cholesterol and ↑ triglycerides.
 - ↑ likelihood of new-onset DM, particularly when combined with a thiazide (combination leads to ~1 new case of DM for every 250 patients treated/year.) Avoid this combination if high risk: strong FH of T2DM, impaired glucose tolerance (FPG ≥ 6.5 mmol/L), clinically obese (BMI >30), or of South Asian or Afro-Caribbean origin.

- Worsen glycaemic control and hypoglycaemic awareness in T1DM (worse with non-selective agents).
- Combined with diltiazem or verapamil, may cause slowing of SA node ± negative inotropic effect.

Table 6.10 Examples of β-blockers

	β ₁ -selectivity ^a	Intrinsic sympathomimetic activity ^b	Membrane-stabilizing activity ^c	α-blocking activity ^d	Major route of elimination ^e
Acebutolol ¹	+	+	+		Renal
Atenolol ¹	++				Renal
Bisoprolol	++				Both
Carvedilol			++	+	Hepatic
Celiprolol		+		+	Both
Labetalol				++	Hepatic
Metoprolol ¹	++				Hepatic
Nadolol ¹					Renal
Nebivolol	+			+	Renal
Oxprenolol ¹					Hepatic
Pindolol ¹		++	+		Both
Propranolol			++		Hepatic
Sotalol ²			†	+	Renal
Timolol ¹					Hepatic

¹ Combination tablet with thiazide diuretic available. Atenolol also available combined with CCB.

² Δ Sotalol is not licensed for use in hypertension. † Sotalol has class III antiarrhythmic properties and can prolong the QT interval.

β-blockers differ in terms of β₁ selectivity, intrinsic sympathomimetic activity (ISA), membrane-stabilizing activity (MSA), α-adrenergic blocking ability, and pharmacokinetic properties.

^a β₁ selectivity: these agents have less effect on β₂ receptors and are, therefore, relatively cardioselective. Applies at lower doses only. Theoretically, an advantage in patients with obstructive airways disease but should still be regarded as a contraindication. May not block arteriolar β₂ receptors, which may be an advantage in T1DM with hypoglycaemia.

^b Intrinsic sympathomimetic activity (ISA): partial agonist activity at β₁ receptors, β₂ receptors, or both. Identified as slight cardiac stimulation, inhibited by propranolol. Cause less bradycardia and AV node slowing, possibly less negatively inotropic, less effect on peripheral vascular resistance. Apparent better lipid profile. Unclear if represents an overall advantage (or disadvantage).

^c MSA: these agents have a quinidine or local anaesthetic-like effect on the cardiac action potential. Usually seen above therapeutic levels and ∴ apparent in overdose.

^d α-blocking activity: antagonistic properties at both α- and β-adrenergic receptors. Causes a reduction in peripheral and coronary vascular resistance. The benefit of carvedilol in heart failure is not dependent on this property.

^e Water-soluble agents are predominantly excreted via the kidney and have a longer half-life. Δ Dose reduction is often necessary if ↓ GFR. Lipid-soluble agents mainly undergo hepatic excretion. Usually shorter acting (requiring bd or tds dosing) and cause more CNS SE (cross the blood-brain barrier).

α -blockers

α adrenoreceptors participate in the regulation of vascular tone by the sympathetic nervous system (SNS) and play a role in the genesis of \uparrow BP and other CV disorders.



Examples

- Selective α_1 antagonists: doxazosin, prazosin, terazosin, indoramin.
 - The bioavailability of modified-release (MR) formulations of doxazosin is \sim 50% of standard release, so doses need to be adjusted when moving between preparations.
- Unselective α_1 and α_2 antagonists: phentolamine, phenoxybenzamine.

Mechanism

- α_1 receptors are post-synaptic. Noradrenaline (norepinephrine) \rightarrow \uparrow intracellular Ca^{2+} flux \rightarrow \uparrow smooth muscle contraction \rightarrow vasoconstriction. Selective α_1 blockade causes \downarrow SVR and BP, with little or no effect on heart rate or cardiac output. α -blockers are essentially vasodilators.
- α_2 receptors are presynaptic. Stimulation \rightarrow \downarrow noradrenaline release.
- Non- α_1 and α_2 selective agents were developed first.
- In normotensive patients with normal sympathetic tone and vascular resistance, α -blockers have minimal BP-lowering effect.

Role

- Antihypertensive effect only modest when used as single agents. Effects are additive with other antihypertensive classes.
- ALLHAT (see Box 6.5 and  p. 494) provided bad press for α -blockers.
- In light of this, not considered first (or even second) line.
- Favourable lipid effects (\downarrow total cholesterol, LDL, triglycerides; \uparrow HDL).
- Safe and effective in renal insufficiency.
- BP-lowering effect, independent of age race and gender.
- Non-selective α -blockers are useful in the management of phaeochromocytoma ( p. 482).

Problems

Prazosin has a short half-life, causing first dose (and postural) \downarrow BP—generally less of a problem with longer-acting agents. Dizziness can persist (even without demonstrable postural \downarrow BP). Caution with sildenafil, tadalafil, and vardenafil (\rightarrow rapid \downarrow BP). Stress incontinence aggravated in ♀ . Can cause fluid retention (\therefore good combined with a diuretic).

Box 6.5 α -blockers and ALLHAT (📖 p. 494)

The doxazosin limb was stopped early (3.3 years' follow-up, ~9,000 patients) because of a 25% \uparrow incidence of CV disease (mainly CCF; no difference in 1° endpoints—fatal and non-fatal MI), compared to the thiazide group. As a result, α -blockers have fallen in popularity with guideline authors and prescribers alike. However, (i) SBP was higher in the doxazosin arm; (ii) randomization deprived many patients with CCF of diuretics, β -blockers, or ACE-I, creating a disadvantage for the α -blocker group.

α -blockers remain a good component of multiple drug regimens for moderate to severe \uparrow BP and are particularly useful in σ^7 with concomitant prostatic disease. Avoid if coexisting CCF.

 α -blockers and bladder outflow symptoms (📖 p. 761)

- Lower urinary tract symptoms (LUTS) associated with BPH and obstruction are common in σ^7 aged >60 .
- Bladder emptying involves relaxation of α_1 receptor-mediated smooth muscle contraction in the bladder neck and prostate.
- α_1 receptors are integral to the bulbospinal pathways from brainstem \rightarrow lumbosacral cord, which inhibit reflex urination.
- α -blockers relieve the symptoms of outflow obstruction and reduce the need for surgery.
- Newer α -blockers, e.g. tamsulosin, are 'uroselective', acting on the α receptor subtypes α_{1a} and α_{1b} , within the bladder neck and prostate, with limited effect on systemic BP.
- α -blockers are effective, with $>60\%$ reporting improvement. Medical therapy is now common, and TURP rates have fallen.
- α -blockers are the best monotherapy for symptom relief of LUTS.
- In those with moderate to severe symptoms and demonstrable prostatic enlargement, combination therapy of an α -blocker and 5 α -reductase inhibitor (block conversion of testosterone \rightarrow dihydrotestosterone), e.g. finasteride, provides effective symptom relief and retards disease progression.

Calcium channel blockers

Examples

- Dihydropyridine (vasodilating) CCBs: nifedipine, amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nisoldipine.
- Non-dihydropyridine (cardiac active) CCBs: diltiazem, verapamil.

Mechanism

- Block voltage-dependent L-type Ca^{2+} channels \rightarrow \downarrow calcium entry into smooth muscle cells \rightarrow \downarrow smooth muscle contraction \rightarrow \downarrow vascular resistance \rightarrow arterial vasodilatation.
 - Dihydropyridines: more selective at Ca^{2+} channels in vascular smooth muscle cells \therefore more powerful vasodilators.
 - Non-dihydropyridines: block Ca^{2+} channels in cardiac myocytes and \downarrow cardiac output. Antiarrhythmic properties via AV node (verapamil $>$ negative inotrope and chronotrope effect than diltiazem).
- Other CCB effects: \downarrow aldosterone release, \downarrow growth and proliferation of vascular smooth muscle cells, anti-atherogenic in animal models.
- Moderately \uparrow Na^+ excretion via natriuresis. \downarrow BP effect is not augmented by dietary Na^+ restriction (unlike other classes).
- Undergo first pass metabolism to some degree. Most are short-acting \therefore require multiple dosing regimens or a slow-release delivery system.

Role

- Recommended with priority over diuretics in BHS/NICE guidelines.
- BP-lowering effect equivalent to most other drug classes, but variability in BP less so may have an advantage.
- Among CCBs, antihypertensive properties are \sim equivalent.
- Can be combined with all other classes (Δ avoid diltiazem or verapamil with β -blockers—cardiac effects are additive).
- Good choice in patients with concomitant angina.
- Effective in low renin \uparrow BP (i.e. black or elderly patients).
- Non-dihydropyridine CCBs can be effectively combined with dihydropyridine CCBs. This combination can be particularly useful in black patients with difficult BP.
- Do not worsen dyslipidaemias.
- \downarrow BP effect not blunted by NSAIDs.
- Nimodipine is used for the prevention of ischaemic deficits, following subarachnoid haemorrhage—not licensed for hypertension.

Problems

- Flushing, tachycardia, or headache; especially short-acting agents.
- Dose-dependent peripheral oedema with dihydropyridine CCBs. This is not due to fluid retention (\therefore diuretic unresponsive) but 2° to mismatched arteriolar and venous vasodilatation. In this situation, consider using a pill-cutter and 2.5mg amlodipine od.
- Gum hypertrophy occurs with dihydropyridine CCBs.
- Avoid in systolic LV impairment (esp. non-dihydropyridine).

- CCBs have many drug interactions—worth checking before prescribing.
- Grapefruit juice inhibits cytochrome P450 CYP3A and ↑ the bioavailability of several dihydropyridine CCBs.
- Several trials have suggested that CCBs are not as effective protection against hypertensive or diabetic renal disease as ACE-I or ARBs ∴ not first line in this situation.
- Verapamil use is often accompanied by constipation.

⚠ Early formulations of some dihydropyridines (e.g. capsular or sublingual nifedipine) had a rapid onset of action, with an unpredictable BP-lowering effect, accompanied by reflex sympathetic stimulation, tachycardia, and RAS activation. These agents have no place in the management of hypertension.

ACE inhibitors (ACE-I)

Examples

Most commonly used: captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril.

Ramipril and trandolapril are the only ACE-I with a half-life long enough to be suitable for once-daily dosing.

Mechanism

- Block conversion of angiotensin I \rightarrow \uparrow angiotensin II (A2) by angiotensin-converting enzyme (ACE). The resulting \downarrow in A2 \rightarrow vasodilatation and \downarrow BP.
- A2 has many actions potentially detrimental to the CV system (📖 p. 456).
- Alternative pathways of A2 production, e.g. chymases and other tissue proteases, are unaffected.
- In the short term, ACE-I reduce AII levels, but, with chronic treatment, they return to normal ('A2 escape'). Other mechanisms of BP lowering are \therefore thought to be active. Possibilities:
 - \uparrow bradykinin \rightarrow \uparrow NO \pm \uparrow PGI₂ (\rightarrow vasodilatation).
 - \uparrow angiotensin-(1-7), a peptide that is antagonistic to A2.
 - \downarrow sympathetic nervous system activity.
 - Direct effect on endothelial function and vascular remodelling.
- ACE-I can be subdivided, according to their affinity for tissue ACE. It is possible that lipophilic compounds with high tissue affinity (e.g. ramipril, quinapril, perindopril) exert greater influence on endothelial function and provide CV benefits independent of BP lowering 🌟.
- Increasing the dose of an ACE-I does not generally alter peak effect but extends duration of response. Many patients benefit from a second daily dose.

Role

- Comparable BP lowering to other classes (but no better).
- Cardioprotective and renoprotective \therefore good choice if: CCF, post-MI, DM, CKD (especially proteinuric), or LVH.
- Patients at high risk of CV disease may have improved survival when treated with ACE-I (independent of BP reduction 🌟).
- Synergistic effects when used in combination with diuretics (diuretics \rightarrow Na⁺ depletion \rightarrow RAS activation \rightarrow A2-dependent (and \therefore ACE-I-responsive) \uparrow BP. ACE-I also help to ameliorate diuretic-induced \uparrow K⁺).
- Also suitable for combination with β -blockers, α -blockers, and CCBs.
- Routine combination with an ARB is not recommended.
- Relatively ineffective as monotherapy in certain groups with low renin \uparrow BP, e.g. black patients, although response highly variable (\downarrow Na⁺ diet increases efficacy). Generally effective in the elderly.
- Documenting plasma renin activity or ACE gene polymorphisms to 'individualize' therapy is not useful—neither predicts response.
- Lack adverse metabolic effects.

Problems and practical considerations

- *Decline in renal function.* When glomerular filtration pressure is dependent on A2-driven efferent arteriolar tone (e.g. volume depletion, renal artery stenosis, CCF), then ACE inhibition may cause a precipitous decline in GFR.
- **⚠ Precautions:**
 - Ensure patient is volume-replete.
 - Check U&E and eGFR before commencing treatment and 5–7 days after. Expect (and allow) a rise in SCr. Stop ACE-I if change in Cr $\geq 30\%$ or \downarrow eGFR of $\geq 25\%$.
 - Ask those on diuretic therapy to take first dose before retiring to bed.
 - Seek specialist help if high index of suspicion of renovascular disease (📖 p. 586).
 - ► Counsel patients that they should avoid NSAIDs and temporarily stop taking their ACE-I in the event of an intercurrent illness, e.g. febrile illness, diarrhoea, vomiting. They should inform their doctor in this circumstance.
- *Hypotension.* Acute falls in BP with ACE-I occur when RAS is activated, e.g. overdiuresis, CCF, accelerated hypertension. Rare when therapy initiated in uncomplicated hypertensive patients (admission to hospital for ACE-I introduction was commonplace in the 1980s). Postural hypotension is actually comparatively uncommon. In elderly or frail, consider starting at night.
- *Hyperkalaemia.* Most common in those with renal impairment \pm other drugs causing \uparrow K⁺ (e.g. amiloride, spironolactone, β -blockers).
 - Patients who develop mild \uparrow K⁺ should not necessarily have their ACE-I stopped, particularly if there is a compelling indication. Dietary advice is usually sufficient to allow re-introduction. Many specialists will tolerate \uparrow K⁺ < 6.0 mmol/L.
- *Cough.* Common (5–40%, ♀ $>$ ♂) and generally resistant to all measures, except drug withdrawal (\uparrow bradykinin \pm other vasoactive peptides, e.g. substance P \rightarrow cough reflex activation).
- *Angioneurotic oedema.* Rare. Black patients $>$ Caucasians; also bradykinin-mediated and potentially fatal. Stop the ACE-I, and avoid for life.
- \downarrow *Erythropoietin secretion.* May cause or worsen anaemia.
- *Pregnancy.* Contraindicated.
- *Rash and altered taste.* Mainly captopril.

A2 receptor blockers (ARB)

Examples

Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan.

Mechanism

- There are two A2 receptor subtypes:
 - AT_1 mediates: (i) vasoconstrictor effects of A2 and (ii) A2-induced growth in the myocardium and arterial wall.
 - AT_2 function is less well understood. Expressed at high levels in fetal tissues, with ↓ expression after birth. Probably responsible for many of the proliferative effects of A2.
- ARB → inhibition of AT_1 → inhibition of vasoconstrictive action of A2 on smooth muscle.
- Two major differences between ACE-I and ARB:
 - ACE-I → ↓ activity of A2 at both AT_1 and AT_2 receptors. ARB only ↓ AT_1 activity, with no effect on AT_2 .
 - ACE is a kininase, so ACE-I lead to ↑ kinins. Kinins are responsible for some ACE-I side effects (esp. cough) but may also mediate some of their beneficial effects, including BP lowering and ↑ insulin sensitivity.
- A2 blockade leads to ↑ renin, ↑ angiotensin I, and ↑ A2, although this accumulation does not appear to overwhelm receptor blockade.

Roles

- Similar BP-lowering effect to ACE-I and other main classes.
- As with ACE-I, synergistic with diuretics.
- ARBs have similar benefits to ACE-I in conditions other than ↑ BP, such as CCF (Val-HeFT and CHARM studies) and post-MI (VALIANT).
- Several major trials (IDNT, IRMA-2, RENAAL) have demonstrated renoprotection with ARB in nephropathy associated with T2DM.

Problems

- Generally well tolerated, similar side effect profile to ACE-I.
- Less cough than ACE-I (as kinin-mediated).
- Angio-oedema has been reported. Cause not clear.
- Altered taste.
- Contraindicated in pregnancy.
- Concerns regarding increased cancer risk led to an FDA analysis, but no overall increase in cancer was found.

Practical points

- Not all ARBs are the same. Losartan and valsartan are relatively short-acting. Give twice daily if BP not controlled.
- Generic preparations mean that cost has reduced.
- Check salt intake if resistant to treatment.
- Some studies suggest increased insulin sensitivity but not conclusive.
- Losartan has a mild uricosuric effect, which may be beneficial in patients with gout.

Combined ACE-I and ARBs (see also p. 614)

Two drugs are not better than one

- Good theoretical rationale for using in combination:
 - ACE inhibitors do not completely block the formation of A2 (other tissue proteases are involved).
 - ARBs are selective for the AT₁ receptor, leaving AT₂ receptor exposed to ↑ A2.
 - With ACE-I, ↑ A2 → renin release, eventually returning A2 towards baseline (termed 'A2 escape').
- Combination therapy is effective in LV dysfunction (Val-HeFT and CHARM studies).
- Small studies (e.g. CALM) raised expectation. One key study (COOPERATE) was retracted after publication.
- ON-TARGET, a large RCT comparing the effects of telmisartan, ramipril, and their combination on CV mortality in high-risk patients found the combination was not associated with an improvement in key outcomes but increased the risk of renal failure.
- Current guidelines do not recommend the use of combination therapy for the treatment of hypertension.

Renin inhibitors

- Direct renin inhibition provides an additional means of antagonizing RAS.
- Aliskiren was the first commercially available example.
- Lowers BP to a similar degree to other agents.
- Anticipated that it might have a useful synergistic role in combination with ACE-I/ARB (as renin increases with long-term use of these agents).
- In the ALTITUDE study, 8,600 patients with T2DM and nephropathy were assigned to either aliskiren or placebo to take, in addition to their pre-existing ACE-I/ARB. The trial was stopped early, as there were no apparent CV or renal benefits, but there was a higher adverse event rate (↑ K⁺, ↓ BP, stroke).
- ⚠ MHRA/FDA now advise not to use aliskiren in combination with ACE-I and ARBs in patients with diabetes or renal impairment.
- They may still have a role in patients with high renin ↑ BP that is inadequately treated despite maximum therapy or multiple drug intolerances.
- Side effects: ↑ K⁺, ↓ BP, angio-oedema, GI symptoms, raised uric acid (→ gout, renal calculi).
- Do not use in pregnancy.
- Important interaction with ciclosporin (→ ↑ blood levels of aliskiren) ∴ avoid this combination.

Other antihypertensive agents

With the exception of methyl dopa and moxonidine, these drugs are rarely seen in the routine treatment of \uparrow BP in the UK. However, they are still widely used around the world—and generic formulations mean lower costs in many instances.

Centrally acting agents

Methyldopa

Metabolized to a methyl-noradrenaline, a false neurotransmitter that: (i) displaces noradrenaline from α adrenergic receptors, preventing smooth muscle contraction and (ii) stimulates adrenergic receptors in the central vasomotor centres, inhibiting sympathetic outflow. Large dose range (250mg–3g daily) and remains widely used to treat \uparrow BP in pregnancy (📖 p. 849). A concomitant diuretic is desirable in non-pregnant patients.

Problems: positive Coombs' test in 20% (though overt haemolytic anaemia rare), dry mouth, oedema, drowsiness, febrile illness, and depression. Avoid in liver disease.

Clonidine

Stimulates adrenergic receptors in the central vasomotor centres, inhibiting sympathetic outflow. Use now rare. Clonidine suppression test occasionally used in the diagnosis of pheochromocytoma (📖 p. 482), and it has also been used off-licence to assist smoking cessation and opiate withdrawal (orally or transdermal release), as it reduces the physiological manifestations of tobacco withdrawal.

Problems: dry mouth, sedation, depression. Associated with severe rebound \uparrow BP when stopped abruptly (may require treatment with parenteral α -blockers).

Moxonidine

A selective imidazole agonist that acts on central receptors to decrease sympathetic outflow. Can be a useful add-on therapy when other classes are insufficient or poorly tolerated. Can be used with caution and careful titration in renal insufficiency.

Problems: dry mouth, headache, fatigue, dizziness, sleepiness. Avoid abrupt withdrawal (if also on β -blockers, stop them first). Avoid if AV block, bradycardia, severe CCF (worse outcomes), and pregnancy.

Direct acting vascular smooth muscle relaxants

Hydralazine and minoxidil

\downarrow arteriolar resistance. The consequent \downarrow peripheral resistance and BP causes reflex sympathetic activation, with tachycardia and palpitations. This can be offset with a β -blocker.

Hydralazine (and nitrate) can be a useful adjunct in NYHA class 3–4 systolic heart failure.

Problems: flushing, headache, palpitations. Avoid in ischaemic heart disease. Cause Na^+ and water retention (especially minoxidil) \therefore give with a diuretic. Hydralazine can cause a lupus-like syndrome, particularly in slow acetylators. Minoxidil causes hirsutism. Hydralazine metabolites accumulate in renal impairment \therefore avoid (minoxidil is OK).

Antihypertensives on the horizon

Endothelin antagonists

The endothelins are a group of potent vasoconstrictor peptides produced in many different tissues. ET-1 is the predominant endothelin secreted by the endothelium where it acts in a paracrine fashion.

Several antagonists are under investigation, and it is hoped they will prove reno- and cardioprotective as well as antihypertensive. Darusentan, a marginally selective ET_A receptor antagonist, has been shown to reduce BP and proteinuria in early studies (e.g. DORADO). Bosentan is already licensed for use in pulmonary hypertension.

Vasopeptidase inhibitors (VPIs)

Simultaneously inhibit both ACE (preventing the conversion of AI → A2) and neutral endopeptidase. The latter is a membrane-bound metalloprotease involved in the enzymatic degradation of natriuretic peptides (ANP and BNP) and various other peptides, so inhibition will prolong their duration of action.

The combined effect of reduced A2 activity and increased natriuretic peptide activity is attractive. Early studies with VPIs showed a very favourable therapeutic effect. However, a significant incidence of potentially life-threatening angio-oedema ultimately led to failed FDA approval and stalled development.

Angiotensin receptor blockers with neutral endopeptidase inhibition (ARNi)

Currently being evaluated in preclinical and clinical studies. Preliminary results suggest increased BP reduction in comparison to ARB alone—and with no increase in angio-oedema.

Non-pharmacological strategies

Introduction

It is important not to forget (and to often revisit) dietary salt restriction, reduced alcohol intake, weight loss, and patient education.

There has also been growing recent interest in novel, often invasive, therapies, particularly in the management of resistant hypertension. These include:

Renal denervation with radiofrequency energy

- It has been known for years that interruption of the renal nerves can lead to a reduction in BP.
- However, surgical intervention to achieve this was associated with appreciable morbidity and mortality and was not selective for renal sympathetic nerves, resulting in more widespread sympathetic denervation.
- Endovascular (or catheter-based) renal nerve ablation has been studied in patients with resistant hypertension (patients on a mean of five drugs, including a diuretic) in a series of trials (including Simplicity HTN-1 and 2).
- Mean reduction in SBP of 28–32mmHg, compared to control.
- An endovascular catheter is placed in the femoral artery and guided to the kidneys. The sympathetic nerves are closely related to the renal arteries, and radiofrequency energy is used to disrupt them at several sites along the vessel.
- Most patients remain on some therapy, but benefits are sustained to 3 years.
- No longer-term outcomes yet available.
- ~15% treatment failure (possibly higher).
- Invasive, uncomfortable procedure. Day case or overnight stay.
- No evidence of new atherosclerotic lesions in the field of RF energy.
- Limited data in patients with CKD, but those available (CKD 3–4 with resistant ↑ BP) show a beneficial BP-lowering effect and favourable safety profile.
- Simplicity HTN-3 (USA-based) is currently recruiting. It incorporates 24h BP measurements and a sham procedure to allow testing for placebo response.

Device-guided respiration

- Portable electronic devices that promote slow and deep breathing (e.g. RESPeRATE®).
- Consist of a control box, a respiration sensor, and headphones (which provide feedback to the patient). The device analyses breathing patterns and creates audible tones for the patient to then synchronize their breathing to. The device gradually slows breathing to <10 breaths per minute.
- Marketed as non-pharmacological treatment for BP reduction but can be used as an adjunct to drug therapy.
- Published trials show a small, but significant, effect (↓ SBP 3.67mmHg and ↓ DBP 2.51mmHg), although they have been of short duration.
- Evidence of long-term benefit currently lacking.

Baroreceptor activation therapy (BAT)

- Electrical stimulation of the carotid sinus baroreflex system, using a surgically implanted device.
- Appears effective but limited outcome data.
- Procedure-related adverse events relatively common.

Resistant hypertension

Introduction

Variably defined but usually a failure to reach target BP despite multiple antihypertensive agents, including a diuretic. It is most commonly a consequence of poorly controlled SBP.

Although thought to be relatively common—up to 20–30% of study populations in clinical trials—the experience, when recruiting to these studies, has been that true resistant hypertension is actually less common if drug therapy is optimized and contributing factors are rectified.

In the UK, resistant hypertension is considered to be BP not controlled to target with maximal recommended and tolerated doses of an ACE-I/ARB + CCB + thiazide. The 2011 BHS/NICE guideline recommends that such patients are managed with a further diuretic (consider spironolactone), an α -blocker, or a β -blocker (and that a referral for specialist input is considered).

Although evidence for treatment strategies are generally limited, more robust guidance will hopefully emerge in the next few years; for example, the BHS PATHWAY 2 study has been designed to evaluate whether resistant hypertension is due to excess sodium retention and whether further diuretic is the most effective treatment. The study also hopes to determine whether plasma renin can be a useful guide to further treatment in this circumstance. At present, some clinicians measure renin concentrations in resistant patients, add a β -blocker or additional ACE/ARB if high and an α -blocker if normal, and change the diuretic (usually to spironolactone) if low. (See Fig. 6.9 for management algorithm.)

Characteristics of patients with resistant hypertension

- Obese.
- Elderly.
- Black patients.
- CKD.
- DM.
- High starting BP.

Checklist

- Is it really resistant BP? Does it meet the definition given earlier? Are you confident about compliance? Does the patient understand the condition, the benefits of treatment, and the role of each tablet?
- Revisit dietary salt restriction (aim to restrict 24h uNa⁺ to <100meq), alcohol consumption, and weight loss (diet and exercise).
- Exclude contributory drugs (e.g. NSAIDs, steroids, COC, ciclosporin, decongestants, ESAs).
- Reconsider secondary causes of \uparrow BP, especially renal disease, sleep apnoea, and primary hyperaldosteronism (📖 p. 474).

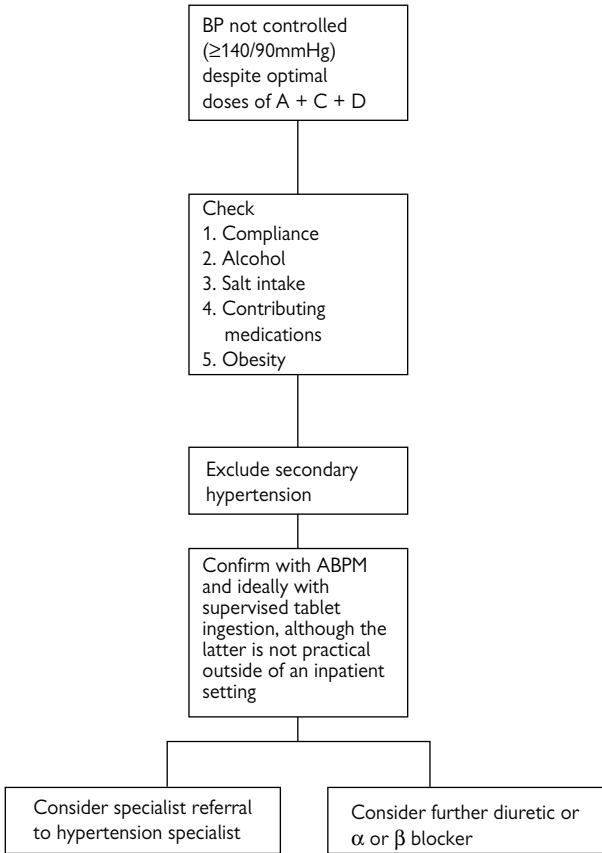


Fig. 6.9 Algorithm for the management of resistant hypertension.

Hypertensive urgencies and emergencies

Definitions

- ▶ Hypertensive crises are classified as *emergencies* or *urgencies*, based on the presence or absence of progressive target organ dysfunction.
 - *Emergencies*: severe ↑ BP complicated by evidence of acute or progressive organ dysfunction, such as cardiac ischaemia, encephalopathy, stroke, pulmonary oedema, or renal failure.
 - *Urgencies*: severe ↑ BP *without* evidence of acute or progressive target organ dysfunction.
- The term *malignant hypertension* was coined before antihypertensive therapy improved an appalling prognosis (1-year mortality ~90%). It is a syndrome of ↑ BP with progressive target organ damage and papilloedema. Pathologically, arteriolar fibrinoid necrosis is the characteristic lesion.
- *Accelerated hypertension* was applied to the scenario of retinal haemorrhages and exudates without papilloedema. The distinction from malignant hypertension is unhelpful, as both carry an identical prognosis.
- There is no threshold of BP above which malignant hypertension develops. DBP ranges from 100–180mmHg, SBP 150–290mmHg.
- ▶ Severity is not determined by BP alone—it is the clinical context and degree of target organ dysfunction.
- Affects <1% of the hypertensive population, but the hypertensive population is large. ♂[?]>♀.
- Essential hypertension accounts for ~2–30% of episodes in Caucasians but ~80% in black patients (▶ therefore, usually avoidable).
- Renal disease (intrinsic and renovascular) accounts for the majority of the rest. Other previously unrecognized forms of secondary ↑ BP may also be responsible.
- The duration of hypertension prior to the development of malignant phase may range from days to years.

Pathophysiology

Vascular autoregulation

Autoregulation describes the ability of organs to maintain their perfusion, regardless of BP. ↑ BP causes distal arteriolar vasoconstriction, protecting end-organs from hypertensive mechanical stress. Hypertensive emergencies are associated with a failure of this process, resulting in transmission of ↑ BP to the microvasculature where mechanical trauma → endothelial injury → ↑ vascular permeability → leakage → platelet and fibrin deposition → fibrinoid necrosis. Catecholamines and vasopressin release also contribute.

Endocrine and paracrine mediators, including RAS, are activated with ↑ A2, leading to further vasoconstriction and ischaemia. Volume depletion due to pressure natriuresis stimulates further renin release and worsens ↑ BP. A vicious cycle of vasoconstriction and worsening ↑ BP ensues.

Pathological changes

Vascular lesions are due to endothelial injury and consist of myointimal proliferation and fibrinoid necrosis, with subendothelial lipid deposition and hyaline thrombi. Vascular smooth muscle hypertrophy and collagen deposition contribute to medial thickening, which, with cellular intimal proliferation, results in the 'onion skin' appearance of small vessels, with luminal narrowing. Ischaemia or infarction of end-organs may occur. These changes are particularly well seen in the kidney, with proliferative endarteritis of the interlobular arteries, fibrinoid necrosis of the afferent arteriole, and glomerular ischaemia (\pm tubulointerstitial damage) (see Figs 6.10 and 6.11).

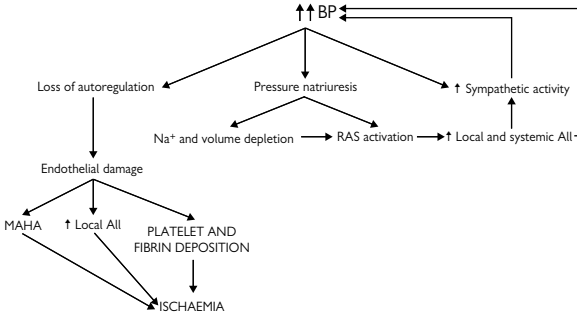


Fig. 6.10 The pathophysiology of malignant hypertension. Redrawn with permission from *Acute Renal Failure in Practice*, Imperial College Press. (MAHA: microangiopathic haemolytic anaemia.)

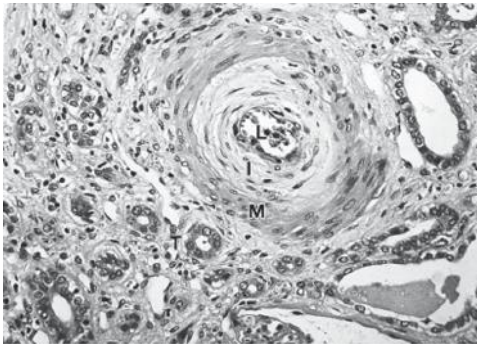


Fig. 6.11 Proliferative endarteritis of an interlobular artery in malignant hypertension. I, arterial intima showing gross proliferative change and 'onion skin' appearance; L, severely narrowed arterial lumen; M, arterial media; T, tubular atrophy and interstitial fibrosis. Reproduced with permission from Davison *AMA*, Cameron JS, Grunfeld J-P, et al. (eds) *Oxford Textbook of Clinical Nephrology*, 3rd edn. (2005) Oxford: Oxford University Press.

Assessing urgencies and emergencies

How does the BP compare to previous readings?

- 160/100 may be sufficiently high to cause acute TOD in a previously normotensive patient.
- A patient with long-standing hypertension may tolerate a higher BP without any evidence of acute TOD.

Clinical assessment

- ► Assess degree of target organ involvement.
- *Urgency* if ↑ BP without acute or progressive TOD.
- *Emergency* if ↑ BP with acute or progressive TOD.

Is there evidence of target organ damage?

Acute TOD

►► *Manage as an inpatient as an emergency:*

- Neurological symptoms: at risk for haemorrhagic or thrombotic stroke, encephalopathy (altered consciousness, fits, focal signs).
- LVF.
- Acute kidney injury failure (send U&E, dipstick urine).
- ⚠ Chest pain. Acute coronary syndrome → MI or aortic dissection. Perform ECG, and check pulses. If in doubt: CT aorta.
- Visual symptoms ± either grade III or IV hypertensive retinopathy.
- Pancreatitis due to haemorrhagic infarction (rare).

What medication has the patient been on until now?

- Continue current medication, adding in further treatment, as necessary.
- Check previous adherence to medication (recent non-compliance is very common in this situation). ⚠ Beware precipitating hypotension by restarting multiple antihypertensives in the previously non-adherent patient.
- ► Remember recreational drug use (cocaine, amphetamines).

Symptoms and signs

- *BP*: no pathognomonic values. Usually >220/140mmHg (range: DBP 100–180mmHg, SBP 150–290mmHg). Check BP in both arms; look for missing pulses, bruits, or an AAA.
- *Eyes*: visual disturbances (35–60%)—often present to ophthalmology.
- *Neurological*: headache (60%), dizziness (30%), neurological deficit, e.g. hemiparesis, cortical blindness (<10%). Posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leucoencephalopathy syndrome (RPLS), is increasingly recognized. PRES is characterized by headache, confusion, seizures, visual loss, and areas of cerebral oedema on MRI. The syndrome tends to resolve with treatment of BP, although visual defects may persist.
- *Renal*: AKI (30%).
- *Cardiovascular*: dyspnoea 2° to LVF (~10%), chest pain (~4%).

Hypertensive retinopathy

Grade 1: arterial narrowing (tortuosity, 'silver wiring' are subjective).

Grade 2: AV nicking.

Grade 3: haemorrhages and exudates.

Grade 4: papilloedema.

Investigations

- **Urinalysis:** proteinuria (can be nephrotic range—send uPCR, haematuria, cellular casts (red cell casts may indicate parenchymal renal disease)).
- **U&E:**
 - *Serum creatinine, eGFR:* acute (or acute-on-chronic) kidney injury.
 - *Potassium:* ↓ K⁺ (2° hyperaldosteronism → hypokalaemic alkalosis; renin and aldosterone are both raised in malignant hypertension), ↑ K⁺ (2° to AKI) also possible.
- **FBC:** microangiopathic haemolytic anaemia—↓ Hb, ↓ platelets, red cell fragments, ↓ haptoglobins, ↑ ESR.
- **ECG (± echocardiogram):** LVH, ischaemia, MI.
- **CT brain:** if ↓ GCS or neurological signs.
- **MRI brain:** PRES/RPLS.
- **Renal biopsy:** a diagnostic or prognostic renal biopsy may be necessary.
 - ⚠ Blood pressure must be controlled first (📖 p. 80).

Secondary hypertension?

Some conditions require specific management. Consider the list in Box 6.6.

Box 6.6 Causes of hypertensive emergencies

- Essential hypertension.
- Renal parenchymal disease:
 - Glomerulonephritis.
 - Tubulointerstitial disease.
- Systemic diseases:
 - Systemic sclerosis.
 - HUS/TTP.
 - SLE.
 - Antiphospholipid antibody syndrome.
 - Vasculitis.
- Renovascular disease:
 - Atheromatous.
 - Fibromuscular hyperplasia.
- Pre-eclampsia/eclampsia.
- Coarctation.
- Endocrine:
 - Conn's syndrome.
 - Pheochromocytoma.
 - Cushing's syndrome.
- Drugs:
 - Cocaine.
 - Amphetamines.
 - Ecstasy.
 - MAOI interactions.
 - Erythropoietin.
 - Ciclosporin.
 - Tacrolimus.
- Tumour-related:
 - Renal cell carcinoma.
 - Lymphoma.

Management of urgencies and emergencies

Hypertensive emergency

Patients with severely raised or rapid rise in BP, with severe grade 3–4 hypertensive retinal changes. Often have evidence of concurrent TOD.

► Treatment when acute, life-threatening organ damage

- Treat in a high dependency environment.
- Continuous BP monitoring.
- Volume depletion may be present—resuscitate with 0.9% NaCl.
- Initial aim of treatment is to ↓ DBP to ~110–115mmHg. Aim to achieve this in 2–6 hours.
- ⚠ A rapid fall may → clinical consequences with ↓ cerebral, spinal cord, and myocardial perfusion or acute kidney injury.
- Parenteral agents are often required.
- Options: see Table 6.11 for drugs used in emergencies.
 - Sodium nitroprusside. The parenteral drug of choice in many centres. Dose 0.25–1.5 micrograms/kg/min, with increase of 0.5 micrograms/kg/min every 5min until adequate response.
 - ⚠ Associated with cyanide toxicity (prevent by protecting drug from light; risk increased at >2 micrograms/kg/min and in renal failure).
 - Labetalol (combined α - and β -blocker) particularly logical in IHD and aortic dissection. 20mg IV initially over 1min, followed by infusion 0.5–2mg/min. Safe in pregnancy.
 - Glyceryl trinitrate (GTN) 2–10mg/h. Useful with symptomatic coronary artery disease or acute LVF. ⚠ Care if volume-depleted. Tachyphylaxis occurs after 24–48h.
- Once BP within target range, transfer to oral agent, and wean IV infusion over 4–8h.

► Treatment when no life-threatening organ damage

- May have features of malignant hypertension with TOD but not life-threatening.
- Aim ↓ diastolic BP to 110–115mmHg over 24–48h.
- Oral agents preferred.
- Low blood volume may manifest after treatment initiated (→ postural drop of >20mmHg suggests hypovolaemia in need of correction).
- Start with slow-release nifedipine, e.g. nifedipine retard/MR 10mg. Repeat the same dose at 2h intervals, with maintenance doses of 20mg 3× day. 1 Do not use capsules or LA preparations.
- Amlodipine is long-acting—it will reduce BP over days ∴ not suitable in urgent situations. Consider starting concurrently with nifedipine MR and then weaning off nifedipine after ~72 hours.
- Second-line therapy is a β -blocker. Particularly helpful with coexisting IHD or resting tachycardia.
- ⚠ ACE-I should be used with caution (→ abrupt ↓ BP, potential hypoperfusion/AKI).
- Diuretics should also be used with caution unless clear fluid overload.

Hypertensive urgency

► Severe uncontrolled hypertension (>130 DBP) with no evidence of acute TOD

- If no acute TOD, does not necessarily require hospital admission.
- Repeat BP after 1–2h to confirm. If DBP still >130mmHg → treat.
- Use the same oral agents as in emergency. Start with a single agent. Aim for diastolic BP 100–110mmHg at first. Recheck BP after 24–48h.
- If still uncontrolled, increase dose, or add in second agent.

Recheck after every 2–3 days until BP at desired level. Treat according to BHS guidelines (📖 p. 488):

- Elderly or black patients → CCB.
- Then A + C.
- Then A + C + D.
- It is appropriate to start an ACE-I (e.g. ramipril) at full dose if normal renal function and unlikely significant RAS.

Prognosis

Without effective treatment: 1-year mortality ~90%, with effective treatment <10%. Many patients who develop renal insufficiency will recover renal function, even if initially dialysis-dependent, although this may take several months.

Table 6.11 Drugs used in hypertensive emergencies

Drug	Route and dose	Comment
Calcium channel blockers	Oral nifedipine MR 10mg 12h; max 40mg 12h (consider concomitant amlodipine 5–10mg; (see text on 📖 p. 522))	NEVER use rapid release formulations Nimodipine used post-subarachnoid haemorrhage
β-blockers	Oral Useful 2nd line (e.g. atenolol 50mg daily)	SE: bronchospasm
ACE inhibitors	Oral Start with low dose (e.g. ramipril 2.5mg or captopril 6.25mg), and titrate up	May cause rapid fall in BP Avoid in AKI Treatment of choice in scleroderma crisis
Diuretics	Oral/IV furosemide 40–120mg 12h	Beware volume depletion
α-blockers	Oral doxazosin MR 4mg 12h (up to 8mg 12h)	Useful because of titration range

(Continued)

Table 6.11 (Continued)

Drug	Route and dose	Comment
Labetalol	IV Up to 2mg/min as infusion or 20–80mg bolus every 10min	Safe in pregnancy. Used in pre-eclampsia Can be converted IV to PO SE: bronchospasm, LVF, heart block
Esmolol	IV 25–200 micrograms/ kg/min Initial bolus of 0.5–1.0mg/ kg	Very short half-life SE: as for labetalol
Sodium nitroprusside	IV Start 0.25–1.5 micrograms/ kg/min. (↑ 0.5 micrograms/ kg/min every 5min until response). Range 0.25–10 micrograms/kg/min	Potent, rapid-acting, vasodilator Requires close monitoring (? arterial line) and light-resistant delivery equipment SE: nausea, vomiting, thiocyanate accumulation (esp. if renal impairment)
Nitrates (GTN)	IV 10–200 micrograms/min	Familiar SE: headache, tachycardia, tachyphylaxis, vomiting
Hydralazine	IV 5–10mg bolus, repeated after 1h. Infusion: start 200–300 micrograms/ min, maintenance 50–150 micrograms/min	Arterial vasodilator used in eclampsia SE: Na ⁺ and water retention, headache, tachycardia, vomiting
Phentolamine	IV 1–5mg, repeated as necessary	Phaeochromocytoma SE: tachycardia, dizziness, flushing, nausea
Fenoldopam	IV 0.1–0.3 micrograms/kg/min	Dopamine-1 agonist and peripheral arterial vasodilator Also ↑ urine flow and both Na ⁺ and K ⁺ excretion attractive if ↓ GFR SE: headache, tachycardia, flushing



Orthostatic hypotension

A frequent clinical problem, particularly in the elderly. Generally defined as a 20/10mmHg (symptomatic) fall in BP within 5min of assuming an upright posture. Symptoms include weakness, dizziness, visual disturbance, presyncope, blackouts, and falls. See Box 6.7 for causes. See Fig. 6.12 for treatment.

Normal response

Standing → splanchnic and lower limb blood pooling → ↓ venous return → cardiac output → ↓ BP → reflex sympathetic and parasympathetic activation → ↑ peripheral vascular resistance → ↑ venous return → ↑ cardiac output → ↑ BP.

Box 6.7 Causes of orthostatic hypotension

- Hypovolaemia.
- Drugs.
- Autonomic dysfunction:
 - ↓ baroreceptor sensitivity (elderly).
 - Pure autonomic failure.
 - Multiple system atrophy (Shy-Drager syndrome).
 - Parkinson's disease.
 - Diabetes mellitus.
 - Amyloidosis.
 - Postural tachycardia syndrome (POTS).
 - Paraneoplastic autonomic dysfunction.
- Endocrine disorders:
 - Addison's syndrome.
 - Hypoaldosteronism.
 - Pheochromocytoma.
- Miscellaneous:
 - Paroxysmal syndromes:
 - Micturition syncope.
 - Cough syncope.
 - Varicose veins.
 - Carcinoid syndrome.
 - Mastocytosis.
 - Postprandial hypotension.

Volume depletion

Requires exclusion in all cases.

Antihypertensive drugs

A frequent culprit. Other drugs include nitrates, opiates, tricyclic antidepressants, and alcohol.

Pure autonomic failure

Characterized by orthostatic ↓ BP, with a static heart rate, ↑ sweating, impotence, nocturia, constipation, anaemia, and supine ↑ BP. Symptoms are slowly progressive and often worse early morning and postprandially. Associated with ↓ levels of plasma noradrenaline and degeneration of post-ganglionic neurons (with Lewy body inclusions).

Multiple system atrophy

Progressive neurodegenerative condition of unknown aetiology. ♂⁷>♀, age >50. Autonomic dysfunction (often first symptom) is accompanied by combinations of extrapyramidal, pyramidal, and cerebellar dysfunction.

Postural tachycardia syndrome (POTS)

Relatively common; age <40, ♀ > ♂. Aetiology uncertain but abnormalities of autonomic regulation implicated. The presence of tachycardia distinguishes it from autonomic failure. Often little or no fall in BP. Tilt-table testing diagnostic.

Decreased baroreceptor sensitivity in the elderly

Mild postural ↓ BP in the elderly, associated with abnormal responses to baroreceptor reflexes, such as tilting. May be associated with ↑ mortality.

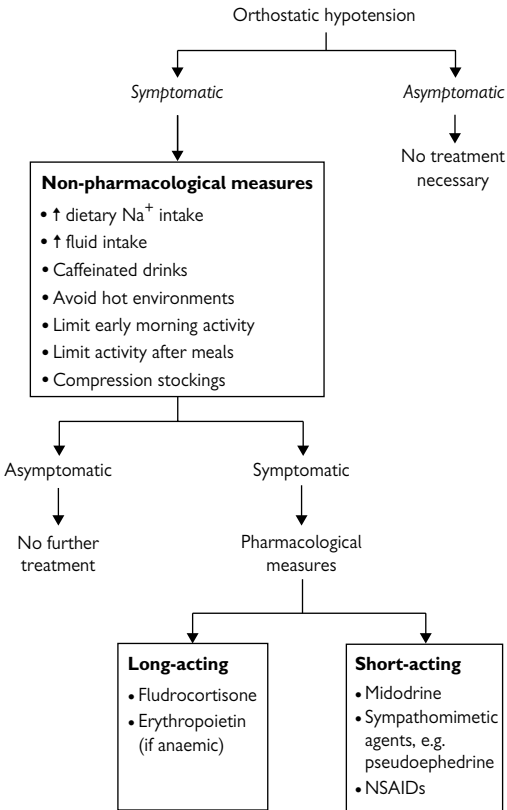


Fig. 6.12 Treatment of orthostatic hypotension. Reproduced from Jens Jordan et al. Contrasting actions of pressor agents in severe autonomic failure. (1998). *Am J Med*, 105; 116–24, with permission from Elsevier.

Diseases of the kidney

- Approaching glomerular disease 530
- Histology of glomerular disease 532
- Acute nephritic syndrome 536
- Nephritis: management overview 538
- Nephritis: overview of immune suppression 540
- IgA nephropathy 544
- IgA nephropathy: management 546
- Post-infectious glomerulonephritis 548
- Mesangiocapillary glomerulonephritis 550
- MCGN: presentation and management 552
- The nephrotic syndrome 554
- The nephrotic syndrome: general management principles 556
- Minimal change disease 558
- Focal and segmental glomerulosclerosis (FSGS) 560
- Membranous nephropathy (MN) 564
- Idiopathic MN: treatment 566
- Hereditary nephropathies 568
- Miscellaneous mesangioproliferative glomerulonephritides 572
- Thrombotic microangiopathies 574
- Thrombotic thrombocytopenic purpura (TTP) 576
- Haemolytic uraemic syndrome (HUS) 578
- Acute tubulointerstitial nephritis 580
- Chronic tubulointerstitial disease 582
- Analgesic nephropathy 584
- Renovascular disease 586
- Management of ARAS 588
- Other renovascular diseases 590
- Autosomal dominant polycystic kidney disease (ADPKD) 592
- ADPKD: complications and treatment 594
- Other cystic kidney diseases 598




Approaching glomerular disease

Introduction

Glomerulonephritis (GN) is classified by clinical syndrome/presentation (e.g. nephritic or nephrotic syndrome), histological appearance (e.g. minimal change disease), or by aetiology (e.g. post-streptococcal GN) (see Fig. 7.1).


Clinical syndromes

For further investigation of these clinical syndromes, see  Chapter 1.


- Asymptomatic urinary abnormalities ( pp. 58 and 66).
- Acute nephritis ( p. 71).
- Nephrotic syndrome ( p. 554).

These may all be accompanied by \uparrow BP \pm renal impairment.

Dipstick-positive proteinuria (p. 58)


Common. Usually detected on routine urinalysis. A positive dipstick for haematuria or proteinuria should be repeated (e.g. after 1–2 weeks). Transient proteinuria is not uncommon, esp. in concentrated urine. If persistent, verify with an albumin to creatinine ratio (uACR) or protein creatinine ratio (uPCR) ( p. 21).

Microscopic haematuria (p. 66)

Dipstick analysis is very sensitive but non-specific. If persistent, ideally arrange urine cytology to confirm haematuria (defined as >2 RBC/hpf), and examine red cell morphology. Dysmorphic red cells, red cell casts, and fragmented red cells (acanthocytes) imply glomerular bleeding ( p. 22).

Urine microscopy will also reveal pyuria and other forms of cast. Urine culture will exclude infection.

Haematuria and proteinuria (p. 61)

Suggests a glomerular lesion, although independent investigation of the haematuria may be necessary in patients aged >40 ( p. 67).

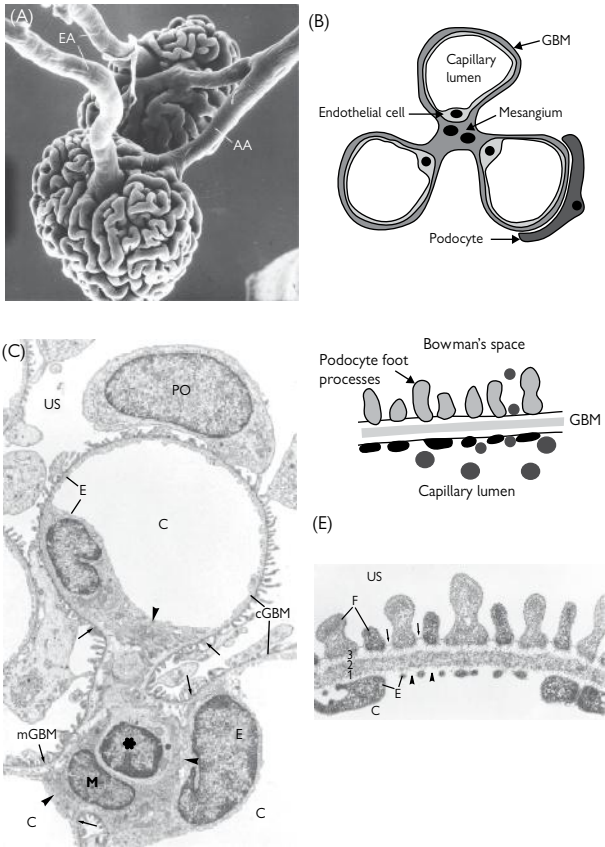


Fig. 7.1 (A) Glomerular vessels: AA, afferent arteriole; EA, efferent arteriole. (B) Cartoon of the glomerular capillaries: GBM, glomerular basement membrane. (C) EM of glomerular capillaries: C, capillary; E, endothelial cell; cGBM, capillary GBM; mGBM, mesangial GBM; PO, podocyte; US, ultrafiltration space. (A–C). (D) Cartoon of glomerular filter. (E) EM of glomerular filter: F, podocyte foot process. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P, et al. (2005), *Oxford Textbook of Clinical Nephrology*. Oxford University Press, Oxford.

Histology of glomerular disease

Introduction

Renal tissue is sampled via renal biopsy (p. 80) and prepared for:

- Light microscopy: various histochemical stains (e.g. H+E, periodic acid–Schiff (PAS), Jones (silver) stains). Useful for morphology, chronicity, and diagnosis.
- Immunohistochemistry: usually by immunofluorescence but also immunoperoxidase staining. Localizes immune reactants (particularly immunoglobulins or complement fractions) within glomeruli, using fluorescein-labelled antibodies. The nature and pattern of staining are characteristic for particular glomerular lesions.
- Electron microscopy (EM): useful for examining cell and basement membrane structure and for characterizing glomerular deposits.

The language of glomerular disease

When examining a preparation of renal cortex, several glomeruli (10–30, on average) are sampled. The following descriptive terms (see Fig. 7.2) are then used:

- *Focal or diffuse?*
 - Focal lesions affect some (<50%) of sampled glomeruli, but not all.
 - Diffuse lesions involve most (>50%) glomeruli, if not all.
- *Segmental or global?*
 - Segmental lesions affect *part* of an affected glomerulus.
 - Global lesions involve *most* of the glomerular tuft.
- *Proliferative or not?*
 - Proliferative lesions describe an increase in local cell number; for instance, an increase in mesangial cells ('mesangial proliferative') is a feature of IgA nephropathy.
- *Crescentic or not?*
 - Glomerular parietal epithelial cells (lining Bowman's capsule) proliferate in response to local inflammatory and procoagulant signals, with fibrin deposition and adhesions filling some, or all, of Bowman's space (→'crescent').
- *Matrix or membrane?*
 - Expansion of matrix produced by mesangial cells, as seen in IgA nephropathy, or increase in GBM width (and thus capillary wall thickness) characteristic of immune deposits.
- *Necrosis or sclerosis?*
 - Necrosis refers to fresh cell death as a result of ongoing injury.
 - Sclerosis reflects a scarred glomerulus or glomerular segment.

Examples

Focal and segmental glomerulosclerosis affects some glomeruli, but not all, and only part of any affected tuft. The disease leads to scarring within glomeruli.

Diffuse proliferative crescentic glomerulonephritis affects most glomeruli, with hypercellularity and the formation of crescents in Bowman's space.

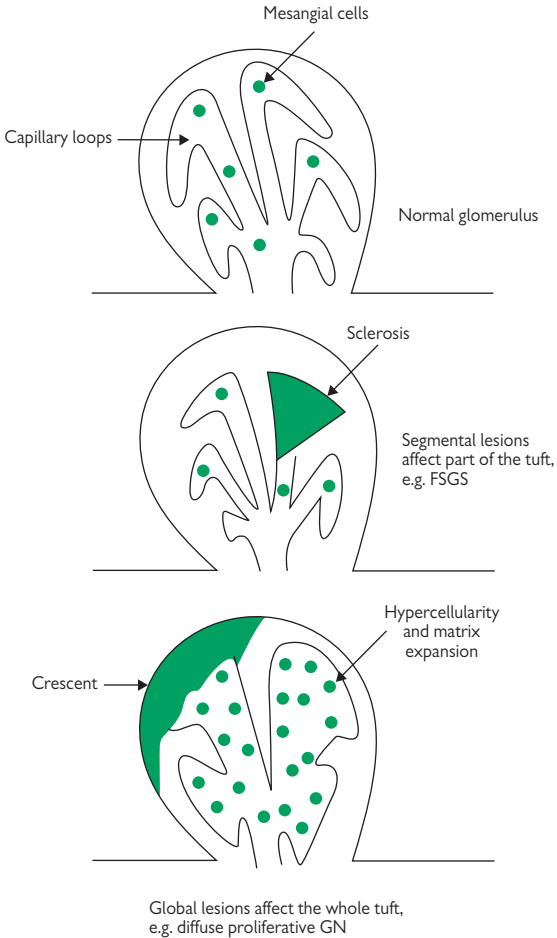


Fig. 7.2 The nomenclature of glomerulonephritis.

Table 7.1 A glossary of histological terms

Term	Definition
Minimal change	Normal appearance by light microscopy. Note that electron microscopy may show fusion of podocyte foot processes, an association with glomerular proteinuria.
Proliferation	Increase in cell numbers, may be mesangial, endocapillary or extracapillary (which may form crescents). E.g. mesangial proliferation = >4 cells per mesangial area.
Exudation	Infiltrated by neutrophils e.g. acute post-streptococcal nephritis (Fig. 15.10).
Membranous	Specific type of glomerular basement membrane thickening associated with subepithelial immune deposits, e.g. idiopathic membranous nephropathy.
Hyalinosis	Accumulation and condensation of plasma proteins into tissues outside a blood vessel lumen, appears as homogeneous pink staining with H&E (see 'H&E' later in table).
Sclerosis	Scar tissue, a fibrous matrix obliterates normal structure so that capillaries collapse and normal cell nuclei are lost.
Tubular atrophy	Thickening and wrinkling of tubular basement membrane around a shrunken tubule with flattened epithelium; implies irreversible tubular damage.
Crescent	Collection of cells in Bowman's space in response to glomerular damage. Initially only composed of inflammatory and epithelial cells (cellular crescent), later organizes with fibrin and collagen (fibrous crescent).
Diffuse	Applying to all glomeruli in a biopsy.
Focal	Applying to some glomeruli, but not others.
Global	Applying to the whole of a glomerulus.
Segmental	Applying to part of a glomerulus, i.e. part of the glomerular capillary tuft is unaffected.
'Humps'	Deposits of Ig and complement in a sub-epithelial site; typical of acute post-streptococcal nephritis.
'Spikes'	Projections of basement membrane between regular sub-epithelial deposits, typical of membranous nephropathy.
Foam cells	Lipid laden cells, usually histiocytes but also mesangial or tubular cells, seen in nephrotic syndrome and Alport's syndrome.

Table 7.1 (Continued)

Term	Definition
Haematoxylin and eosin (H&E)	Routine histological technique which stains cytoplasm pink and nuclei blue. Allows inspection of all renal structures but is poor at distinguishing deposits or visualizing the basement membrane.
Periodic acid-Schiff (PAS)	Routine histological technique which clearly delineates basement membranes and allows visualization of cellular components.
Silver	Silver stains highlight connective tissue structures such as reticulin, basement membrane, and collagen, which appears black. Very useful for assessment of glomerular capillary basement membrane architecture such as 'spike formation' (see 'Spikes' earlier in table).
Congo red	Stain used for the detection of amyloid, which appears red with 'apple green' birefringence using polarized light examination.
Martius scarlet blue (MSB)	Stain which highlights fibrin deposits as red, collagen in blue, and erythrocytes in yellow.
Toluidine blue	Stain used primarily to visualize 'thin sections' prior to electron microscopic examination.
Glomerulonephritis	Inflammation of the glomerulus.
Tubulointerstitial nephritis	Inflammation of the tubules and interstitium.
Electron dense deposits	Dark lesions identifiable on electron microscopic examination, usually corresponding to sites of immunoglobulin or complement deposition.
Immunohistochemistry (IHC)	Technique for detecting and localizing specific antigens in tissue sections using a detection system visible on routine light microscopy, e.g. immunoperoxidase.
Immunofluorescence (IF)	Technique for detecting and localizing specific antigens in tissue sections using a detection system visible on fluorescence microscopy. Sometimes more sensitive than IHC but requires fresh tissue and is not stable.
Thin basement membrane (thin BM) disease	Age 9–68 years: thin GBM: 262–330nm; normal: 331–547nm.
'Basket weave' GBM	The disordered replication of lamina densa of the GBM in Alport's nephropathy.

Modified from Taylor CM, Chapman S (1989). Renal biopsy. In *Handbook of renal investigations in children*, pp.160–71. Taylor CM, Chapman S (eds). Wright, London.

Acute nephritic syndrome

Introduction

The clinical syndrome associated with underlying glomerulonephritis (📖 p. 71). Presents (often rapidly) as:

- Haematuria and proteinuria.
- Impaired renal function.
- Oliguria with signs of salt and water retention.

It is a spectrum of disease with a variety of aetiologies but with a common site of primary injury: the glomerulus. Onset may be insidious, with urinary abnormalities alone, or fulminant, with a rapidly progressive crescentic GN, AKI, and other organ involvement or failure (📖 p. 71).

Causes

- IgA nephropathy and Henoch–Schönlein purpura.
- Lupus nephritis.
- Post-infectious GN.
- Anti-GBM disease.
- ANCA-associated vasculitis.
- Mesangiocapillary GN (MCGN).

Mechanisms of glomerular injury

The injury leading to most GN is immunologically mediated, with loss of tolerance to autoantigens, provoking both the cellular and humoral arms of the immune system. These antigens may be native to the glomerulus itself (occurring normally within the tuft, e.g. the GBM in anti-GBM disease) or circulating antigens/antigen-antibody complexes that become trapped in glomerular structures.

Antibody to antigen binding may then fix and activate complement (forming immune complexes, ICs) or recruit inflammatory cells (see Fig. 7.3). The nature of the injury will depend on the site of the IC (e.g. IgA-containing mesangial complexes activate mesangial cells to cause IgA nephropathy). Local complement activation and cell recruitment (neutrophils, macrophages) generate oxidant species, proteases, inflammatory cytokines, growth factors, vasoactive factors, and procoagulants.

Damage to, and activation of, surrounding cells and matrix then lead to the changes evident on histological examination and the clinical syndrome of haematuria, proteinuria, and impairment of glomerular filtration. The number of ICs formed and the host response to them will determine the extent of the injury.

Cellular immunity may also contribute to structural glomerular damage—this is especially true of pauci-immune GN (e.g. the GN associated with ANCA-positive vasculitis) where ICs play no pathological role.

Resolution of inflammation might return an inflamed glomerulus to normal or, if the healing phase is poorly regulated, may result in cellular dropout, scarring, glomerulosclerosis, and CKD.

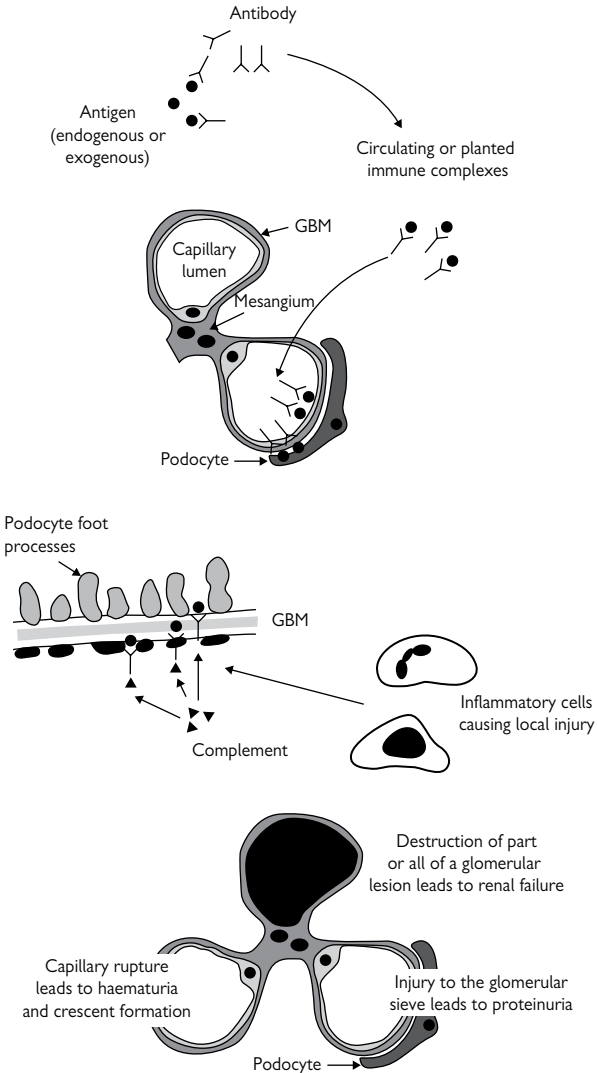


Fig. 7.3 An example of an immune complex-mediated GN.

Nephritis: management overview

Investigations

- Dipstick urine for haematuria, proteinuria.
- Urine microscopy for red morphology \pm casts (📖 p. 22).
- Amount of proteinuria variable (often $<1\text{g/day}$, i.e. uACR $<70\text{mg/mmol}$ and uPCR $<100\text{mg/mmol}$, but may be nephrotic range).
- SCr, eGFR, U&E, FBC, bone profile, LFT.
- Acute phase markers (CRP, ESR).
- Immunological and serological ('nephritic') screen (📖 p. 40).
- USS kidneys.
- Renal biopsy (📖 p. 80).

Salt and water restriction

- ▶ It is vital to correctly assess volume status.
- Fluid overload \pm pulmonary oedema often complicates oliguric GN. If present:
 - Limit salt intake $<80\text{mmol/day}$ ($<5\text{g/day}$).
 - Set oral intake at $500\text{--}1,000\text{mL/day}$ (adjusted according to volume status and UO).
- Diuretics may promote a natriuresis and provide symptomatic relief: use loop diuretic, e.g. furosemide $40\text{--}160\text{mg/day}$ PO or IV, titrated against response and renal function.
- Less commonly, dehydration may be present, in which case increased oral intake or rehydration with IVI 0.9% NaCl may be needed.
- Review volume status and monitor weight daily, and chart input and output to plan following day's fluid balance. Indwelling catheter only rarely required.

Control BP

- \uparrow BP is usually volume-related and may be significant. Aim for target BP of $\leq 130/80\text{mmHg}$.
- Suggested treatment:
 - Diuretic (as described in salt and water restriction).
 - Stepwise add-on therapy, using β -blockers \pm calcium channel blockers.
 - ACE-I or ARB: titrate up from low dose with daily increments. ACE-I or ARB offer theoretical advantages in the control of \uparrow BP secondary to renal disease due to their antifibrotic and anti-proteinuric effects. However, their use in GN-associated with AKI may precipitate a further decline in renal function. ⚠ Careful monitoring is essential.

Other supportive measures

- ▶ Prompt treatment of infection.
- Adequate nutrition.
- Management of the complications that may be associated with a systemic disease causing GN (e.g. lupus, vasculitis).
- Renal replacement therapy, according to standard indications (📖 p. 172).

Specific therapies: immunosuppression

Almost always tailored to a histological diagnosis (so a renal biopsy is often indicated as soon as is possible). See Nephritis: overview of immune suppression (📖 p. 540) and under each particular diagnosis.

KDIGO clinical practice for glomerulonephritis

This important guideline, first published in 2011, aims to help clinicians caring for patients with GN understand the evidence (or lack of) that underpins current clinical practice in this area. The recommendations contained within it are based on a comprehensive review of relevant literature across many kidney diseases. The strength of all the evidence presented is graded, current shortcomings are acknowledged and proposals for future research are offered.

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *KI, Suppl.* 2012; **2**: 139–274.

Available online at 🌐 <http://www.kdigo.org>

Nephritis: overview of immune suppression

Introduction

⚠ Treatment of glomerulonephritis often involves toxic therapies in the short term to improve long-term renal and patient outcomes. The initial goal is to *achieve remission* before altering therapy to *maintain remission*.

When considering and commencing therapy, the dictum of 'first do no harm' always applies. These are potentially dangerous drugs—does the risk:benefit assessment justify their use?

Preventing drug toxicity

Corticosteroids

- Issue patients with a steroid card, and counsel regarding the risks of abrupt steroid withdrawal as well as the potential need to increase dose with stressors (such as intercurrent illness or anaesthesia). Check blood glucose at start of therapy.
- ⚠ Warn diabetic patients and those with impaired glucose tolerance to monitor blood sugars closely whilst on corticosteroid therapy and to inform their diabetic team.
- Prophylaxis against gastric irritation: proton pump inhibitor or H₂ receptor antagonist by convention (⚠ although evidence poor).
- Steroid-induced bone demineralization is an early event (within first few months of treatment).
 - Consider bisphosphonate (e.g. risedronate 35mg weekly or alendronic acid 70mg weekly) in those at risk (or if >5mg prednisolone/day for >3 months). ⚠ Many bisphosphonates require a dose reduction in renal impairment.
 - Calcium (1,500mg/day) and vitamin D₃ (800 IU/day) preparations are a less effective alternative.
 - Consider baseline and interval DEXA if long-term steroids.
- Treat steroid-exacerbated hyperlipidaemia with a statin.

Tapering steroids

Prednisolone is the most widely used oral corticosteroid. Its use in renal disease is usually for >3 weeks and it will therefore often require slow tapering to allow recovery of a suppressed hypothalamic–pituitary axis.

A potential regimen from 20mg/daily prednisolone might be:

- Reduce by 5mg every fortnight until on 5mg/day.
- Reduce to 5mg, alternating with 2.5mg daily for 2 weeks.
- Reduce to 2.5mg daily for 2 weeks.
- Reduce to 2.5mg alternate days for 2 weeks.
- Stop.

Advise re potential Addisonian symptoms, and warn to seek medical help if unwell.

Others, e.g. alkylating agents (cyclophosphamide, chlorambucil)

- **⚠** Monitor toxicity: FBC, U&E, and LFT weekly to fortnightly at induction of therapy (see **📖** p. 542).
- Offer prophylaxis against PCP for duration of cyclophosphamide therapy (e.g. co-trimoxazole 480mg bd PO or nebulized pentamidine if allergic).
- In those at high risk for tuberculosis (e.g. previous TB, recent exposure, patients from endemic areas), consider primary prophylaxis with isoniazid + pyridoxine (**🔍** evidence poor).
- Recommend influenza and pneumococcal vaccines. Live vaccines should be avoided for the duration of treatment.

Commonly used drugs

- Induction (I) brings about disease remission.
- Maintenance (M) maintains remission.

Prednisolone (I, M)

- To induce remission, either as high dose PO (1mg/kg/day) or as 'pulsed' IV (0.5–1g/day for 3 days).
- Corticosteroids are also used at lower dose for maintenance.
- Potent anti-inflammatory action, modulating both B and T cell-mediated immunity. Also inhibit the effector function of both monocytes and neutrophils through regulation of cytokine-driven responses.
- SE: insomnia, weight gain, ↑ BP, impaired glucose tolerance, dyslipidaemia, mood disturbance, poor wound healing, osteoporosis.

Cyclophosphamide (I)

- Either orally (e.g. 1.5mg/kg) or as periodic (monthly) IV pulses.
- A cytotoxic alkylating agent that binds to purine bases and impairs cellular DNA replication (→↓ cell turnover and cell death), with consequent restriction of lymphocyte proliferation.
- SE:
 - Leucopenia (see **📖** p. 542) and ↑ risk of infection, esp. *Herpes zoster*.
 - Gonadal toxicity. Discuss loss of fertility prior to starting treatment—in ♀, measure LH/FSH before therapy. Limit cumulative exposure as much as possible (>15–20g causes infertility in ~50% of those aged >30. The risk is lower in younger patients). Consider GnRH analogues in ♀ (see **📖** p. 542). Egg preservation may be possible, but the pace of disease (and ∴ need for swift intervention) often renders this impractical. Discuss sperm banking in ♂.
 - Haemorrhagic cystitis → longer-term risk of bladder cancer. **⚠** Use mesna if giving IVI (see **📖** Using IVI cyclophosphamide (CYC), p. 542); low threshold for investigating haematuria in those previously exposed (mesna binds to the cyclophosphamide metabolite acrolein that is the cause of urothelial toxicity).
 - **🔍** Oral cyclophosphamide (CYC) is potentially more toxic to ovaries and bladder than IVI because cumulative doses are usually higher.
 - Nausea and vomiting, esp. if given IVI.
 - Teratogenic; contraindicated in pregnancy (although not associated with birth defects in ♀ who receive it prior to pregnancy).
 - SIADH.

Using IVI cyclophosphamide (CYC)

- Body surface area is calculated as $\sqrt{(\text{height (cm)} \times \text{wt (kg)})/3,600}$.
- Counsel re side effects and potential risks.
- Protect the bladder from haemorrhagic cystitis: vigorous oral fluids, with 1L 0.9% NaCl over 4h post-therapy. Oral mesna at -2, +2, and +6h as $(0.2 \times \text{cyclophosphamide dose in mg})$ per dose.
- Antiemetics, e.g. granisetron 1mg (can repeat at +12h) + dexamethasone 10mg PO at -2h.

Monitoring for CYC-induced neutropenia

- Check WCC weekly for the first month, every 2 weeks for the second and third, and monthly thereafter.
- If WCC $<4 \times 10^9/L$, then discontinue temporarily. Restart with a 25% dose reduction when WCC has recovered, and resume weekly monitoring.
- If the WCC is falling rapidly, e.g. by $>2 \times 10^9/L$ between tests, reduce the dose by 25% pre-emptively.
- If WCC $<1 \times 10^9/L$ or WCC $<4 \times 10^9/L$ persists for >2 weeks, then restart at low dose (e.g. 25–50mg/day) only after WCC recovers.
- For IV CYC, check WCC the day of the proposed pulse. If $<4 \times 10^9/L$, postpone until $>4 \times 10^9/L$, and reduce dose by 25%.
- Check WCC 14 days after each pulse; if WCC nadir:
 - $2-3 \times 10^9/L$, reduce the dose of the next pulse by 20%.
 - $1-2 \times 10^9/L$, reduce by 40%.

Protecting against gonadal cyclophosphamide toxicity

Glomerular disease, particularly SLE, often affects ♀ of childbearing age. Cyclophosphamide (CYC) treatment is associated with a significant risk of premature ovarian failure (POF). This may play an important role in the choice of induction therapy but must be balanced against the risks of potential undertreatment.

When given continuously, GnRH analogues induce reduced ovarian blood flow and limit ovarian exposure to CYC. In small observational studies, the administration of GnRH analogues during treatment with CYC for lupus nephritis demonstrably preserves ovarian function. An example regimen is depot leuprolide acetate, ideally administered at least 10 days prior to the commencement of CYC.

Calcineurin inhibitors (I, M)

- Ciclosporin and tacrolimus (📖 p. 386).
- Limit IL-2-driven nuclear transduction, and thus T cell activation.
- ⚠ Nephrotoxic: monitor GFR throughout use.
- Given orally (although IVI available).
- SE (ciclosporin (C) and tacrolimus (T)):
 - Infection (T + C), ↑ BP (C), tremor, hirsutism (C), gum hypertrophy, dyslipidaemia, impaired glucose tolerance (T > C), gout (C), nephrotoxicity (T + C), microangiopathy (T + C), amongst others.

Azathioprine (M)

- Antiproliferative pro-drug metabolized to 6-mercaptopurine.
- Restricts lymphocyte proliferation through the inhibition of folate-dependent DNA synthesis.
- ⚠ Interaction with allopurinol may precipitate profound leucopenia.
- Given orally, usually as a single daily dose.
- SE: infection, myelosuppression, hepatotoxicity (check WCC, LFT 14–21d after starting). Long-term risk of skin cancers.

Mycophenolate mofetil (I, M)

- Antiproliferative agent that inhibits lymphocyte expansion and antibody production. It can also promote T cell apoptosis and affect cell:cell interactions.
- Given orally in divided doses (IVI available).
- SE: infection, myelosuppression, GI toxicity (diarrhoea is not uncommon—divide dose qds, rather than bd, or reduce dose). Teratogenic.

Rituximab (I, possibly M)

- A chimeric anti-CD20 monoclonal antibody against B cell surface marker that induces B cell lysis. Given IVI. Results in widespread B cell and antibody depletion over time.
- SE: cytokine release type syndrome during infusion, infection—particularly serious viral infections, including CMV and JC virus (the latter the cause of progressive multifocal leucoencephalopathy). Others: fever, headache, nausea, abdominal pain, hepatitis, bronchospasm, hypogammaglobulinaemia. Serious neutropenia is uncommon.
- Circulating B cell counts may be helpful to guide dosing.

IgA nephropathy

Introduction

The most common primary glomerulonephritis in the world, affecting an estimated 1.5% of the population. Often presents with haematuria in the 2nd and 3rd decades.

Usually idiopathic, but IgAN is also found in association with Henoch–Schönlein purpura (📖 p. 650), alcoholic cirrhosis, GI disorders (coeliac disease, inflammatory bowel disease), and skin and joint disorders (spondyloarthropathies, dermatitis herpetiformis, psoriasis).

⚠️ Previously considered relatively benign, it is now recognized that 30–50% will progress to significant CKD over time. The remainder will either enter remission or have persistent low-grade haematuria/proteinuria

Pathogenesis

The majority of IgA (both IgA1 and 2) is produced by plasma cells and freely circulates before hepatic metabolism. In IgAN, abnormally glycosylated polymeric IgA1, with an increased tendency for self-aggregation and complex formation, is deposited in the glomerular mesangium. These deposits are seen in 3–16% of healthy individuals with no renal disease, suggesting that deposition of IgA alone is insufficient to induce injury. Co-deposits of IgG and C3 may contribute to severity. The predominance of IgA1 over IgA2 is due to the abnormal glycosylation of O-linked polysaccharides that are unique to the hinge region of IgA1.

IgA binding of mesangial Fc receptors → mesangial cell activation → production of platelet-derived growth factor and other cytokines → mesangial cell proliferation, matrix synthesis, inflammatory cells recruitment, and local injury (see Fig. 7.4).

Infection, particularly mucosal, and hypersensitivity are suggested precipitants. However, it seems likely that an aberrant IgA immune response is more important than a particular antigen, with polymeric IgA found in plasma cells.

There is evidence of a genetic influence, but it is complex and polygenic and difficult to study, owing to the often 'latent' nature of the disease.

Symptoms and signs

- Often presents as asymptomatic urinary abnormalities, particularly microscopic haematuria.
- Haematuria may be macroscopic, classically timed with upper respiratory illnesses (so-called 'synpharyngeal haematuria').
- Associated proteinuria is common, although nephrotic range proteinuria (>3g/day) is unusual (<15%).
- Consider in young adults presenting with urinary abnormalities ± CKD.
- ↑ BP is common and often difficult to control.
- ► IgAN may present as a rapidly progressive GN with AKI (📖 p. 71).
- Extrarenal manifestations, including a purpuric skin rash, can occur, and there appears to be overlap with Henoch–Schönlein purpura (HSP). For discussion, see 📖 p. 651.

Investigations

- SCr, U&E, eGFR, serum albumin, bone profile, lipid profile.
- Elevated serum IgA in ~50%.
- Urine microscopy for dysmorphic RBCs and red cell casts (📖 p. 22).
- Elevated uPCR or uACR.
- Biopsy of associated skin rash, if present, may show IgA deposition on immunofluorescence.
- Renal biopsy (📖 p. 80).

Histology

- *Light microscopy*: mesangial cell proliferation and increased mesangial matrix (may be focal or diffuse).
- *Immunostaining*: confirms mesangial IgA deposits with C3. Possible co-deposition of IgG and IgM.
- *Electron microscopy*: mesangial deposits near the paramesangial GBM.

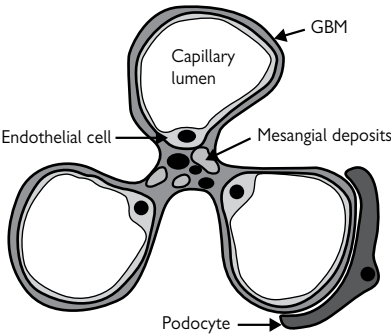


Fig. 7.4 Cartoon of mesangial IgA deposits.

Classification

A lack of historical agreement concerning precise histological classification has rendered trial data difficult to interpret and accord on best treatment difficult to reach. The 2009 Oxford Classification was based on a consensus view of 265 biopsy specimens. The following variables were associated with renal outcome, independent of baseline features and control of BP and urinary protein excretion:

- Mesangial hypercellularity score.
- Segmental glomerulosclerosis.
- Endocapillary hypercellularity.
- Tubular atrophy/interstitial fibrosis.
- (One drawback is that the classification does not include crescentic/necrotic lesions.)

It is hoped that this classification may help to stratify an individual patient's prognosis and determine their treatment at the time of biopsy (e.g. endocapillary proliferation may help to predict steroid responsiveness).

IgA nephropathy: management

Introduction

The treatment of IgAN is unsatisfactory because of the heterogeneity of the disease itself and the paucity of good clinical trial data. Prevention of progressive renal impairment is the key therapeutic goal. However, many patients have slowly progressive disease (decline in GFR of $\sim 1\text{--}3\text{mL/min/yr}$), so long-term studies are urgently required.

Current options are broadly divided into non-immunosuppressive and immunosuppressive strategies.

Stratifying patients: key features of a poor prognosis at presentation

- Impaired renal function.
- Heavy proteinuria ($>3\text{g/day}$).
- (Difficult to control) hypertension.
- Significant tubulointerstitial fibrosis and glomerulosclerosis on renal biopsy (see Oxford classification, [p. 545](#)).
- Rapidly progressive crescentic IgAN.

Low-risk patients (no poor prognostic features)

- Normal GFR.
- Isolated microscopic, or episodic macroscopic, haematuria.
- Proteinuria $<500\text{mg/day}$ (uPCR $<50\text{mg/mmol}$).
- Normotensive.

No specific treatment is necessary in this group, but regular surveillance (e.g. annual BP, SCr, eGFR, uPCR) is recommended. Many centres will manage these patients without a renal biopsy and, therefore, without a specific diagnosis of IgAN ([p. 67](#)). Persistent haematuria implies ongoing immune activity. Proteinuria implies more severe disease, and the amount will increase with activity and progression.

Medium-risk patients (no poor prognostic features)

- Older age.
- Normal GFR or only slight \downarrow .
- Proteinuria $>500\text{mg/day}$ (uPCR $>50\text{mg/mmol}$).
- Hypertension.

Non-immunosuppressive treatment

- Reduce BP and proteinuria.
 - Aim for target BP of $\leq 125/75\text{mmHg}$, ideally with ACE-I as first agent (ARB if not tolerated).
 - If normal BP, but proteinuria, ACE-I for proteinuria reduction.
 - Dual blockade of A2, using combined ACE-I + ARB, may offer additional benefit (\downarrow proteinuria but no data on renal outcomes).
 - If tolerated, titrate therapy to reduce proteinuria to $<1\text{g/day}$ (uPCR $<100\text{mg/mmol}$) and ideally $<0.5\text{g/day}$ (uPCR $<50\text{mg/mmol}$).

- *Fish oils* (omega-3 fatty acids):
 - Limited data to suggest a role in the prevention of progression.
 - However, study data are conflicting—and not all patients included were on ACE-I/ARB.
 - Presumed to modulate the production/action of eicosanoids.
 - Given as fish oil (e.g. Maxepa® 5g bd).
 - GI intolerance (including halitosis) often limits patient acceptability.
 - Overall, a safe and justifiable adjunct to ACE-I. Consider in those where uPCR >100mg/mmol despite ACE-I/ARB.

High-risk patients

- Difficult to treat, with progression to ESRD not uncommon.
- Significant proteinuria, e.g. >1g/day (uPCR >100mg/mmol), esp. if nephrotic range (>3g/day; uPCR >300mg/mmol).
- Proteinuria fails to decrease with ACE-I/ARB therapy.
- Significantly impaired renal function at outset or progressive ↓ in GFR.
- Crescentic change on biopsy.
- Significant chronic histological damage, such as glomerulosclerosis, heralds a poor prognosis, regardless of treatment.

Non-immunosuppressive treatment

- As for medium-risk patients.

Immunosuppressive treatment

- Give in conjunction with ACE-I/ARB.
- Optimum therapy uncertain. Conflicting data from small studies of inadequate duration where inclusion of low-risk patients skews outcomes.
- Corticosteroids:
 - Some evidence of benefit if proteinuria >1g/day and eGFR >50mL/min.
 - Trial of 0.5mg/kg prednisolone alternate days for 6 months or, if nephrotic range proteinuria, 0.5–1mg/kg/day for 8 weeks.
- *Cyclophosphamide*:
 - Reserved for severe active disease (rapidly progressive clinical course and >50% crescentic change, with severe active inflammation) where aggressive treatment may spare renal function.
 - Prednisolone 0.5–1mg/kg/day + cyclophosphamide 2mg/kg/day for 8 weeks, followed by tapering prednisolone and conversion to maintenance azathioprine 2mg/kg/day.
 - Severity of renal dysfunction and degree of chronic damage on kidney biopsy will significantly influence outcomes.
 - Limited evidence that treating as an RPGN with pulse MP/cyclophosphamide ± PEX may improve renal prognosis.
- Other:
 - MMF may ↓ proteinuria and rate of GFR decline—however, data are not consistent, so further studies are awaited.
 - Tonsillectomy is not generally recommended for synpharyngeal disease.

Post-infectious glomerulonephritis

Introduction

PIGN is classically associated with streptococcal infection, but infection of almost any cause may be associated with an acute nephritic syndrome and a diffuse proliferative GN on kidney.

► Beware chronic, deep-seated, and concealed sources of sepsis, e.g. endocarditis (📖 p. 692), foreign bodies (e.g. ventriculoatrial shunt), and abscesses.

Common associations of post-infectious GN

- *Bacterial*: streptococcal, staphylococcal, pneumococcal, meningococcal, salmonella, mycobacterial, syphilis.
- *Viruses*: influenza B, mumps, rubella, coxsackie, hepatitis B, EBV, CMV.
- *Fungi*: *candida*, *Coccidioides*, *Histoplasma*.
- *Parasites*: malaria, filariasis, toxoplasmosis, or schistosomiasis.

Acute post-streptococcal GN

Introduction

An immune complex-mediated GN that usually occurs in childhood (age <7 years). Now rare in developed countries. Classically, follows 10–21 days after a streptococcal sore throat but often occurs after infection elsewhere, e.g. tonsillitis, pharyngitis (commonly), impetigo, otitis media, and cellulitis.

Pathophysiology

Infection with nephritogenic Lancefield group A β -haemolytic *Streptococcus* (esp. types 12 and 49) is followed by a latent period during which immune complexes form, circulate, and then deposit in glomeruli. Nephritis-associated plasmin receptor (NAP1r) and streptococcal pyrogenic exotoxin B (SPE-B) are two suggested culpable antigens.

Clinical presentation

Varies from asymptomatic microscopic haematuria through to an acute nephritic syndrome, with frank haematuria, oliguria, oedema, \uparrow BP, pulmonary oedema, and AKI. Bilateral loin pain or renal angle tenderness 2° renal engorgement may occur.


Investigations

Urinalysis. Urine microscopy for red cell casts \pm pyuria. SCr, U&E, FBC, Ca^{2+} , LFT. uPCR. Anti-streptolysin O titre (ASOT) or anti-DNase B (for group A streptococci) may be positive. Δ Note if only ASOT is used to screen, it can be falsely negative or blunted, particularly in skin infections (or if antibiotics have been given). Complement components: \downarrow C3, with normal C4. Rheumatoid factor may be positive. Consider full immunological and serological screen if in diagnostic doubt, particularly in adults (see 📖 p. 40).

In children, suspect if good clinical history and documented evidence of relevant infection. A renal biopsy is rarely necessary, unless resolution does not begin within 1 week.

In adults, main differentials are IgAN, MCGN, SLE, HSP, and other vasculitides. A biopsy is more likely to be undertaken to confirm the diagnosis.


Histology

Diffuse proliferative changes with hypercellularity. Extensive neutrophilic infiltration and red cell casts. Crescentic change and frank necroses are unusual. Immunofluorescence: IgG and C3 deposition in diffuse granular pattern in both the mesangium and glomerular capillary walls. EM: 'dome-shaped', electron-dense deposits in the subepithelial aspects of the capillary walls, with endothelial cell swelling. Similar to the changes seen in MCGN (for graphic, see  p. 551).

Clinical course

Generally, PIGN is self-limiting once (if) the underlying infection resolves. It is associated with a full renal recovery (even after AKI). Resolution usually begins after 7–10 days. Recurrence is rare. Urinary abnormalities may persist for many years after recovery, although isolated microscopic haematuria has little prognostic value. Proteinuria, ↑ BP, and CKD also occur, so patients should be offered follow-up.

Treatment

- ► Ensure the predisposing infection has resolved. If ongoing, treat actively with a penicillin or other appropriate antibiotic.
- If volume overload: restrict salt (<80mmol/day or <5g/day) and fluid (assess volume status and UO regularly to tailor restriction, e.g. 500–1000mL/day).
- Treat ↑ BP: salt and water overload is common, so start with loop diuretic (e.g. furosemide 40–160mg PO/IV). Escalate with additional agents, such as a CCB or an ACE-I (with caution), as necessary.
- Renal replacement, as per standard indications ( p. 172).

Shunt nephritis

Originally coined to describe the GN associated with a chronically infected ventriculoatrial or ventriculojugular shunt used to treat hydrocephalus. In the modern era, bacterial biofilms on an indwelling central venous cannula or cardiac pacing apparatus are more likely to be the source of low-grade infection (→ immune complex formation and glomerular deposition).

Clinical features in such scenarios include:

- Fever.
- Haematuria, proteinuria, and ↑ SCr.
- Splenomegaly.
- ↑ ESR, CRP, ↓ Hb, and ↓ C3.
- Histology is similar to PIGN.

Removal of the foreign body is essential for resolution.

Mesangiocapillary glomerulonephritis

Confusingly, also called *membranoproliferative* glomerulonephritis (MPGN).

Introduction

MCGN is a histological term used to describe a pattern of injury, rather than a distinct GN. Can be idiopathic but commonly secondary to a variety of causes.

MCGN associations

With cryoglobulins

- Hepatitis C (less commonly B) (📖 p. 686).
- Mixed cryoglobulinaemia unrelated to HCV (📖 p. 634).

Without cryoglobulins

- Shunt nephritis and other chronic infections, including endocarditis and visceral abscesses (📖 p. 692).
- SLE, Sjögren's syndrome.
- HBV, HCV, HIV, parvovirus B19.
- TB, leprosy.
- Malaria, schistosomiasis.
- Complement deficiencies (e.g. factor H).
- TMA.
- Plasma cell dyscrasia (e.g. myeloma), lymphoma.
- Transplant glomerulopathy (📖 p. 415).

Classification and histology

The subendothelial and mesangial deposition of immune complexes implies a common pathogenic mechanism (see Fig. 7.5). All subtypes have a characteristic 'double contour' or 'basement membrane splitting' appearance of the GBM 2° to the interposition of mesangial cell cytoplasm between the endothelium and GBM.

Type I MCGN

- Characterized by mesangial hypercellularity and discrete immune deposits in the mesangium and subendothelial space. Monocyte infiltration causes a lobular pattern to the glomerular tufts. Crescentic change can occur. Immunofluorescence shows granular IgG and C3 deposition within capillaries and mesangium.
- Commonly associated with cryoglobulinaemia (with HCV).
- Also associated with SLE, endocarditis, plasma cell dyscrasias (e.g. MIDD and AL amyloid), and HBV infection.
- Less commonly, a primary idiopathic MCGN (consider this a diagnosis of exclusion).


Dense deposit disease (type II MCGN)

- Continuous, dense, ribbon-like intramembranous deposits along the GBM, tubule, and Bowman's capsule. These contain C3 but no immunoglobulin.
- Related to deficiency in complement factor H (often with partial lipodystrophy and retinal abnormalities).

Type III MCGN

- Immune deposits, as in type I, but complete disruption of the GBM with membranous change.
- Three distinct varieties of type III MCGN have been described.
- An inherited form is associated with chromosome 1q32.

C3 glomerulopathy

- Isolated deposition of C3, often with similar features to type I, but with no immunoglobulin deposition.
- Associated with genetic or acquired abnormalities of complement regulation.
- Serum C3 nephritic factor is positive (see  p. 552).
- Probably part of the spectrum of dense deposit disease.

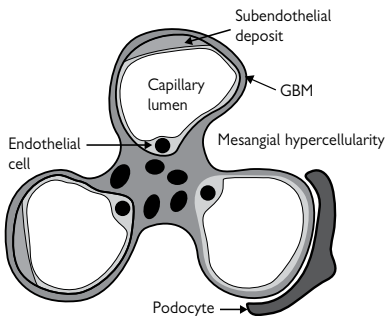


Fig. 7.5 Cartoon of subendothelial deposits in MCGN.

MCGN: presentation and management

Presentation

Idiopathic MCGN tends to affect ♂ = ♀ aged 8–30. It carries a relatively poor prognosis: ~50% ESRD at 10 years.

Symptoms and signs

All may present as asymptomatic urinary abnormalities, acute nephritis, nephrotic syndrome, or progressive renal failure. ↑ BP is particularly common.

For presentation of cryoglobulinaemia, see 📖 p. 634.

MCGN type II may be associated with partial lipodystrophy (absent subcutaneous tissue in the face and upper limbs) and retinal abnormalities (pigmentation and visual field deficits).

Investigations

- SCr, eGFR, U&E, albumin, LFTs, uPCR (or uACR), microscopy for red cell casts.
- ► Consider potential underlying causes: immunoglobulins, serum and urinary protein electrophoresis (± serum free light chains), hepatitis serology (for HCV and MCGN, see 📖 p. 686), rheumatoid factor, cryoglobulins, complement components, and C3 nephritic factor (📖 p. 41).

Complement in MCGN

- Type I MCGN:
 - Classical pathway is activated by immune complexes → normal/↓ C3 and ↓ C4).
- Type II MCGN (dense deposit disease):
 - Alternate pathway is activated → ↓ C3, normal C4.
 - A stabilizing IgG binding a C3 convertase (C3Bb) occurs in dense deposit disease → persistent cleavage of C3. This is termed the C3 nephritic factor.
- Type III MCGN:
 - Findings similar to type II but without the C3 nephritic factor.

Management

- ► Exclude 2° causes of MCGN prior to treatment.
- For treatment of HCV-related MCGN, see 📖 p. 688.
- ⚠ Evidence-based treatment strategies are lacking for primary MCGN. Many early studies almost certainly (inadvertently) included patients with 2° MCGN.

General measures

- Stop smoking (as in all progressive nephropathies).
- Treat ↑ BP vigorously.
- Reduce proteinuria: use ACE-I or ARB.
- Restrict salt intake ± diuretic (📖 p. 538).
- Dual antiplatelet therapy with aspirin and dipyridamole is no longer widely advocated.

Immune suppression

The following strategies may offer benefit. They are generally reserved for patients with the nephrotic syndrome and progressive renal impairment.

- Corticosteroids (tapering prednisolone started at 1mg/kg/day). An alternate day, long-term corticosteroid regimen has been common in paediatric practice.
- Corticosteroids ± cyclophosphamide 1.5–2mg/kg/day for ≤6 months.
- Corticosteroids ± MMF for ≤6 months is a potentially less toxic alternative.

MCGN: towards a new classification

Until recently, MCGN was generally classified as described on p. 550; i.e. either 1° (idiopathic) or 2° if an underlying cause could be identified. 1° MCGN was further classified into I–III based on ultrastructural appearances and distribution of electron-dense deposits. More recently, a better understanding of the pathogenetic role of complement in MCGN has informed a new view of the lesion, with categorisation into either Ig-mediated disease (driven by the classical complement pathway) or non-Ig-mediated disease (driven by the alternative complement pathway) (see Fig. 7.6). The non-Ig-mediated group, referred to as C3 glomerulopathy, includes dense deposit disease and C3 glomerulonephritis. C3 glomerulopathy is a proliferative lesion, usually with a MCGN-type appearance on light microscopy. C3 alone on immunostaining suggests overactivity of the alternative complement pathway.

Historically, clinical trials within MCGN have selected patients with comparable histology on light microscopy – meaning that many different etiologies were probably represented. It is hoped that advances in clinicopathological understanding will foster diagnostic clarity and generate disease-specific therapies.

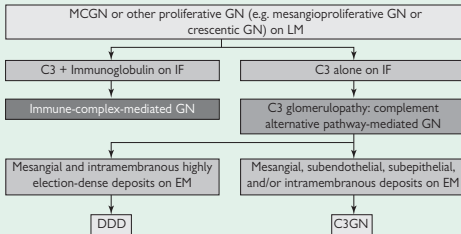


Fig. 7.6 Reclassification of MCGN has promoted a new group of diseases called C3 glomerulopathies. The classification may also be usefully extended to other forms of proliferative GN, even if they do not have an MCGN pattern on light microscopy. An Ig-mediated GN should prompt an investigation into infectious, malignant, or autoimmune causes (immune-complex formation). A GN with C3 staining alone suggests overactivity of the alternative complement pathway; i.e. a complement-mediated GN. Such diseases, including C3GN and Dense Deposit Disease, have been termed C3 glomerulopathies and should suggest investigation of the alternative complement pathway (e.g. functional assays, genetic mutation analysis, and autoantibody screening). From Bomback, A.S. and Appel, G.B. *Nat. Rev. Nephrol.* 8, 634–642 (2012), with permission from Macmillan Publishers.

The nephrotic syndrome

Introduction

A clinical syndrome defined as proteinuria $>3.5\text{g}/1.73\text{m}^2/\text{day}$ that is associated with hypoalbuminaemia, oedema, hyperlipidaemia, lipiduria (and thrombotic tendency).

The syndrome arises as a result of a failure of the glomerular filtration barrier to restrict the passage of proteins into Bowman's space. It implies structural abnormalities within the glomerular filter.

Primer: the glomerular filter (see p. 916)

- Comprises:
 - Charged endothelial cell glycocalyx layer.
 - Endothelium and its fenestrations.
 - The glomerular basement membrane (GBM).
 - Interdigitating podocytes that form a slit diaphragm.
- The passage of albumin, with its net negative charge, through the glomerular filter is prevented by size-specific factors (e.g. the slit diaphragm) and charge-specific factors (e.g. the anionic endothelial glycocalyx and GBM).
- Any albumin that escapes into Bowman's space is efficiently reabsorbed in the proximal tubule via receptor-mediated endocytosis. It is then degraded and returned to the circulation as peptide fragments.

Many primary and secondary causes of the nephrotic syndrome are now thought to be due to abnormalities of, or injury to, podocytes and the slit diaphragm ('podocytopathies').

How does proteinuria cause the clinical syndrome?

- The cause of hypoalbuminaemia is not as straightforward as one might think. The liver is actually capable of synthesizing 25g albumin/day: much higher than urinary losses.
- Potential explanations:
 - Larger quantities of albumin pass through the glomerular filter but are reabsorbed and catabolized within the renal tubules (i.e. the degree of proteinuria underestimates protein losses).
 - Other circulating factors alter the production of albumin by the liver in response to protein losses.
- Hypoalbuminaemia itself is not usually severe enough to directly explain the profound oedema of the nephrotic syndrome.
- Potential explanations:
 - The (classical) 'underfill' hypothesis: low plasma oncotic pressure \rightarrow \downarrow circulating volume \rightarrow Na^+ and water retention.
 - The 'overfill' hypothesis: proteinuria directly causes \uparrow tubular Na^+ reabsorption.

- Hyperlipidaemia is caused by ↑ hepatic lipoprotein synthesis 2° to reduced plasma oncotic pressure.
- Thrombotic tendency is caused by ↑ hepatic synthesis of procoagulant factors, ↑ platelet aggregation, and ↑ urinary losses of anticoagulant factors.

Causes of the nephrotic syndrome

In descending order of frequency in adults:

- Membranous nephropathy.
- Minimal change nephropathy.
- SLE.
- Focal and segmental glomerulosclerosis.
- Mesangiocapillary (or membranoproliferative) glomerulonephritis (MCGN).
- Renal amyloidosis.
- IgAN.
- Light chain deposition disease.

► Diabetic nephropathy may also present with nephrotic range proteinuria and the nephrotic syndrome.

Investigation of the nephrotic syndrome

- SCr, eGFR, U&E, albumin and total protein, LFT, bone profile.
- Lipid profile (preferably fasting).
- Urine microscopy for casts or lipid bodies (📖 p. 25).
- uPCR (or uACR).
- Urinary selectivity index (particularly in children). Calculated as the transferrin:IgG ratio. Selective proteinuria refers to loss of proteins of lower MW (<100kDa), such as albumin or transferrin. Non-selective proteinuria includes proteins of higher MW, such as Igs (📖 p. 60).
- Consider full immunological and serological screen (📖 p. 40).
- USS kidneys.
- Renal biopsy (📖 p. 80).

The nephrotic syndrome: general management principles

Salt and fluid restriction

- ↑ Na⁺ retention and ↑ blood volume → dependent oedema.
 - ► Monitor volume status carefully. Include regular measurement of weight, aiming for 0.5–1kg loss/day. Chart intake and output wherever possible (however, urinary tract catheterization is rarely necessary).
 - Salt-restrict to ≤2g/day.
 - Diuretics: a loop diuretic, such as furosemide, e.g. 40mg/day PO, increasing, as necessary, to 250mg daily. In massive oedema, IV diuretics may be required to overcome impaired oral drug absorption (2° to gut oedema).
 - Many clinicians use IV furosemide in combination with salt-poor albumin (e.g. 50–100mg furosemide in 100mL 20% human albumin solution over 1h) to augment natriuresis and diuresis; however, the enhanced effect may simply be due to volume expansion.
 - Add-on thiazide-type diuretics (e.g. metolazone 2.5–5mg PO od) may help to promote diuresis through a synergistic effect with high-dose loop diuretics (⚠ requires regular (often daily) measurement of Na⁺ and K⁺ to prevent profound electrolyte imbalances—use with caution, especially in an outpatient setting).

Reduction of proteinuria

- Proteinuria will itself aggravate tubulointerstitial inflammation (→ fibrosis) and ∴ accelerate renal damage and functional decline.
- Heavy proteinuria exposes nephrotic patients to infection and malnutrition.
 - Use ACE-I or ARB for their anti-proteinuric effect. Titrate carefully toward full dose (consider night-time administration if hypotension).
 - May reduce proteinuria by up to 50% at 8 weeks and ∴ prevent progression.
 - Treat ↑ BP, aiming for ≤125/75mmHg.
 - Protein restriction to 0.8g/kg/day. ⚠ This requires careful nutritional assessment and dietetic supervision.

Hypercoagulability

- Risk factors for thrombosis in nephrotic syndrome:
 - Duration of syndrome.
 - Degree of proteinuria.
 - Serum albumin <20g/L.
 - Underlying membranous nephropathy (📖 p. 564). ► Up to 20% of patients with nephrotic syndrome 2° to membranous nephropathy will develop a DVT.
- ►► Breathlessness in a nephrotic patient may not always be 2° to volume overload; it may indicate pulmonary thromboembolism.

- Flank pain and haematuria suggest renal vein thrombosis (📖 p. 590).
- Prophylactic anticoagulation with SC heparin (and sometimes warfarin) in high-risk patients (📖 p. 892).
- Formally anticoagulate those with proven DVT or thromboembolic episode.
- Treat for the duration of the nephrotic syndrome; aim INR 2–3.

Infection

- Low IgG levels predispose to infection.
- Treat infections promptly, with appropriate cover for polysaccharide encapsulated organisms: *Strep pneumoniae*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Salmonella typhi*, *Cryptococcus neoformans*, *Pseudomonas aeruginosa* (mnemonic: **Some Nasty Killers Have Some Capsule Protection**).
- Offer persistently nephrotic patients vaccination against pneumococcal disease.
- Infection may also complicate immune suppressive treatment of the nephrotic syndrome (📖 p. 540).

Dyslipidaemia

- Nephrotic syndrome → ↑ hepatic synthesis and ↓ catabolism of LDL cholesterol (possibly in response to ↓ plasma oncotic pressure).
- Successful treatment of elevated LDL cholesterol may prevent CV morbidity and slow decline in renal function.
- Dietary restriction is usually insufficient and drug treatment with statins is often appropriate.
- Treatment of underlying nephrotic syndrome will lead to resolution of dyslipidaemia.

Minimal change disease

Introduction

MCD is less common in adults (~25% of cases of the nephrotic syndrome) than in children. It generally carries an excellent prognosis.

The pathogenesis of minimal change nephropathy (MCD) is uncertain, but altered T lymphocyte activity and production of a glomerular permeability factor (→ podocyte dysfunction) are suspected. Albuminuria essentially results from a failure of the glomerular filter.

Aetiology

May be idiopathic (1°) or 2° to:

- Drugs: NSAIDs (most common), antimicrobials, lithium, bisphosphonates, and penicillamine (many others).
- Cancer: haematological malignancies (most common), solid organ malignancies (rare: more commonly associated with membranous nephropathy).
- Infections (rarely): esp. TB, syphilis, HIV, mycoplasma, HCV.
- Atopy: 30% of MCD patients.
- Immunizations.

Symptoms and signs

- Oedema, often massive, with facial and periorbital swelling, ascites, pleural and pericardial effusions.
- Proteinuria and, rarely, microscopic haematuria on urinalysis.
- Urine may be foamy (protein has a detergent effect).
- Lipiduria may be visible on microscopy as fat bodies.
- May present with infections (esp. skin and soft tissue) or hypotension (2° to hypovolaemia).
- Abdominal pain 2° to spontaneous peritonitis.
- Venous thrombosis (e.g. renal or deep vein).
- AKI (2° to ATI).

Investigations

- SCr, eGFR, U&E, ↓ albumin, LFT, bone profile, ↑ cholesterol.
- uPCR or uACR (tests for selective proteinuria may be helpful) (📖 p. 60).
- Urine microscopy (may show lipid bodies, hyaline or granular casts).
- Renal biopsy in adults.

Histology

- Normal on light microscopy (hence 'minimal change').
- Negative immunohistochemistry or immunofluorescence.
- EM reveals diffuse effacement of podocyte foot processes.

Treatment

- Symptomatic treatment, as outlined on 📖 p. 556.
- MCD remits rapidly with corticosteroids therapy; 80–90% of adults will be in remission after 12 weeks of therapy.

- Prednisolone 1mg/kg daily (to maximum of 80mg/day) until remission achieved.
- Taper prednisolone fortnightly, then weekly, until discontinued.
- ► Ensure treatment is continued for at least 12 weeks at first presentation to minimize risk of relapse.
- Taper slowly, e.g. over 6 months.
- See initiating immunosuppression (📖 p. 540).
- Relapse can be expected in 30–70% of cases.
 - First relapse and infrequent relapses should be treated as described earlier. If relapses are more frequent and respond quickly to steroids, then taper immediately on remission, aiming for a shorter course.
- Certain subgroups will be more difficult to treat.
 - Recurrent relapses occur despite initial response to treatment. ‘Frequent relapse’ is generally defined as two relapses inside 6 months.
 - Relapse occurs during steroid treatment or within 2 weeks of steroid withdrawal (‘steroid-dependent’).
 - No response to steroids at all, i.e. no remission within 12 weeks of treatment (‘steroid-resistant’).
- ► In these situations, it is important to review the histology to ensure diagnosis is definitely MCD, rather than a potentially less steroid-responsive alternative, such as FSGS (📖 p. 560). In some cases, this may necessitate a repeat kidney biopsy to ensure that glomerular sampling has been adequate.
- See initiating immunosuppression (📖 p. 540).
- Consider:
 - Cyclosporin 3–5mg/kg/day in two divided doses for 12 months.
 - ⚠ Monitor GFR carefully (⁵¹Cr-EDTA GFR is the most accurate method for monitoring any subtle decline in GFR, e.g. annually) to avoid or limit ciclosporin nephrotoxicity.
 - Tacrolimus 0.05–0.1mg/kg/day in divided doses is an alternative.
 - CNIs can be cautiously tapered to the minimum dose required to sustain remission once this has been achieved for 3 months. Consider stopping therapy at 1–2 years.
 - Cyclophosphamide 2–2.5mg/kg/day for 8–12 weeks, then stop.
 - If remission not achieved with one regimen, consider the other. CNIs may be preferred in ♀ of childbearing age.
 - MMF has been used as a steroid-sparing agent in children, and small studies suggest modest benefit in adults.
 - Rituximab: several case reports suggest benefit. Further clinical trials are awaited.

Focal and segmental glomerulosclerosis (FSGS)

Background

FSGS is used primarily as a histological description, but also to refer to a particular disease entity.

2° FSGS occurs in the context of glomerular damage and 'dropout' in an already injured kidney where haemodynamic stresses damage remaining nephrons (so-called 'hyperfiltration injury').

1° or idiopathic FSGS refers to a *de novo* glomerulopathy, rather than the result of associated disease.

Primary FSGS

Introduction

- ♂ > ♀ (with an additional higher risk of progressive CKD in ♂).
- It is 3× more common in black patients (where 1° FSGS causes ~2/3 of the nephrotic syndrome). Black patients are more likely to have mutations in the apolipoprotein L1 (*APOL1*) gene.
- Cause remains uncertain, however podocyte injury with subsequent abnormal podocyte responses is characteristic of the disease.
- As 1° FSGS disease recurs after transplantation (often immediately), a circulating factor capable of disturbing glomerular permeability has been implicated in some patients. This has not yet been fully characterized, but candidates include the soluble form of the urokinase receptor (suPAR) and VEGF.

Symptoms and signs

- Proteinuria (often very heavy); nephrotic syndrome ~80%.
- Microscopic haematuria (~50%).
- ↑ BP (~40%).
- Impaired renal function (~25% at presentation).

Young black men presenting with heavy proteinuria (>10g/day), profound hypoalbuminaemia (albumin <20g/L), and renal impairment tend to follow a more severe course, often resulting in ESRD.

Investigations

- SCr, eGFR, U&E, ↓ albumin, LFT, ↑ total and LDL cholesterol.
- Urinalysis, uPCR, or uACR (tests for non-selective proteinuria may be helpful) (📖 p. 60).
- Urine microscopy (may show lipid bodies, hyaline or granular casts).
- Renal biopsy.

Histology

- A focal (affecting some, but not all, glomeruli) and segmental (affecting part, but not all, of the glomerular tuft) process (see Fig. 7.7).
- Mesangial matrix expansion, glomerular sclerosis, endocapillary hypercellularity (including foam cells) and hyalinosis (hyaline deposits in the permeable capillary wall) are all variably present.

- No abnormalities may be apparent if the sample size is small, reflecting the focal nature of the disease. Such cases may then be mislabelled as minimal change disease. Biopsies that include juxtaglomerular glomeruli from the corticomedullary junction (affected early in the course of the disease) have a greater chance of detecting sclerotic lesions.
- ATN and tubulointerstitial fibrosis are not uncommon.
- Immunostaining: no immune deposits, but IgM and C3 may be trapped in sclerotic lesions.
- EM: foot process effacement and podocyte degeneration.

Sub-classification

Sub-classification of both 1° and, to a lesser extent, 2° FSGS into several histological variants may have prognostic significance:

- *Classic FSGS*: the prototype.
- *Cellular variant*: at least one glomerulus has segmental endocapillary hypercellularity with capillary occlusion.
- *Tip variant*: at least one segmental sclerosis affects the outer 'tip' of the glomerulus alongside the proximal tubule. Potentially more steroid-responsive with a better prognosis.
- *Collapsing variant*: collapsing FSGS is characterized by collapse and sclerosis of the entire glomerular tuft, with GBM wrinkling, cystic tubular changes, and interstitial fibrosis. There is no endocapillary proliferation.
 - ▶ Often due to HIVAN (📖 p. 676), but occurs with other viral diseases (esp. parvovirus B19). Also described in other situations, e.g. following high-dose bisphosphonates. Collapsing FSGS typically presents with torrential nephrotic syndrome and rapidly declining renal function.
- *Perihilar variant*: perihilar hyalinosis and sclerosis in >50% of the glomeruli with sclerotic lesions. Often seen with the hyperfiltration injury of 2° FSGS.

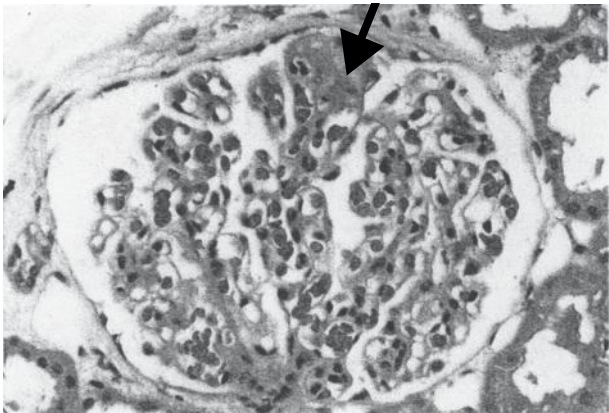


Fig. 7.7 FSGS: a segmental sclerosis in an affected tuft.

Secondary FSGS

A less specific histological finding, usually resulting from glomerular hyperfiltration (an adaptive response to maintain GFR). Histologically, glomerulomegaly and perihilar sclerosis may be more prominent, with less marked podocyte hyperplasia and, on EM, less widespread foot process effacement.

Secondary FSGS tends to present with less proteinuria and hypoalbuminaemia than the primary variant; however, progressive CKD is relatively common. It is associated with the following conditions:

- Familial (see below).
- Infection (podocyte invasion):
 - HIV-associated nephropathy (HIVAN), parvovirus B19.
- Drugs (podocyte toxicity):
 - Pamidronate, lithium, α interferon, and heroin.
- Congenital or acquired nephron mass reduction:
 - Renal dysplasia, reflux nephropathy, renovascular disease, partial or unilateral nephrectomy.
- Hyperfiltration as part of a disease process:
 - Morbid obesity, diabetic nephropathy, pre-eclampsia, sickle cell disease.
- Any cause of glomerular disease with progressive scarring:
 - E.g. membranous GN, IgAN, Alport syndrome, thrombotic microangiopathy, vasculitis.

Inherited FSGS

Genetic diseases may lead to FSGS through the mutation of genes responsible for podocyte differentiation and function. These provide useful insights into podocyte function and podocytopathies. However, genetic testing is unnecessary in adults, unless there is a family history, as mutations are found in a small minority only and do not influence treatment.

Transient receptor potential cation 6 channel (TRPC6)

AD inheritance. A non-selective cation channel that localizes to the slit diaphragm where it associates with podocin and nephrin. Mutations cause childhood nephrotic syndrome.

α -actinin 4


AD inheritance. ACTN4 is an actin-bound cross-linking protein important for podocyte cytoskeletal integrity. Presents with low-grade proteinuria and slowly progressive CKD.

Podocin (NPHS2)

AR inheritance. NPHS2 encodes podocin, an integral membrane protein that is localized to the slit diaphragm where it interacts with nephrin. Almost 50 mutations have now been identified. May be responsible for ~1/3 of steroid-resistant nephrotic syndrome in children.

FSGS management

Overview



- Symptomatic treatment, as outlined on  p. 556.
- ► For 2° FSGS, treat the underlying cause where possible.
- For 1° FSGS, the initiation of immune suppression is based on estimates of renal prognosis and likely response. For non-nephrotic proteinuria, symptomatic treatment and watchful waiting are generally advocated.

Poor prognostic factors

- Severe proteinuria (e.g. >10g/day).
- Progressive CKD.
- Interstitial fibrosis on histology.
- Black race.
- No response to treatment.
- Histology: presence of collapsing variant (bad) or tip lesion (good).

If nephrotic, spontaneous remission is uncommon. Progression to ESRD in ~50% at 5 years if untreated. Some have a more protracted course, with slow decline in kidney function over decades.

Disease-modifying treatment.

- ► See initiation of immune suppression on  p. 540.
- Prednisolone 1mg/kg/day (max 80mg) (or alternate day 2mg/kg) for a minimum of 4 weeks. Continue, as tolerated, for 16 weeks or until remission is achieved. ▲ FSGS is slow to respond, and shorter courses of steroids are unlikely to be of benefit.
- If response, taper steroids to cessation over 6 months.
- Unlike minimal change, a degree of proteinuria often persists: remission may be complete (<0.3g/day urinary protein + serum albumin >35g/L + normal renal function) or partial (<3.5g/day urinary protein + 50% reduction from peak + stabilization of renal function).
- Expect complete or partial remission in ~40–60%.
- Those that relapse whilst on (tapering) steroids or <2 weeks after cessation (on ×2 occasions) are 'steroid-dependent', and those with no reduction in proteinuria at 16 weeks are 'steroid-resistant'.
- In these groups:
 - Continue low-dose (0.15mg/kg/day) prednisolone.
 - Add ciclosporin 3–5mg/kg/day in two divided doses. Treat for 6 months. Aim for trough levels 125–225ng/mL. Consider measuring accurate isotopic GFR at baseline.
 - If response (expect in ~70%): continue for 12 months, then taper dose, and stop. Ciclosporin dependence, with relapse on drug withdrawal, is not uncommon.
 - Tacrolimus 0.1–0.2mg/kg/day in two divided doses is an alternative.
 - MMF or cyclophosphamide (both with corticosteroids) have been used in this situation but do not enjoy a robust evidence base.
- 🩺 Plasma exchange is sometimes used as adjunctive therapy in severe disease unresponsive to other measures, with the aim of removing a pathogenic circulating factor in some cases. Relapse after treatment is common. PEX is an important part of the treatment of recurrent FSGS post-transplantation ( p. 418).

Membranous nephropathy (MN)

Introduction

Membranous nephropathy (MN) is one of the commonest causes of the nephrotic syndrome worldwide, with a peak incidence in the 4th to 6th decades, 2 ♂:1 ♀.

May be idiopathic (IMN) (75%) or secondary (25%) (📖 p. 565).

Pathogenesis

Animal models of MN suggest *in situ* formation of immune deposits on the outer surface of the GBM (see Fig. 7.8). These deposits activate complement, leading to podocyte injury. Several proteins have been implicated in the development of MN.

- The phospholipase A2 receptor: a transmembrane receptor present in podocytes. Autoantibodies to this receptor (anti-PLA2) have been demonstrated in ~70% of 'idiopathic' MN.
- Neutral endopeptidase: anti-neutral endopeptidase antibodies have been implicated in a rare antenatal form of MN.
- Cationic bovine serum albumin (cBSA): antibodies to cBSA have been demonstrated in a small number of MN in childhood cases. This protein may be absorbed through the immature GI tract and subsequently lodge in the glomerular capillary wall.

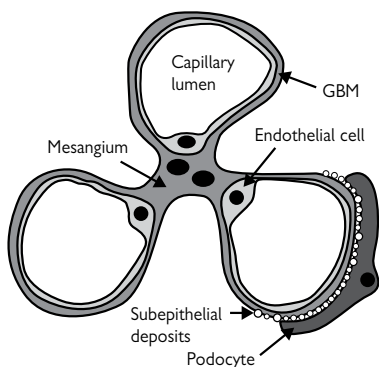


Fig. 7.8 Cartoon of subepithelial deposits in MN.

Symptoms and signs

- Proteinuria, occasionally sub-nephrotic or asymptomatic, but often heavy and associated with the nephrotic syndrome (~80%).
- Microscopic haematuria is relatively common.
- ↑ BP.
- Venous thromboembolism (▶ up to 20% of patients with nephrotic syndrome 2° to membranous nephropathy will develop a DVT).

Secondary MN

- More common worldwide than IMN. Presentation with nephrotic syndrome may not coincide with presentation of underlying disease. MN may precede the presentation of malignancy by many years. Development of nephrotic syndrome in a patient with a known malignancy may herald a relapse of their cancer.
- Infections: HBV, HCV, HIV, malaria, syphilis, leprosy, schistosomiasis.
- Neoplasms: solid tumours (including lung, colon, breast, kidney, stomach, oesophageal, ovarian, prostate), lymphoma, leukaemia, mesothelioma.
- Autoimmune disease: SLE, thyroiditis, dermatitis herpetiformis, sarcoidosis, inflammatory bowel disease, myasthenia gravis.
- Drugs and toxins: NSAIDs, captopril, gold, penicillamine, lithium, clopidogrel.

Investigations

- SCr, eGFR, U&E, ↓ albumin, LFT, bone profile, ↑ total and LDL cholesterol, ↓ Igs common (IgG > IgA), HBV and HCV serology, ANA.
- uPCR or uACR (tests for non-selective proteinuria may be helpful) (📖 p. 60).
- Urine microscopy (may show lipid bodies, hyaline or granular casts).
- Renal biopsy.
- Consider investigations for 2° causes of MN.

Approaching MN

Careful history and examination are essential. Focus on:

- Drug history.
- Risk factors for hepatitis viruses or other infections (travel, sexual history, blood transfusions, etc.).
- Malignancy?
 - <10% of cases, but proportion increases with age.
 - Check for recent weight loss and any localizing symptoms.
 - If history and physical examination alone do not suggest an associated neoplasm, extensive investigation is unwarranted and unlikely to reveal a tumour.
 - 🏥 Some clinicians advocate additional imaging (e.g. CT chest, abdomen, pelvis, mammography in ♀) + upper and lower GI endoscopy in patients aged >50.

Histology

- *Light microscopy*: often normal, but, in more advanced cases, diffuse GBM thickening, with 'spikes' of GBM extending around subepithelial deposits, are usually evident (best seen on silver stains). Variable degrees of ATI and tubulointerstitial fibrosis may also be seen.
- *Immunostaining*: granular IgG ± C3 deposits within capillary wall. Presence of the IgG4 subclass may be a pointer toward 2° MN.
- *EM*: subepithelial electron dense deposits. Foot process effacement.

Idiopathic MN: treatment

Treatment

General measures

Symptomatic treatment of the nephrotic syndrome (📖 p. 556).

Treatment of secondary MN

Treating the underlying condition (e.g. treatment of HBV or resection of tumour) may lead to remission of the MN and the nephrotic syndrome in many cases. There is rarely, if ever, a role for immune suppression.

Natural history and risk stratification

The natural history of IMN is variable, with 20–30% progressing to ESRD and about 25–40% remitting spontaneously. It has ∴ traditionally been referred to as a ‘disease of thirds’: ~1/3 spontaneously remit, ~1/3 continue to exhibit low-grade proteinuria with normal renal function, and ~1/3 have progressive CKD, eventually leading to ESRD.

Remission may be complete (<0.3g/day urinary protein, with normal serum albumin and normal renal function) or partial (<3.5g/day urinary protein and 50% reduction from peak protein excretion, with an improvement in serum albumin and stabilization of renal function).

Aim to predict the course of the disease.


Low risk

- Normal renal function.
- Age <50.
- ♀.
- Proteinuria <4g/day or spontaneously declining proteinuria.
- Management:
 - Symptomatic treatment (📖 p. 556).
 - Expect remission (may occur up to 2 years after diagnosis; mean ~15 months), but regularly reassess risk.

High risk

- Progressive renal impairment.
- Age >50.
- ♂.
- Proteinuria >8g/day.
- Persistent proteinuria >4g/day for >6 months, with no evidence of decline (despite ACE-I/ARB).
- Management: consider disease-modifying treatment with immune suppression, unless renal biopsy demonstrates excessive interstitial scarring (∴ likely to be irretrievable) or kidneys are small on USS. Most clinicians will wait for 6 months to see if spontaneous remission occurs, but treat earlier if severe, symptomatic nephrotic syndrome, or early decline in renal function.

Immune suppression

- Disease-modifying therapy: the aim of immunosuppression is to reduce proteinuria, spare renal function, and induce complete, or partial, remission.
- Achievement of either complete or partial remission, either spontaneously or after treatment, is associated with a much improved prognosis.
- ► See initiation of immune suppression on  p. 540.
- Alternating monthly steroids and alkylating agents for 6 months—the ‘Ponticelli regimen’:
 - Month 1: IV methylprednisolone 1g × 3, then oral methylprednisolone (0.5mg/kg/day) for the remainder of the month.
 - Month 2: oral cyclophosphamide 2.0mg/kg/day (or chlorambucil 0.15–0.2mg/kg/day).
 - Month 3: repeat month 1.
 - Month 4: repeat month 2.
 - Month 5: repeat month 1.
 - Month 6: repeat month 2.
- For practical reasons, many clinicians adapt this to a non-cyclical regimen, giving prednisolone 1mg/kg/day PO daily (max 60 mg) (with or without 3× pulses of IV methylprednisolone at the outset) + cyclophosphamide 1.5–2.0mg/kg/day PO, tapering steroids against response. 🌀 Whilst this is common practice, it does not have the evidence base available for the cyclical regimen.
- Most clinicians are less familiar with chlorambucil so prefer to use cyclophosphamide.
- CNIs are an alternative, particularly where alkylating agents are undesirable (or have been unsuccessful).
 - Cyclosporin 3.5–5mg/kg/day in two divided doses, with low prednisolone (0.15mg/kg/day) for at least 6 months.
 - Tacrolimus 0.05–0.075mg/kg/day in two divided doses may also be used.
 - Start at lower dose, and titrate up, as tolerated. ⚠ Watch GFR closely. CNI levels should be monitored, particularly during the initial stages.
 - If no response, stop at 6 months. In those that respond, aim to reduce to the minimum dose that maintains remission, and continue for at least 12 months.
- MMF may have a role (in combination with steroids), but supporting evidence is currently lacking, and there appears to be a higher risk of relapse.
- Rituximab (e.g. 375mg/m² weekly × 4 doses) has been used, with encouraging success in observational studies. Long-term follow-up is currently lacking, so relapse rates are unknown.

Relapse

- Treat with the same regimen that was successful initially, although an alkylating agent should, in general, only be used once more.

Hereditary nephropathies

Alport syndrome

Classically presents as a triad of:

- Family history of progressive nephropathy.
- Sensorineural deafness.
- Ocular abnormalities.

Defective basement membrane formation in the glomerulus, cochlea, and eye accounts for these findings. Although inheritance is varied, an X-linked inherited mutation in the *COL4A5* gene (>200 described) that encodes $\alpha 5$ type IV collagen accounts for 80% of cases. This leads to afflicted σ° , with ρ carriers. Autosomal recessive (AR) forms account for ~15% and autosomal dominant (AD) for ~5% (gene: *COL4A3/COL4A4* on chromosome 2).

Affects ~1 in 5,000 live births.

Thin membrane disease (TMD)

A common AD inherited (occasionally sporadic) familial condition, presenting with microscopic haematuria, almost always with normal renal function. TMD was previously known as 'benign familial haematuria'. It is present in ~5% of post-mortem studies and is a relatively common finding during the assessment of potential live kidney donors. The normal GBM is ± 350 nm thick—but, in TMD, it is often less than 200nm (although otherwise structurally normal).

The underlying defect probably affects type IV collagen integration into the GBM and results in a partial failure of basement membrane function. 40% of families have mutations in *COL4A3/COL4A4* (>20 described, usually a single nucleotide substitution associated with a single family). These probably represent the benign end of the spectrum of Alport syndrome. The additional TMD genetic loci have not yet been identified.

Symptoms and signs

Both present with persistent microscopic haematuria. This occurs earlier in Alport's—no haematuria by age 10 in a σ° makes the diagnosis unlikely.

Alport's: proteinuria (often nephrotic range) and \uparrow BP usually present by adolescence. Progressive CKD \rightarrow ESRD by the 3rd to 4th decade (~2% of an ESRD programme). Severity is often consistent within a family. High-tone sensorineural deafness (in the majority) and anterior lenticonus (conical, rather than spherical, lens, leading to distorted vision: ~20%). X-linked ρ carriers often have microscopic haematuria alone. However, proteinuria and progression to ESRD by 5th decade in ~10–15%.

The AR form is clinically similar to disease in X-linked σ° . The AD form is clinically very heterogeneous.

TMD: often a diagnosis of exclusion. Probably accounts for ~25% of all microscopic haematuria presenting to a renal clinic (the majority of whom will not undergo a renal biopsy). Macroscopic haematuria in ~20%. Proteinuria, \uparrow BP, and renal impairment are rare. TMD has no extrarenal manifestations.

Investigations

See Table 7.2.

- Documentation of inheritance may be very helpful: AD inheritance of haematuria, with no proteinuria, CKD, or extrarenal manifestations, suggests TMD (although a confirmatory biopsy in at least one family member is desirable).
- Urinalysis \pm microscopy, uPCR or uACR. SCr, eGFR, U&E, albumin.
- Audiometry for subclinical hearing deficits and ophthalmic assessment.
- Skin biopsy with negative $\alpha 5$ type IV collagen staining is much less invasive than a renal biopsy and may be helpful in the assessment of possible X-linked Alport syndrome.
- Renal biopsy:
 - *Alport's*: non-specific glomerulosclerosis and tubulointerstitial scarring on LM (esp. if \uparrow SCr). A thin GBM on EM, with a characteristic 'basket weave' pattern, is characteristic.
 - *TMD*: normal light microscopy. EM demonstrates reduction in GBM thickness.
 - Staining of the GBM for the α chain of type IV collagen is instructive. In X-linked and AR Alport syndrome, the $\alpha 3$, $\alpha 4$, and $\alpha 5$ chains are absent (with a mosaic pattern of expression in ♀ carriers); in AD Alport syndrome, the $\alpha 4$ and $\alpha 5$ chains are absent, whereas, in TMN, normal α chain distribution is preserved.
- Genetic testing for *COL4A3/A4/A5* mutations is available, but the large number of mutations means it is not always straightforward. However, it may be useful for prenatal diagnosis in previously characterized families.

Management

- Patients with uncomplicated TMD can be reassured but should be followed up at annual intervals (urinalysis \pm uPCR, BP, and eGFR).
- No specific treatment for Alport syndrome. As with all progressive nephropathies, good control of BP, use of ACE-I/ARB, and proteinuria reduction should be considered early; this includes ♀ carriers.
- Family members should be screened for haematuria and \uparrow BP.
- Offer genetic counselling.

Transplantation and Alport syndrome

In $<5\%$, transplanted Alport patients may develop *de novo* anti-GBM antibodies that cause an RPGN; i.e. donor $\alpha 5$ type IV collagen is recognized as non-self. It is not a contraindication to transplantation.

Table 7.2 TMD or Alport syndrome

	TMD	Alport
Haematuria	+ to +++	++
Proteinuria	±	+++ (>3g/day)
↑ BP	–	+++
Renal dysfunction	±	+++
Deafness/lenticonus	–	++
History of ESRD	–	+
Father-to-son transmission	+	– (if x-linked)

Nail-patella syndrome

A rare (~20 pmp) autosomal dominant condition that has renal involvement in ~50% cases.

It is caused by mutation of the *LMX1B* gene found on chromosome 9q34. This codes for a transcription factor critical to other genes involved in the maintenance of GBM structure and function, including *COL4A3* and *COL4A4*.

Renal disease Usually presents in adolescence: microscopic haematuria, proteinuria, ↑ BP, and CKD. ESRD in <10%, usually in middle age.

Other features Absent or hypoplastic patellae (~70%), often leading to secondary osteoarthritis. Hypoplasia of the radial head and distal humerus leads to a limited range of forearm movement. 80% develop iliac horns (symmetrical osseous processes arising from the iliac wings), which are asymptomatic but visible on X-ray. Bilateral, symmetrical nail abnormalities are present (from birth) in the majority, affecting both fingers and toes, but commonly the thumb and index finger. Nails may be absent, dysplastic, misshapen, ridged, or discoloured.

Histology Light microscopy can resemble FSGS. Immunostaining may show IgM and C3 in sclerotic areas. EM is diagnostic, demonstrating irregular basement membrane thickening with areas of rarefaction, giving rise to a 'moth-eaten' appearance. Foot process effacement will also be present.

Management As for all progressive proteinuric nephropathies. No specific treatment is available. Offer genetic counselling.

Miscellaneous mesangioproliferative glomerulonephritides

Introduction

These uncommon lesions, sometimes referred to collectively as 'mesangial proliferative GN' remain partially characterized. They are increasingly viewed as part of the spectrum of minimal change or FSGS and usually present with proteinuria (often nephrotic range), microscopic haematuria \pm \uparrow SCr. They are all characterized, in part, by focal or diffuse mesangial proliferation, which might be a relatively non-specific glomerular response to injury, although consensus on the specific histological criteria required for diagnosis are lacking. They are often a diagnosis of exclusion.

They tend to be poorly steroid-responsive and associated with a poor renal prognosis. Cytotoxic therapy has been tried, with variable degrees of success.

C1q nephropathy

A mesangial proliferative GN, originally recognized for its close histological resemblance to lupus nephritis, in the absence of any serological or clinical criteria for the diagnosis of SLE. Histology shows a characteristic heavy deposition of C1q-containing deposits in the mesangium and elsewhere, with varying degrees of mesangial hypercellularity and 'wire loop' capillary wall thickening. There are two dominant clinical and pathological phenotypes: (i) a minimal change or FSGS-like lesion, which typically presents as steroid-unresponsive nephrotic syndrome; (ii) an immune complex-mediated glomerulonephritis, associated with several different types of glomerular lesion, typically presenting as CKD. C1q nephropathy is now generally considered as an FSGS variant.

IgM nephropathy

Is a similar lesion, again characterized by mesangial hypercellularity on light microscopy, with diffuse granular mesangial IgM and C3 deposition on immunostaining. IgM may also be non-specifically deposited in areas of sclerosis in many glomerular diseases, but here it is seen in the mesangium of non-sclerotic glomeruli. EM reveals generalized foot process effacement. It is still debated whether it represents a distinct disease entity or a variant of minimal change disease or FSGS. The most important clinical distinction is that it is poorly steroid-responsive and \therefore associated with a poorer prognosis. Presents with proteinuria, often heavy, \pm microscopic haematuria.

Idiopathic mesangial proliferative GN

Essentially, a diagnosis of exclusion. There is mesangial proliferation on biopsy but no immune complex deposition on immunostaining.

Thrombotic microangiopathies

Introduction

Thrombotic microangiopathy (TMA) is a histologic description encompassing several rare, but related, disorders, characterized clinically by a triad of haemolysis, consumptive thrombocytopenia, and tissue ischaemia (caused by platelet aggregation and thrombotic occlusion of small vessels) (see Table 7.3).

The two classical clinical presentations involving TMA are thrombotic thrombocytopenic purpura (TTP) (p. 576) and the haemolytic uraemic syndrome (HUS) (p. 578) (see Table 7.3).

These conditions affect both adults and children and carry a very poor prognosis if left undiagnosed and untreated.

► Suspect in the context of otherwise unexplained thrombocytopenia and microangiopathic haemolytic anaemia (MAHA).

HUS vs TTP?

These two conditions are increasingly considered as different presentations of the same underlying pathophysiological process (with the exception of diarrhoea associated (D+) HUS, particularly in childhood (see p. 578)).

- TTP—predominantly neurological ± AKI (minimal).
- HUS—AKI generally dominates the clinical picture. Neurological involvement minimal/absent.

In view of this, they are now often referred to as 'TTP-HUS', with less weight being given to differentiating between the two.

Clinical assessment

- Take a careful history for a diarrhoeal illness. Examine for petechiae, purpura, signs of systemic sclerosis, splenomegaly. Check BP and fundi.
- Urinalysis for haematuria, proteinuria, and bilirubinuria (haemolysis).
- FBC (↓ Hb, ↓↓ Plt), film for red cell fragments (MAHA), clotting, D-dimers/FDP, G&S, ↓ haptoglobins, Coombs' test (negative).
- ↑↑ LDH, ↑ β-HCG., U&E, LFT (↑ bilirubin), urate.
- Blood and stool cultures.
- ANA, dsDNA, complement, antiphospholipid antibodies (p. 40).
- ADAMTS13 activity (see p. 576).
- Consider renal biopsy only once (and if) platelet count normalizes.

Histology

All TMAs share similar renal histology. Fibrin thrombi are present in the glomerular capillaries, with resultant ischaemia. Fluorescence for Ig and complement negative. EM shows capillary thrombi, fibrin deposition, and endothelial injury and swelling.

Table 7.3 Causes of TMA

Primary TTP-HUS	Secondary TTP-HUS
Hereditary ('atypical') Idiopathic/autoimmune	'Typical' HUS secondary to Shiga toxin Malignant hypertension Autoimmune/vascular: <ul style="list-style-type: none"> ● SLE ● Systemic sclerosis ● Rheumatoid arthritis ● Systemic vasculitis ● Antiphospholipid syndrome ● PNH Drugs: <ul style="list-style-type: none"> ● Hypersensitivity reaction (e.g. quinine, ticlopidine, clopidogrel) ● Dose-related (e.g. ciclosporin, chemotherapy) Pregnancy/post-partum HIV Metastatic malignancy DIC Allogeneic haematopoietic cell transplantation

Broad categories of TMAs are shown. These differ in target population and pattern of organ involvement. Clinical and laboratory findings often overlap, and diagnostic uncertainty is not uncommon.

Thrombotic thrombocytopenic purpura (TTP)

Pathogenesis

von Willebrand factor is released from endothelial cells as a large polymer and cleaved to form the mature polypeptide that acts as a matrix for haemostasis. The protease responsible for this cleavage is the zinc metalloproteinase ADAMTS13. If vWF-cleaving protein activity is impaired (either an IgG autoantibody directed against the protease or an inherited mutation of the gene encoding ADAMTS13), then abnormally large vWF multimers enter the circulation where they bind and activate platelets. This leads to spontaneous platelet aggregation, platelet-rich (though fibrin-poor) thrombus formation and a systemic microangiopathy, with widespread deposition of platelet-vWF complexes (e.g. brain/kidney/mesenteric vessels).

Interestingly, ADAMTS13 knockout mice do not develop a TMA, suggesting a 'second hit' (e.g. an inflammatory or a prothrombotic stimulus) is required to initiate the disease.

Causes

- Hereditary: rare, congenital mutations of the *ADAMTS13* gene (e.g. Upshaw–Schulman syndrome)
- Autoimmune: 40–70% of all TTP. Autoimmune inhibition of ADAMTS13. IgG autoantibodies against ADAMTS13 have also been demonstrated in drug-related TTP (e.g. ticlopidine, clopidogrel).

Clinical features

Classic pentad:

- Fever.
- Microangiopathic haemolytic anaemia.
- Thrombocytopenic purpura.
- CNS involvement (confusion, fits, or other neurological abnormality).
- Renal involvement (AKI).

↑ BP is more common with HUS than TTP.

△ Note: patients with profound ADAMTS13 deficiency can present with bloody diarrhoea (non-infectious), presumably secondary to gut ischaemia.

Investigations (see also p. 574)

For disease monitoring: ↓↓ Plt, blood film for red cell fragments, ↑↑ LDH, ↓ haptoglobins. Low ADAMTS13 activity (<5% normal) in the correct clinical context is diagnostic (however, the result of this specialist investigation may not be available to inform management decisions).

Management

Treatment aims to restore the ability to cleave vWF.

Plasma exchange (PEX) Allows large-volume plasma infusion as well as removal of vWF-cleaving protein inhibitor, esp. if AKI with oligo-anuria (where plasma infusion without exchange may cause volume overload).

- Initiate ASAP, and continue daily until 2 days after remission (Plt count and LDH normalize). Usually 7–16 days.
- Exchange one plasma volume/day (📖 p. 950).
- May require hydrocortisone 100 mg + chlorphenamine 10 mg IVI to prevent allergic reactions to large volumes of plasma.

Fresh frozen plasma (ideally platelet-poor) or cryosupernatant infusion. As 25–30mL/kg/day until improvement. ► But only if passing urine: beware volume overload. This is inferior to PEX but is efficacious if PEX is not available.

Rituximab may have a role in more severe disease (particularly with severe neurologic involvement), non-responders to PEX, and if disease worsens despite treatment. Rituximab 375mg/m² weekly × 4 (given in addition to steroids and PEX) appears to be safe and effective and reduce relapses.

Other avoid platelet transfusion unless life-threatening bleeding ('fuels the fire'). No role for aspirin or anticoagulants. For severe disease, consider add-on prednisolone 1mg/kg/day or IV immunoglobulin, in addition to rituximab.

Prognosis

Mortality remains ~10–20%. Prompt recognition and treatment will reduce this. A third will relapse. Renal survival is good, with dialysis-requiring AKI unusual in TTP (more common in HUS).

Haemolytic uraemic syndrome (HUS)

Introduction

HUS is a renal-limited TMA, with widespread complications. There are three forms: (i) typical, (ii) atypical, and (iii) autoimmune. All present with AKI, thrombocytopenia, and MAHA.

Typical (80–90%)

Associated with diarrhoea (D+).

Peak incidence in summer. Usually affects children <5 years. Occurs after food poisoning (esp. undercooked meat, unpasteurized milk). Pathogenic bacteria produce a Shiga-like exotoxin that is able to translocate, perhaps via neutrophils, across inflamed colonic mucosa into blood. It then binds glomerular epithelial cells with high affinity causing the release of prothrombotic factors and ultra-large vWF multimers.

Atypical (10–15%)

Not associated with diarrhoea (D–).

Factor H deficiency (a complement regulatory protein) causes relapsing or familial HUS. Deficiencies in other factors, e.g. C3, B, I, and CD46 (membrane cofactor protein), cause a similar syndrome.

Drugs and non-diarrhoeal infections can cause an HUS-like syndrome. These are generally associated with no (or only minor) reduction in ADAMTS13, suggesting a different pathophysiology to TTP.

Autoimmune—DEAP-HUS (deficiency of complement factor H-related (CFHR) plasma proteins and autoantibody-positive HUS) is a novel subtype, affecting children. It is due to a combination of acquired and genetic factors and has a favourable response to treatment.

Several hypotheses have been proposed for the pathophysiological basis of HUS-TTP in context of a normal ADAMTS13. These include endothelial injury (→ loss of, or deficient, VEGF leads to TMA) and increased plasminogen activator inhibitor.

Infections associated with D+ HUS

- *E. coli* O157:H7 subtype (70% of D+ HUS in developed countries).
- *Shigella dysenteriae* serotype 1.
- *Salmonella*, *Campylobacter*, or *Yersinia*.

Associations of D– HUS

- Inherited HUS.
- Drugs: quinine, ciclosporin, tacrolimus, sirolimus, ciprofloxacin, the contraceptive pill, heparin, chemotherapy.
- Infections, e.g. *S. pneumoniae* or rickettsial.



Clinical features

- Triad of microangiopathic haemolytic anaemia, thrombocytopenia, and renal injury.
- Watery or bloody diarrhoea.
- Fever, ↑ BP, AKI, and volume overload.
- May progress to multiorgan failure, with pancreatitis and a cardiomyopathy.

Investigations (see p. 576)

- ↑ WCC common.
- Fresh stool for culture.
- Disease monitoring: ↓ Plt, red cell fragments on film, ↑↑ LDH.

Management

- ► If in doubt, treat as TTP until diagnosis confirmed.
- For D+ HUS, management is supportive alone (including RRT if required).
- No role for anticoagulation. Antibiotics may paradoxically increase Shiga toxin release and should be avoided.
- PEX or plasma infusion do not improve outcome (as, unlike TTP, there is no underlying replaceable causative factor).
- Eculizumab is a monoclonal antibody that blocks complement activity by cleavage of C5 ( p. 391). There is great interest in its use in atypical HUS and for the prevention of relapse post-transplantation ( p. 420).

Prognosis

Poor prognostic factors: ↑ age, high WCC, D- HUS, *S. pneumoniae* or *Shigella* infection, complete anuria.


Acute tubulointerstitial nephritis

Introduction

Acute (tubulo-)interstitial nephritis (AIN) is a common parenchymal cause of AKI. Peak incidence in middle age but can affect all ages. ♂ = ♀. 70–90% of cases are drug-induced, although the spectrum of causative agents has changed.

AIN is characterized by an inflammatory cell infiltrate in the renal interstitium. This is occasionally associated with a systemic delayed-type hypersensitivity reaction (fever, arthritis, rash). Recurrent disease is common on repeat drug exposure.

Common causes of AIN

- Drugs:
 - NSAIDs (including COX-2 inhibitors).
 - Penicillins (classically methicillin), cephalosporins, rifampicin, and sulfonamides. Consider any antibiotic as a potential cause.
 - Proton pump inhibitors.
 - Diuretics.
 - Allopurinol.
 - Antiretrovirals.
- Infections:
 - Tuberculosis, legionellosis, and leptospirosis.
- Autoimmune disease:
 - Sarcoidosis.
 - Sjögren's syndrome.
 - TINU (see  p. 581).

Symptoms and signs

Often asymptomatic until AKI supervenes. The classical presentation of fever, arthralgia, rash, and AKI is rare (~10%). Flank pain (renal swelling → capsular stretch) is uncommon.

Causative drugs may have been started 3–21 days previously, although delayed AIN, occurring up to 18 months after starting a drug, has been described.

There may be clinical evidence of an associated systemic condition, such as Sjögren's syndrome or sarcoidosis.

Investigations

- Urine dipstick may be bland or have modest proteinuria (uPCR usually <100mmol/mg or <1g/day). Microscopic haematuria is rare, and its presence may point toward a glomerular lesion. Urine microscopy may reveal eosinophiluria and white cell casts. EMU for AFB in high-risk patients.
- U&E, bone profile (?↑ Ca²⁺—esp. in sarcoidosis), LFT, FBC + differentials (eosinophilia may be present), ↑ ESR. Consider ANA, anti-Ro, and anti-La (? Sjögren's syndrome).
- USS shows normal-sized (or slightly enlarged) kidneys.
- CXR and serum ACE (? sarcoid).
- Renal biopsy: usually necessary to confirm diagnosis.

Histology

Intense interstitial inflammatory cell infiltrate, consisting of lymphocytes and monocytes (\pm eosinophils). Giant cells and granulomata may point to TB or sarcoidosis. The presence of interstitial fibrosis imparts a worse prognosis, as in all forms of renal injury. Glomeruli are normal.

Management

- Depends, to an extent, on the underlying cause or precipitant.
- Treatment of sarcoidosis (📖 p. 670) are outlined elsewhere.
- ▶▶ Stop offending drug(s).
- 🏠 Corticosteroids:
 - Widely used, although there is no good evidence to support this practice. May hasten recovery but do not appear to influence overall prognosis.
- A reasonable approach:
 - Dialysis-dependent: treat with corticosteroids.
 - Dialysis-independent: observe for up to 14 days following drug withdrawal; if improvement, continue expectant management; if no improvement, treat with corticosteroids.
 - Information from a renal biopsy may also inform decision-making; e.g. acute inflammation with interstitial oedema may favour steroid treatment, whilst established fibrosis would not.
- Treatment with prednisolone 1mg/kg/day PO, tapering slowly against response for a 3–6 month course (📖 p. 540).
- For drug-related AIN:
 - Outcomes: 40% will be left with CKD, and 10% will progress to ESRD. Final GFR does not correlate with the maximal value during the early acute phase. Of those with milder disease, the majority will return to baseline renal function. Even those requiring renal replacement therapy for AKI usually regain independent renal function. Mortality rate <5%.

Tubulointerstitial nephritis and uveitis syndrome (TINU)

Uncommon. Unlike AIN, affects predominantly younger ♀. Presents as anterior uveitis (often bilateral) and AIN (which may be separated in time). Additional features include weight loss, \downarrow Hb, \uparrow ESR, and deranged LFT. Pathophysiology is poorly understood, although IgG antibodies against modified C-reactive protein, (mCRP) may be relevant. Differential diagnosis: autoimmune disease (esp. Sjögren's) and sarcoidosis.

Ophthalmology input should be sought urgently. Treat the renal lesion with 1mg/kg/day prednisolone, tapering slowly against resolution for 3–6 months. Relapse is common, and complete steroid withdrawal may not be possible.

Chronic tubulointerstitial disease

Introduction

Chronic tubulointerstitial disease encompasses a variety of disorders that share similar histological appearances on kidney biopsy. The tubulointerstitial compartment is extensively fibrosed, often with a lymphocytic infiltrate in scarred areas. Tubules are often dilated and atrophic. Glomeruli are largely spared (although glomerular obsolescence may be seen as a result of nephron dropout).

Chronic tubulointerstitial nephritis exists as a distinct diagnosis (drug-induced AIN of any cause may progress if exposure is not limited or the underlying condition is not treated) but chronic tubulointerstitial injury is a feature of progressive CKD of any cause, including glomerulonephritis (📖 p. 200).

Causes

- Drugs (NSAIDs).
- Reflux nephropathy (📖 p. 712).
- Sarcoidosis.
- TB.
- Autoimmune diseases (Sjögren's syndrome).
- Metabolic causes, e.g. chronic \downarrow K^+ (e.g. in anorexia nervosa).
- Heavy metals (see 📖 p. 583).
- Balkan endemic and Chinese herbal nephropathies.

Clinical features

- Impaired urinary concentration (nocturia, polyuria).
- Often normal BP (due to relative salt-losing state).
- LMW tubular proteinuria (e.g. β_2 microglobulin).
- Glycosuria (impaired tubular handling) \pm renal tubular acidosis.
- CKD.
- Small, symmetrical kidneys on USS (exception: reflux nephropathy where asymmetry is common).

Investigations

MSU for M,C+S, EMU for AFB, uPCR or uACR (proteinuria often $<1\text{g/day}$), U&E, bone profile (? \uparrow Ca^{2+}), serum ACE, ANA, anti-Ro/La, USS kidneys.

Lithium-induced nephropathy

(See 📖 p. 904.)

Balkan endemic nephropathy (BEN)

Affects men and women >30 years old inhabiting lands drained by the Danube River. Characterized by tubulointerstitial atrophy and scarring. Cause remains unknown. Patients are usually normotensive, with a urinary concentrating defect (polyuria), and may have LMW tubular proteinuria ($<1\text{g/day}$) and glycosuria. USS shows small, symmetrical kidneys. There is an increased incidence of transitional cell carcinoma of the entire urinary tract; new haematuria should be fully investigated, and urine cytology is recommended at least annually.

Chinese herb nephropathy (📖 p. 901)

A histological disorder similar to BEN, with tubulointerstitial scarring and glomerular sparing as the principal features. Appears to be due to aristolochic acid, an ingredient in many Chinese herbal preparations (notably as a slimming agent). Clinical presentation and histology are so similar to BEN that a similar aetiology has been suggested, although this remains to be proven. The incidence of urothelial malignancies is very high, and surveillance is mandatory. In those considered for transplantation after ESRD, bilateral native nephroureterectomy is often recommended to reduce the risk of malignant disease following immunosuppression.

Lead nephropathy

Exposure to lead, including occupational, may cause chronic poisoning, with progressive tubulointerstitial nephritis. Tubular injury results in decreased urate excretion with hyperuricaemia and gout. At-risk individuals with unexplained CKD, associated with high serum urate concentrations, should be assessed for total lead burden by either bone X-ray fluorescence or an EDTA lead chelation test. Treatment includes long-term lead depletion with EDTA or DMSA.

Lead has also been shown to be a risk factor for progression of CKD of other causes. *Cadmium* exposure causes a similar nephropathy.

Salt-losing nephropathy

- Refers to inappropriate renal losses of sodium (and thus) water.
- It generally occurs in the context of chronic tubulointerstitial disorders.
- Losses rarely exceed 100mmol Na⁺ (2–3L/day), as increased delivery of Na⁺ to the macula densa causes protective afferent arteriolar vasoconstriction with ↓ GFR (so-called ‘tubulo-glomerular feedback’).
- However, hypovolaemia and hyponatraemia can be clinically significant, if untreated.
- Management: appropriate fluid and salt intake. Dietary input may suffice for the latter. If not, salt supplementation.

Analgesic nephropathy

Introduction

Analgesic nephropathy (AN) was first described after chronic phenacetin use (a pro-drug of paracetamol). Fortunately, it has declined in prevalence over the last 3 decades from ~3% to ~0.2%.

The use of *combination* analgesic preparations now accounts for most cases (e.g. paracetamol + codeine, or paracetamol + aspirin). Aspirin alone will not usually cause AN, although paracetamol, if used in sufficient quantities, might (>2kg cumulatively; equivalent to about 8 years of daily full-dose ingestion).

Renal injury begins with ischaemic changes in the medulla, progressing to tubulointerstitial scarring, glomerulosclerosis, and papillary necrosis (📖 p. 585). (See Fig. 7.9)

Analgesic nephropathy is also associated with accelerated atherosclerosis, although the mechanism is unclear.

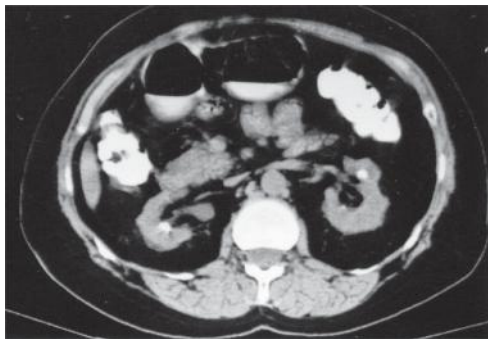


Fig. 7.9 Irregular, ragged renal outline, characteristic of analgesic nephropathy. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P, et al. (2005) *Oxford Textbook of Clinical Nephrology*. Oxford University Press, Oxford.

Symptoms and signs

A history of analgesic use may be difficult to elicit: suspect if chronic pain syndromes, such as headaches or backache. Dyspepsia is common. Nocturia and polyuria (loss of concentrating ability), episodic colicky flank pain, and frank haematuria due to papillary necrosis (sloughed papillae) may occasionally be evident in the urine. ↑ BP, as CKD develops.

Investigations

Urine dipstick often bland or modest proteinuria only. Sterile pyuria on urine microscopy. ↓ Hb, ↑ SCr, and ↓ eGFR. Classical IVU appearances historically (small kidneys with clubbed calyces), but CT is now preferred.

Management

Stop all analgesics. This is often extremely difficult, but reducing the analgesic burden slows disease progression (those who continue have a 6-fold risk of reaching dialysis or death in an observational study of 78 patients).¹ The input of a specialist pain management team is highly desirable.

► Surveillance for urothelial malignancies (transitional cell carcinoma occurs in up to 10% of confirmed cases of analgesic nephropathy). May be multiple, in unusual sites, or even bilateral. New haematuria merits full urological investigation. Annual urine cytology is a useful screening tool.

Papillary necrosis

The end result of chronic medullary hypoxia: vulnerable papillae suffer a further (acute) ischaemic injury, undergo necrosis, and are shed into the renal pelvis.

Clinical presentation

- May be asymptomatic.
- Colicky flank pain (as the papilla traverses the ureter).
- Visible passage of a papilla (or part thereof).
- Frank haematuria.
- Unilateral ureteric obstruction.

CT may show calcified papillae and an irregular renal contour. Historically, IVU showed contrast tracking into eroded papillae and ring shadows around detached papillae ± calcification.

Causes of papillary necrosis

- Analgesic nephropathy.
- Diabetes mellitus.
- Post-obstructive uropathy.
- Sickle cell nephropathy.
- Tuberculosis.
- Severe acute pyelonephritis.

Reference

1. Mackinnon B, Boulton-Jones M, McLaughlin K (2003). Analgesic-associated nephropathy in the West of Scotland: a 12-year observational study. *Nephrology Dialysis Transplantation*, **18**, 1800–5.

Renovascular disease

Introduction

Renovascular disease (RVD) refers to diseases of the large, medium-sized, and small renal vessels (excluding vasculitis). Atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasia (FMD) predominantly affect the larger vessels. The umbrella term 'ischaemic nephropathy' is used to describe vasculopathy involving small intrarenal vessels.

ARAS and ischaemic nephropathy

Increasing incidence with ↑ age (\pm 7% in people aged >65) and in those known to have atherosclerotic disease elsewhere (\pm 50% if known PVD). However, anatomic ARAS may be haemodynamically unimportant and is associated with ↑ BP in only 50% of cases. Generally, any stenosis >70% tends to be functionally significant, as is bilateral ARAS or disease in an artery to a single functioning kidney. Patients with ARAS or ischaemic nephropathy have a substantial excess risk for CV death (MI and stroke).

ARAS should be suspected in older patients with clinically evident peripheral, coronary, or cerebrovascular atherosclerotic disease, or those with known risk factors (dyslipidaemia, smoking, diabetes, ↑ BP).

Clinical presentation

- ↑ BP—often resistant to treatment (i.e. >140/90mmHg on three drugs).
- Renal dysfunction.
- ↑ SCr or ↓ eGFR of up to 20% with ACE-I or ARB.
- Fluid retention, often diuretic-resistant.

Pathophysiology

Atherosclerotic plaque involves the ostium or proximal 2cm of the renal artery, often extending from the aorta. Renal disease is caused by a fall in perfusion, resulting in sympathetic overactivity and renin release. This leads to overproduction of A2 (→ vasoconstriction) and aldosterone release (→ salt and water retention).

The pro-fibrotic actions of these factors, in combination with hypoxia, drive a complex cellular activity termed epithelial-mesenchymal transition (EMT). An essential process developmentally; EMT involves loss of epithelial cell apico-basal polarity and cell-cell adhesion characteristics. Cells become motile and acquire a fibroblast phenotype. EMT underpins progressive renal fibrosis and scarring, with loss of functioning tubules (→ CKD clinically).

Symptoms and signs

- Evidence of central or peripheral vascular disease is perhaps the most important clinical finding.
- ↑ BP, peripheral oedema, pulmonary congestion, abdominal bruits (low predictive value in isolation), palpable AAA.
- Generally, bland urine on dipstick or low-grade proteinuria only (e.g. <1g/day). This can be a helpful clinical clue, although the development of 2° FSGS may lead to higher levels.

- *Flash pulmonary oedema* refers to sudden, often episodic, pulmonary oedema, with \uparrow BP and without any precipitating cardiac event (or in the context of relatively normal LV function). It is caused by exaggerated activity of the RAAS (\rightarrow acute salt and water retention and volume overload). Probably overdiagnosed: thorough cardiac assessment is mandatory.
- Loin pain, a sudden decline in renal function, and new haematuria may indicate renal infarction.

Investigations

(See Fig. 7.10)

- SCr, eGFR, U&E (? \downarrow K^+ due to \uparrow aldosterone), lipids. Plasma renin will be high, but this is therapeutically unhelpful.
- Urine dipstick, uPCR or uACR.
- Evidence of vascular disease elsewhere, e.g. ECG.
- Potential imaging includes:
 - USS kidneys for renal size and symmetry. A difference of >1.5 cm in renal length is suspicious.
 - CT angiography is increasingly sensitive for ostial lesions.
 - MRA. However, gadolinium-enhanced MRA is relatively contraindicated in individuals with a GFR <30 mL/min (p. 51). MR also tends to overestimate the extent of a stenosis. Newer MRI software is enabling non-gadolinium MRA scanning.
 - Duplex USS with Doppler examination. Resistive index (RI) is a surrogate for impeded flow. Only useful in experienced hands.
 - Captopril isotope scintigraphy. With captopril, affected kidneys may show a 30% decline in GFR using DTPA or MAG-3 (p. 54).
 - Formal angiography. Remains the gold standard for diagnosis and allows endovascular intervention.

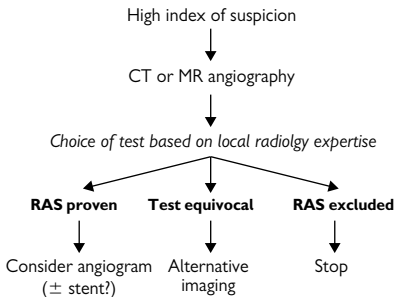


Fig. 7.10 A suggested algorithm for the investigation of suspected ARVD.

Management of ARAS

General management

ARVD is associated with a 16% PA mortality risk, predominantly attributable to associated CVD. Modification of CVD risk factors is \therefore a primary objective: stop smoking, exercise, healthy diet, statins. Consider aspirin 75mg od.

Control BP

Aim for <130/85mmHg, using non-ACE-I/ARB drugs, for example:

- Calcium channel blocker or β -blocker.
- Early use of loop diuretics titrated vs response (e.g. furosemide 40–160mg daily) can be effective, as \uparrow BP is driven by salt and water overload.

Further management

The primary goal is to prevent loss of renal function. Two treatment options exist, conservative or interventional. Selection can be difficult.

Interventional management

- Includes percutaneous transluminal renal angioplasty (PTRA) \pm stenting and surgical revascularization.
- PTRA alone is associated with a high incidence of restenosis—stenting is \therefore widely advocated.
- However, the ASTRAL trial (📖 p. 589) has suggested only a limited role for interventional management.
- The selection of candidates who may benefit from intervention is difficult and without a robust evidence base. However, many clinicians would consider such a strategy in the following situations:
 - Bilateral critical ARAS or critical ARAS to a single functioning kidney.
 - ARAS that is known to be of recent onset.
 - Refractory \uparrow BP and volume overload.
 - Flash pulmonary oedema (📖 p. 587).
 - Rapidly deteriorating renal function.
- Other factors to consider if an interventional approach is considered:
 - The stenosis should be high grade (>70%).
 - The kidney(s) should be >7.5cm in length, implying meaningful nephron mass and \therefore potentially salvageable renal function.
 - The absence of scars on ^{99m}Tc -DMSA isotope scintigraphy may usefully predict recoverable renal function.
 - The presence of heavy proteinuria may imply hyperfiltration injury and 2° FSGS in a scarred kidney (📖 p. 562).

The risk of cholesterol emboli, arterial dissection (with potential limb injury), and contrast-induced AKI (📖 p. 148) should be weighed against potential benefits.

Surgical revascularization is usually reserved for those undergoing simultaneous aortic surgery.

Conservative management

- Given the pathophysiological importance of A2, a trial of ACE-I/ARB is often warranted under close supervision. ACE-I/ARB will reduce CV risk and may retard progression of CKD. They will also block A2-mediated vasoconstriction and fibrosis. ► However, they will also drop renal perfusion pressure and may precipitate AKI.
 - ⚠ Patients must be adequately hydrated (check for postural drop).
 - Start with low dose, and measure SCr regularly, e.g. alternate days.
 - Increase dose, according to BP, if no deterioration in renal function (↑ SCr or ↓ eGFR >20% from baseline).

Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial

ASTRAL is the largest trial, to date, of PTRAs + stenting + medical therapy vs medical therapy alone; 806 patients were randomized in an unblinded fashion.

Primary endpoint Slope of the reciprocal creatinine plot.

Secondary endpoints Time to renal and major adverse cardiovascular events (MACE), BP, and mortality.

Results A borderline significant difference ($p = 0.06$) in the slope of the reciprocal creatinine plot between the two groups. However, this translated into a clinically meaningless $1.6 \mu\text{mol/L}$ (0.02mg/dL) difference in SCr between the intervention and medical therapy groups. No significant improvements in BP or reductions in renal adverse events, MACE, or mortality were seen.

Conclusion Revascularization offered no benefit over medical therapy in the management of ARAS but was associated with an increased risk of morbidity (two procedural related deaths and three limb amputations).

Caveat There is a consensus view (non-evidence-based) that individuals with flash pulmonary oedema, high-grade bilateral stenosis (or a high-grade stenosis affecting a single functioning kidney), or those presenting with AKI should be offered intervention. Such scenarios were probably underrepresented in the ASTRAL cohort.

ASTRAL Investigators (2009). Revascularization versus medical therapy for renal-artery stenosis. *New England Journal of Medicine*, **361**, 1953–62.

Other renovascular diseases

Fibromuscular dysplasia (FMD)

Affects asymptomatic young women (15–50 years), often with ↑ BP. Renal function is generally normal. Much less common than ARAS. True prevalence in both normotensive and hypertensive populations unknown. Characterized by arterial fibroplasia that may affect many vascular beds (intracranial, carotid, coronary, and limb). Pathogenesis unknown. A genetic predisposition operates in some (with autosomal dominant inheritance). Often involves both renal arteries, classically affecting the mid-distal renal portion of the vessel (rather than the ostium in ARAS).

Angiography shows a 'string of beads' appearance with normal-calibre vessels on either side (see Fig. 7.11). ↑ BP of FMD may be cured (withdrawal of all drugs) or improved by angioplasty, particularly in woman <50 years with ↑ BP of <8 years' duration and with few stenoses in other arterial beds.

Renal vein thrombosis (RVT)

RVT is usually found in association with the nephrotic syndrome (particularly membranous nephropathy, [p. 564](#)) when it may be uni- or bilateral. It is very rare without some form of concomitant hypercoagulable state. It may be seen in association with tumours, esp. renal cell carcinoma, where there is invasion and distortion of the renal vein.

May present as: pulmonary emboli, renal infarction (loin pain, haematuria, ↑ SCr, ↑ AST, and ↑ LDH).

Contrast-enhanced CT angiography/venography or Doppler USS (operator-dependent) of the renal veins should be diagnostic. Proven RVT should be treated with anticoagulation.

Cholesterol emboli

May cause partial occlusion of the small renal vessels, with downstream ischaemia. Showers of emboli may present suddenly as AKI or, more commonly, as a gradual decline in renal function. Characteristically occurs in elderly patients known to have extensive atherosclerosis who undergo endovascular intervention (particularly aortic). It is an important differential diagnosis of contrast-induced AKI ([p. 148](#)). Anticoagulation (and thrombolysis) are also risk factors.

Patients may also develop embolic infarcts in other end-arterial territories, including digits, retina, GI tract, and skin (→ livedo reticularis). The urine is usually bland (although proteinuria may occur over time). Eosinophilia, eosinophiluria, and ↓ C3/C4 may be present. Renal biopsy shows characteristic intravascular clefts where cholesterol emboli were present before tissue preparation. No specific therapy is helpful, although aggressive CV risk factor management, including BP and cholesterol, may improve patient survival. Renal prognosis is often poor.



Fig. 7.11 Digital subtraction angiogram demonstrating 'beaded' appearance of the renal artery in FMD.

Autosomal dominant polycystic kidney disease (ADPKD)

Introduction

ADPKD is the most common inherited kidney disease, affecting ~ 1:800 live births. It is responsible for 5–10% patients in an ESRD programme.

Inheritance

ADPKD is inherited in an autosomal dominant manner. Mutations in the genes *PKD-1* (located on chromosome 16) and *PKD-2* (chromosome 4) result in defective synthesis of the proteins polycystin-1 and -2, respectively. Both polycystin-1 and -2 are ubiquitously expressed by epithelial cells throughout the body. *PKD-1* mutations are seven times more common than *PKD-2* and associated with more aggressive disease (onset of ESRD, on average, 15 years earlier).

Pathophysiology

Polycystin-1 is a membrane receptor signalling protein that co-localizes with polycystin-2 (a calcium-permeable channel) within the cilia of renal collecting duct epithelial cells. This polycystin complex acts as an extracellular mechanosensor (luminal flow disturbs the cilia and triggers the apparatus) that assists in the regulation of cell proliferation, adhesion, differentiation, and maturation (→ all ultimately maintain tubular integrity and calibre). Failure of normal polycystin complex formation results in dysregulated cell turnover and uncontrolled cell proliferation in response to growth factors. Proliferating tubular cells form tubular cysts that close off the associated nephron and expand in size over time.

It is estimated that <1% of nephrons undergo such cystic transformation. However, local tissue ischaemia and pro-fibrotic cytokine release drive a process of EMT (📖 p. 586), resulting in scarring and ultimately progressive CKD.

Clinical presentation

Patients may present with a family history of ADPKD. A careful history for renal disease, ↑ BP, stroke (intracranial haemorrhage), or premature death may pinpoint carriers of the gene mutation. Inheritance is autosomal dominant, so 50% of offspring should be affected.

► Importantly, 25–40% of new patients will have no family history.

Patients being investigated for ADPKD should be given information about the disorder before and after testing.

Clinical features include:

- Flank or loin pain arising from large cysts. Acute pain may suggest cyst rupture or bleeding.
- Dipstick-positive haematuria ± episodic frank haematuria.
- ↑ BP.
- Nocturia and polyuria (loss of urinary concentrating ability).
- Low-grade proteinuria may be present (usually <1g/day).
- If presenting late, uraemic symptoms (📖 p. 212).

Investigations

USS remains the investigation of choice. As ADPKD is an evolving disease, the timing of the scan is important. In otherwise asymptomatic at-risk individuals, USS should be performed after age 20 to improve negative predictive value. For confirmation of diagnosis, the Ravine criteria are useful (see Table 7.4).

Table 7.4 Ravine criteria

Age	+ve family history	-ve family history
<30 years	2 cysts in either kidney	5 cysts in either kidney
30–60 years	4 cysts in either kidney	5 cysts in either kidney
>60 years	8 cysts in either kidney	8 cysts in either kidney

► Valid for PKD-1 mutation alone. PKD-2 mutations present later, so these criteria tend to give false negative results.

Other radiological features

Increased renal size is common (often >20cm in length). Cysts in other organs (liver, pancreas, spleen) may also be present and helpful to differentiate ADPKD from multiple simple cysts. (See Fig. 7.12)

Genetic testing

Is available through specialist centres but is not currently widely used. It has accuracy rate >95% for ADPKD1 and ADPKD2. An important indication would be a young adult with a negative USS who is under consideration as a potential kidney donor.

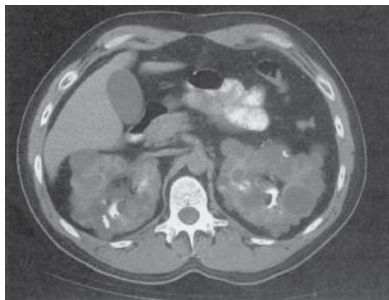


Fig. 7.12 Contrast-enhanced CT scan of a patient demonstrating the number, size, and location of the cysts in the anterior portion of the left kidney and the posterior aspect of the right kidney. Reproduced with permission from Watson ML, Torres VE (eds) (1996) *Polycystic Kidney Disease*, p. 214. Oxford: Oxford University Press.

ADPKD: complications and treatment

Hypertension

↑ BP may be the first presentation of ADPKD, affecting ~60% of those with normal renal function. It is thought to be 2° to increased renin generation in ischaemic renal tissue compressed by expanding cysts. Meticulous BP control (aiming for target BP <130/80mmHg) is important to protect an often young cohort of patients from progressive end-organ damage. Although proteinuria is not a dominant feature of the disease, ACE-I/ARB are still favoured as first-line therapy, with escalation to other agents, as necessary (📖 p. 204).

CKD

Although many patients with ADPKD will never reach ESRD, progressive CKD is nonetheless common. Males diagnosed at a younger age, early ↑ BP, large kidneys, black race, and the *PKD-1* mutation have a worse renal prognosis.

At ESRD, ADPKD patients enjoy better survival following dialysis and transplantation than the non-ADPKD ESRD population, reflecting a younger age and lower burden of CV disease in this group.

Cyst haemorrhage

Presents with unilateral flank pain of abrupt onset ± haematuria (if the cyst communicates with the urinary space) (see Table 7.5). Management is conservative, with hydration and analgesia. Individuals with a history of repeated cyst haemorrhage have an earlier onset of ESRD. Recurrent haemorrhage may sometimes necessitate nephrectomy (either bilateral or unilateral).

Cyst infection

Flank pain, fever, and systemic upset (see Table 7.5). Culture blood and urine, and give a prolonged course of antimicrobials (according to sensitivities, but ciprofloxacin and co-trimoxazole have good cyst penetration). CT, ^{99m}Tc-ciprofloxacin, and PET scanning may demonstrate infected cysts if there is doubt regarding the source of infection. Recurrent cyst infection may sometimes necessitate nephrectomy (either bilateral or unilateral).

Nephrolithiasis

20% of ADPKD patients have associated renal stones, usually uric acid or calcium oxalate. Diagnosis is best made with CT scanning (📖 p. 716).

Intracranial aneurysms (ICAs)

4–10% of ADPKD patients have ICAs. Specific mutations appear to predispose to aneurysm formation, so certain family pedigrees may have a positive history. Such families merit screening with MRA. Symptomatic ICAs or those >10mm diameter need surgical intervention, but the optimal management of asymptomatic ICAs of <10mm is less certain. Rupture presents as subarachnoid haemorrhage, most commonly in patients age <50 years with poor BP control (50% mortality or severe disability).

Table 7.5 ADPKD: haemorrhage, infection, or stone?

	Haemorrhage	Infection	Stone
Fever	±	++	±
Leucocytosis	±	++	–
Frank haematuria	++	–	+
Renal colic	–	–	+
+ve blood cultures	–	+	–

Extrarenal cysts

Hepatic, splenic, pancreatic, mesenteric, and in the seminal vesicles. Occur in 10–40% (most commonly multiparous women). Liver cysts rarely interfere with synthetic liver function but can cause biliary obstruction. Large cysts may cause epigastric fullness and abdominal discomfort. Needle puncture or surgical de-roofing may be possible.

Other manifestations

Mitral valve prolapse and aortic regurgitation, diverticular disease, and hernias are more common in patients with ADPKD.

Clinical trials and potential future treatments

- A better understanding of the pathogenesis of ADPKD has offered hope for future therapies that might ameliorate cyst development.
- As cyst formation begins *in utero*, such interventions would require ADPKD diagnosis and treatment from an earlier age.
- Experimental therapies have shown promise in both animal models and human pilot studies. These include:
 - Vasopressin receptor antagonists to ↓ cyst formation (via ↓ cAMP).
 - mTOR inhibition (or paclitaxel) to reduce cell proliferation.
 - Antagonism of epidermal growth factor.
 - Long acting somatostatin analogues.
- However, it can be difficult to select appropriate outcome measures in clinical trials that aim to assess such therapies—given the length of time it takes to develop CKD and eventual ESRD (if at all), a very long follow-up period is required.
- Two clinical trials involving mTOR inhibition have failed to show a beneficial effect on GFR (although one did demonstrate a reduction in cyst growth with everolimus).
- The CRISP study demonstrated that a combination of kidney and total cyst volume, as determined by MRI, is negatively associated with GFR. Many trials now use such volumetric assessments as outcome measures.
- It is hoped that risk stratification for progressive CKD may identify a subpopulation of patients who will benefit the most from interventions to retard cyst growth (and ∴ be the ideal participants in future clinical trials).


- One such risk factor for progressive CKD is increased 24h urine osmolality. Animal studies have suggested that ADH may have a role in cyst growth, so V2 receptor blockade could be of therapeutic benefit. This is the subject of ongoing clinical trials; e.g. the vasopressin V2 antagonist tolvaptan has been shown to slow progression of ADPKD in a 3-year, multi-centre, blinded study of ~1500 patients, halving the rate of kidney volume expansion and slowing GFR reduction by 30%. However, safety concerns (particularly regarding liver toxicity) mean it is not yet approved for this indication.
- A recent 3-year study suggested that the somatostatin analogue called octreotide long-acting release (LAR), delivered as a monthly IM injection, might reduce kidney and cyst volume and slow CKD progression². SE: common (including cholecystitis).

Reference

2. Caroli A, Perico N, Perna A, et al, for the ALADIN study group. *Lancet*. Aug 20 2013.

Other cystic kidney diseases

Simple cysts (see p. 742)

Solitary or multiple renal cysts are common in the elderly: 50% of those aged 50 years or more have one or more such cysts. So-called 'simple' cysts are usually asymptomatic and are found on imaging the urinary tract for other reasons. Simple cysts have no further significance—complex (echoic) cysts need detailed evaluation by CT scanning to exclude malignancy (see  p. 742–3).

Acquired cystic disease

Acquired cysts refer to cysts arising in the context of advanced CKD and widespread tubulointerstitial scarring. They can be multiple and bilateral and may be confused with ADPKD. Unlike ADPKD, acquired cysts occur in scarred and thus small kidneys, and are rarely >2–3cm in size (most are \pm 5mm).

Age at presentation, family history, presence of \uparrow BP, and site of the cysts on imaging can help discriminate the various cystic renal diseases (see Table 7.6).

Table 7.6 Classification of cystic kidney diseases

	Age	Family history	CKD	BP	Site
ADPKD	Any	++	\pm	+	Cortex
Juvenile PKD	<10	\pm	+	+	Cortex
Simple cysts	>65	–	–	\pm	Cortex
Medullary sponge kidneys	Any	–	–	–	Medulla
Medullary cystic kidneys	20–30	++	++	–	Medulla
Nephronophthisis	<15	+	++	–	Medulla

Autosomal recessive polycystic kidney disease (ARPKD)

Caused by a rare mutation of the *PKHD1* gene (located on chromosome 6) encoding polyductin. It is a disease of infancy and childhood, presenting with polycystic kidneys, progressive CKD, congenital hepatic fibrosis, and portal hypertension. It is much less common than ADPKD (estimated prevalence 1:20,000 live births).

Juvenile nephronophthisis

A recessively inherited condition (~1 in 50,000), characterized by cystic change and tubulointerstitial fibrosis, presenting in early childhood (age >1 year) and leading to ESRD in adolescence. Mutations in at least five NPHP loci have been described, most commonly NPHP1 (associated with earlier onset). Imaging characteristically reveals echo-bright kidneys with a few corticomedullary cysts. Clinical features: polydipsia and polyuria but often presents as ESRD. Unlike medullary cystic kidney disease, extrarenal

manifestations, including oculomotor apraxia, hypoplasia of cerebellar vermis (Joubert's syndrome), developmental delay, bone abnormalities (cone-shaped epiphyses), situs invertus, and hepatic and portal fibrosis) also occur. May also be associated with retinitis pigmentosa in the Senior-Løken syndrome.

Medullary sponge kidney

A common, benign condition characterized by diffuse medullary cyst formation. It is a developmental, rather than a genetic, anomaly. Clinically, there is no family history, and patients are usually identified either incidentally or when investigated for UTI or stones (see Table 7.7). Impaired calcium handling in the collecting ducts predisposes to formation of calcium-containing stones (often in cysts). Consider the diagnosis in young patients presenting with calcium stones. Haematuria (microscopic or gross) and recurrent UTIs may also complicate the disorder. Diagnosis is made on imaging; traditionally IVU (typical 'calyceal brush'), now CT. Renal impairment is very rare, and management should be directed at infection and prevention of stone formation.

Medullary cystic kidney disease

Autosomal dominant inheritance, presenting in early adulthood with progressive renal impairment. The affected genes *MCKD-1* and *-2* encode key signalling proteins in the renal cilia. Small cysts (1–10mm) form at the corticomedullary junction, with associated tubulointerstitial inflammation and scarring (glomeruli are unaffected). Affected individuals have a positive family history and present with nocturia, polydipsia, and polyuria (impaired concentrating ability). Urine dipstick is usually bland and BP often normal (there may be relative salt loss) (see Table 7.7). Investigation shows small to normal-sized kidneys on USS. CT may demonstrate the cystic change. Impaired urate excretion and hyperuricaemia (\pm gout) may occur. Renal function usually declines to ESRD by age 60. No specific therapy available. Correction of salt and water depletion may be necessary.

Table 7.7 Sponge or cystic kidney disease?

	Medullary sponge kidney	Medullary cystic kidney disease
Age	Any	20–30 years
CKD and ESRD	–	++ (ESRD age <60)
Salt-losing state	–	++
Calcium stones	++	–
UTI	+	–
+ve family history	–	+

Tuberous sclerosis

A multisystem disease associated with the growth of hamartomatous lesions in multiple organs. Caused by mutations in the *TSC1* (9q34) and *TSC2* (16p13) tumour suppressor genes. *TSC2* (more common) lies adjacent to *PKD-1*, suggesting a role for *PKD-1* in the development of cystic disease in some patients with tuberous sclerosis. Predominantly a neurological (presenting with epilepsy and developmental delay) and skin (e.g. facial angiofibroma, shagreen patches, ungula fibromata) disease, but there are a number of characteristic renal features.

- Angiomyolipomata: these benign hamartomas are present in ~80% from early childhood. They can be a cause of significant bleeding (requiring embolization) and occasionally obstruction.
- Cystic disease: ~20% patients have simple cysts, while ~5% have polycystic disease that may be associated with progression to ESRD.
- Renal cell carcinoma: <1%. Suspect if angiomyolipoma changes appearance during surveillance.
- Management:
 - Monitor BP, SCr, and eGFR (particularly if polycystic disease).
 - Renal USS annually ± CT, as necessary. Angiomyolipomata have a characteristically high fat content.
 - Refer to a specialist unit.

Bardet-Biedl syndrome

AR inheritance (~1 in 140,000) but genetically heterogeneous, with mutations in at least 12 BBS loci described. Presents in childhood with short stature, weight gain, polydactyly, progressive visual loss, hypogonadism, ↑ BP, CKD, and genital abnormalities in ♀. Diabetes mellitus may occur later. Renal abnormalities in >90%: fetal lobulation, calyceal cysts and clubbing, cystic dysplasia, and VUR. Progressive CKD in a minority. Lawrence Moon is similar, with additional spinocerebellar degeneration

Other syndromes

For renal disease associated with other syndromes, see Table 7.8.

Table 7.8 Renal disease associated with syndromes

Associations and renal anomalies	Renal anomaly	Clinical findings
VATER and VACTERL	40% unilateral agenesis, others varied	Vertebral defects, anal atresia, tracheoesophageal fistula with oesophageal atresia, and radial dysplasia (VATER) with cardiac malformations and limb anomalies (VACTERL)
CHARGE	Dysplasia	Coloboma, heart defects, atresia (choanal), retarded growth and development, genital and ear anomalies
COACH	Cystic dysplasia	Cerebellar vermis hypo/aplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis
Chromosomal abnormalities		
Trisomies and deletions	Variable and common	Variable
Turner and Noonan	Variable structural anomalies	Short stature, webbed neck, heart defects
Williams (microdeletion chromosome 7)	Infantile hypercalcaemia with nephrocalcinosis, renal agenesis, pelvic kidney, renal artery stenosis, hypertension	Supravalvular aortic stenosis, multiple peripheral pulmonary arterial stenosis, elfin face, mental and statural deficiency, characteristic dental malformation
DiGeorge (microdeletion chromosome 22)	Varied	Hypocalcemia arising from parathyroid hypoplasia, thymic hypoplasia, and outflow tract defects of the heart
Single gene defects		
Meckel–Gruber (AR)	Cystic dysplasia	Encephalocele, hepatic ductal dysplasia and cysts and polydactyly
Jeune (asphyxiating thoracic dystrophy) (AR)	Cystic dysplasia	Severely constricted thoracic cage and respiratory insufficiency, cysts in the liver and pancreas, retinal degeneration, short limbs, abnormal pelvis
Joubert (AR)	Cystic dysplasia	Cerebellar vermis hypoplasia, dysregulation of breathing pattern and eye movement, developmental delay, retinal dystrophy
Senior–Løken (AR)	Renal dysplasia or nephronophthisis	Mutations in genes causing nephronophthisis may also cause retinitis pigmentosa or retinal aplasia, consistent with Leber amaurosis.

(Continued)

Table 7.8 (Continued)

Associations and renal anomalies	Renal anomaly	Clinical findings
Bardet–Biedl (AR)	Abnormal calyces (on IVP), renal dysplasia	Retinal dystrophy, polydactyly, mental retardation and obesity
Lawrence–Moon (AR)	Renal dysplasia	Similar to Bardet–Biedl, with spino-cerebellar degeneration
Branchio-oto-renal (AD)	History of Potter's syndrome, agenesis, and dysplasia	Ear pits, hearing loss, branchial cysts
Nail–patella (AD)	Congenital NS or glomerulonephritis	Dysplasia of the nails and absent or hypoplastic patellae
Neurofibromatosis (AD)	Arterial stenosis and hypertension	Neurofibromas, pigmented patches
Renal coloboma syndrome (<i>PAX2</i> mutations)	Renal cysts or hypoplasia	Overexpression causes renal cysts and tumours; underexpression causes renal hypoplasia. Coloboma


(see, Online Mendelian Inheritance in Man (OMIM),  www.ncbi.nlm.nih.gov).

The kidney in systemic disease

- Diabetic nephropathy 604
- Diabetic nephropathy:
 - progression 606
- Diabetic nephropathy:
 - pathology 608
- Diabetic nephropathy:
 - prevention, screening, and assessment 610
- Diabetic nephropathy:
 - management 612
- Diabetic nephropathy:
 - management 2 616
- Other diabetes-related urinary tract disorders 618
- Plasma cell dyscrasias 620
- Myeloma: cast nephropathy 622
- Monoclonal Ig deposition disease 626
- Renal amyloid: AL amyloid 628
- Renal amyloid: AA amyloidosis 630
- Renal amyloid: other forms 632
- Cryoglobulinaemia 634
- Sickle cell nephropathy 636
- The kidney in systemic vasculitis 638
- ANCA-associated vasculitis 640
- ANCA-associated vasculitis:
 - investigations 642
- ANCA-associated vasculitis:
 - treatment 644
- ANCA-associated vasculitis:
 - monitoring response and predicting relapse 646
- Henoch–Schönlein purpura 650
- Polyarteritis nodosa 652
- Churg–Strauss syndrome 654
- Anti-GBM (Goodpasture's) disease 656
- Lupus nephritis 658
- Lupus nephritis: initial treatment 660
- Lupus nephritis: further treatment 662
- Antiphospholipid syndrome (APS) 664
- Systemic sclerosis 666
- Rheumatoid arthritis 668
- Sarcoidosis 670
- Fabry's disease 672
- HIV and renal disease 674
- HIV and renal disease:
 - HIVAN 676
- HIV and renal disease: other lesions 678
- Hepatitis B 680
- HBV-related renal disease 682
- HBV and ESRD 684
- Hepatitis C-related renal disease 686
- HCV-related disease:
 - management 688
- HCV and ESRD 690
- The kidney in infective endocarditis 692
- Renal tuberculosis 696
- Renal tuberculosis: TB-TIN and TB in patients with ESRD 698
- Schistosomiasis 700
- Malaria 702


Diabetic nephropathy

Introduction


Diabetic nephropathy (DN) is one of the most significant complications of diabetes mellitus. It is the leading cause of CKD (and ESRD) in the western world, and its incidence is rising in developing countries. This increase has been driven by the increased incidence of T2DM, improved life expectancy for these patients and better access to ESRD care. DN, therefore, consumes a very significant amount of healthcare resource. The topics on  pp. 604–619 are among the most important in this book.

► There is very good evidence that the quality of diabetes care has a significant impact on the natural history of DN, with *early* treatment delaying or preventing onset.

Definitions

- The earliest evidence of diabetic renal disease is the appearance of microalbuminuria, i.e. low, but abnormal, amounts of albuminuria ($\geq 30\text{mg/day}$) ( p. 60).
 - Patients with microalbuminuria are often said to have ‘incipient’ nephropathy.
 - DN (‘overt’ nephropathy) describes a clinical syndrome characterized by:
 - Persistent albuminuria ($>300\text{mg/day}$) on at least two occasions, 3 months apart.
 - \uparrow BP.
 - Progressive \downarrow GFR.
- As well as a hallmark of DN, incipient and overt nephropathy are important markers of \uparrow CV morbidity and mortality in both T1DM and T2DM. They warrant aggressive intervention to improve all CV risk factors (e.g. LDL cholesterol, BP, smoking cessation, exercise, etc.).

Epidemiology

- ~20–30% of patients with diabetes mellitus develop DN.
- ~15% of ESRD in the UK is 2° to DN and is much higher elsewhere (~40% in the US). >90% of these individuals will have T2DM.
- Incidence and natural history depend on ethnicity, e.g. Pima Indians ( p. 8) have a 40% incidence of ESRD 10 years after developing microalbuminuria.
- Patients who have no proteinuria after 25 years of diabetes have only a very small risk of developing DN.

T1DM

- Microalbuminuria will develop in 20–30% of patients after 15 years.
- ↑ BP often appears at the same time as microalbuminuria.
- Without treatment, ~80% will increase their urinary albumin excretion at a rate of ~10–20% per year, with overt nephropathy developing over 10–15 years.
- Overt DN rarely develops within 10 years of diagnosis of T1DM.
- Without treatment, overt DN will lead to a progressive fall in GFR over time. The rate is highly variable between individuals (2–20mL/min/year).
- 50% of those with overt DN will develop ESRD within 10 years (>75% within 20 years).
- Patients who progress from no microalbuminuria to microalbuminuria or from microalbuminuria to overt albuminuria are likely to have higher HbA1C and BP values.
- The overall long-term prevalence of ESRD in T1DM has recently fallen to <10%, having previously been higher.

T2DM

- ~3% of patients will have overt DN at the time of diagnosis of T2DM (diabetes may have been present for some time prior to discovery).
- Proteinuria is less specific for DN in T2DM.
- Without treatment, 20–40% of those with microalbuminuria will progress to overt DN.
- In the UKPDS study, annual risk for progression from no microalbuminuria → microalbuminuria was 2.0%; from microalbuminuria → macroalbuminuria 2.8%, and from macroalbuminuria → ↑ SCr or ESRD 2.3%.
- The rate of decline of GFR is variable but less predictable than for T1DM (T2DM = older patients with associated CV disease).
- After 20 years of overt DN, ~20% will have progressed to ESRD. These numbers are hugely significant because of the higher prevalence of T2DM.
- ► The greater risk of death from associated CV disease in T2DM prevents many with earlier nephropathy from progressing to ESRD.

Diabetic nephropathy: progression

Natural history

The evolution of DN can be described in stages (see Table 8.1). This applies to both T1DM and T2DM, although the latter is much less predictable.

Table 8.1 Stages of DN

Stage	Duration	Clinical and pathological correlation
1	At diagnosis	Hyperfiltration with renal hypertrophy and ↑ GFR
2	<5 years	Early histological changes though clinically silent
3	5–15 years	Microalbuminuria. BP now starts to rise
4	15–25 years	Overt diabetic nephropathy with declining GFR
5	>25 years	Advanced CKD/ESRD

- ►► Mortality risk increases at each stage.
 - In the UKPDS, annual mortality risks were 1.4% (no microalbuminuria); 3.0%, (microalbuminuria); 4.6% (macroalbuminuria); and 19.2%, (CKD and ESRD). Risk of death was higher than the risk for progression to the next phase once microalbuminuria present.
 - Happily, more recent studies, e.g. IDNT and RENAAL, have challenged these data in an era of better diabetes care, demonstrating what improved care may achieve.
 - Nonetheless, CV mortality in T2DM remains a significant public health issue. See Box 8.1.
- Intensive monitoring and treatment influence natural history, preventing incipient, and progression to overt, nephropathy.
 - The DCCT trial randomized >1,400 non-hypertensive type 1 diabetics to either intensive or conventional insulin therapy. During a mean 6.5 years' follow-up, HbA1C levels were significantly lower in the intensive group, with a reduction in microalbuminuria.
 - The benefits of good glycaemic control for preventing progression in T2DM were clearly demonstrated in the UKPDS study.

►► Box 8.1 Diabetic nephropathy and risk of death

- T2DM is associated with substantially increased risk of premature death—a risk that is primarily focused on those with nephropathy.
- 10-year mortality data in ~15,000 subjects in the 3rd US National Health and Nutrition Examination Survey (NHANES III) revealed:
 - Reference group (subjects without diabetes or kidney disease), 10-year cumulative all-cause mortality of 7.7%.
 - For T2DM without kidney disease, this rises to 11.5%. For T2DM with kidney disease, this rises to an astonishing 31.1%, representing an absolute risk difference with the reference group of 23.4% (adjusted for demographics, smoking, and BP)!

Development and progression

The following are important risk factors for the development and progression of DN in both T1DM and T2DM:

- Poor glycaemic control.
- Onset of T1DM before age 20.
- ↑ BP:
 - 30% have ↑ BP at diagnosis of T2DM.
 - 70% have ↑ BP at diagnosis of DN.
- Smoking.
- ♂ gender.
- Ethnicity (Indo-Asians, African Americans, Pima Indians in the US).
- Familial tendency.
- Socio-economic factors, esp. poverty.
- Once established the most important factors fuelling progression are:
 - BP.
 - Glycaemic control.
 - Degree of proteinuria.

Diabetic nephropathy: pathology

Introduction

The pathogenesis of DN is multifaceted, with several mechanisms contributing to the renal injury and development of the characteristic histological changes.

Histology

- Ultimately, renal hypertrophy, hyperfiltration (initially with \uparrow GFR to above normal), and intrarenal hypertension cause mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis.
- The cardinal histological features are:
 - Mesangial expansion (\rightarrow intercapillary, or Kimmelstiel–Wilson, nodule formation, often with capillary lumen encroachment).
 - Glomerular and tubular basement membrane thickening.
 - Nodular glomerulosclerosis.
- Vascular changes are also usually present:
 - Vessel changes from \uparrow BP.
 - Arteriosclerosis.
 - Afferent and efferent arteriolar hyalinosis.
- Tubular atrophy and interstitial fibrosis appear as DN (and \therefore CKD) progress.
- Immunostaining may demonstrate non-specific linear staining for IgG in glomerular and tubular basement membranes and Bowman's capsule.
- Arteriolar damage, interstitial fibrosis, and 2° FSGS may be the dominant lesions in older T2DM patients (often with less proteinuria and more vascular disease clinically).

Pathophysiology

Hyperglycaemia

- The magnitude of hyperglycaemia correlates with the functional and structural changes of DN.
 - Long-term studies in T1DM (DCCT) and T2DM (UKPDS) have demonstrated that blood glucose concentration is related to the development of microalbuminuria and progression to overt DN.
 - Time-averaged HbA1c and BP correlate with loss of renal function.
- Hyperglycaemia:
 - Stimulates mesangial cell matrix production and cell growth, leading to early glomerular enlargement.
 - Causes to advanced glycation end-product (AGE) formation:
 - AGEs result from non-enzymatic reaction between glucose and proteins.
 - They normally undergo renal excretion and accumulate as DN progresses, particularly in the circulation and the kidneys.
 - AGEs: (i) impair function of glycosylated proteins; (ii) cause abnormal cell-to-cell interactions through cross-link formation; (iii) bind endogenous receptors for AGEs (RAGE), with deleterious consequences.
 - Causes \uparrow oxidative stress.

- Leads to activity of protein kinase C and hexosamine pathways (both \rightarrow \uparrow production of various profibrotic cytokines, including TGF- β).
- Increases expression of glomerular TGF- β (and other mitogens) \rightarrow cellular hypertrophy, \uparrow collagen synthesis, and \uparrow matrix deposition.
- Promotes \rightarrow \uparrow VEGF expression, possibly via the adenosine A_{2B} receptor (\rightarrow endothelial injury, vascular change, and podocytopathy).

Glomerular haemodynamics

- Glomerular hypertension and hyperfiltration occur early.
 - A GFR of 25–50% above normal is observed in 50% of patients with T1DM of 5 years' duration.
 - Hyperfiltration appears to be caused by mediators involved in RAS, nitric oxide, and cyclo-oxygenase pathways.
 - Endothelin -1 is a potent vasoconstrictor, the levels of which are increased in both plasma and renal tissue of diabetic subjects. The expression of receptors ET-A and ET-B is also increased. ET-1 function is receptor-dependent (ET-A \rightarrow smooth muscle vasoconstriction and glomerulosclerosis; ET-B \rightarrow vasodilation).
 - Systemic \uparrow BP also drives glomerular \uparrow BP.
 - Haemodynamic disturbance \rightarrow arteriolar and glomerular sclerosis.

Podocyte function and proteinuria

- Podocyte function is abnormal, with reduced expression of nephrin and altered glomerular permeability.
- Proteinuria further promotes tubular injury and interstitial fibrosis.

Renin–angiotensin system

- Local renal RAS activation \rightarrow cell growth and matrix accumulation.
- Angiotensin II generates reactive oxidative species and NADPH oxidase in vascular smooth muscle and the kidney.
- These may explain some of the additional benefit of RAS inhibition beyond BP control.

Genetics

- A poorly understood genetic predisposition appears to operate.
 - DN is more common in Northern Europe and the USA.
 - Certain ethnic groups are affected more than others, e.g. Indo-Asians in the UK, African Americans, Pima Indians (astonishingly, by age 20, ~50% of Pima Indians with diabetes will have developed DN, and 15% will have progressed to ESRD).
 - DN is more likely in relatives of diabetic patients with nephropathy.
 - It is unclear why new cases of DN are rare after 15 years of diabetes.

Diabetic nephropathy: prevention, screening, and assessment

Primary prevention

- Improve glycaemic control:
 - Aim HbA1C <7%.
 - ► Clinical trials (e.g. DCCT and UKPDS) have consistently demonstrated the benefits of intensive blood glucose control for primary prevention of DN.
- Target BP <130/80mmHg.
- Stop smoking. Encourage weight loss and exercise.
- 🦋 The role of RAS blockade with ACE-I or ARB for prevention of microalbuminuria is controversial.
 - Several studies (e.g. DIRECT-Renal, BENEDICT, and ROADMAP) have attempted to address this issue.
 - Some evidence of benefit for prevention of microalbuminuria in high-risk T2DM with concomitant ↑ BP, but the cumulative findings fail to support 'pre-emptive' RAS blockade.

Screening

- Early detection affords the opportunity to delay or prevent progressive CKD and ∴ ESRD.
- Annual screening by uACR should be performed (preferably an early morning sample, no UTI, stable glucose control) (see Table 8.2).
- Start after 5 years of T1DM and at the time of diagnosis of T2DM.

Table 8.2 uACR in diabetic nephrology

uACR (mmol/mg)	24h albuminuria
<2.5	<30mg/day
2.5–30	30–300mg/day (microalbuminuria)
>30	Overt proteinuria

Diagnosis

A clinical diagnosis is usually possible.

- T1DM:
 - Proteinuria, retinopathy, DM of >10 years' duration.
- T2DM:
 - Retinopathy often not present, duration of DM frequently uncertain.
 - Non-specific renal damage (e.g. arteriolar damage, interstitial fibrosis, and 2° FSGS) is a differential diagnosis of DN in T2DM and may be indistinguishable in terms of clinical presentation. Management is essentially identical, however.

Role of the renal biopsy in DN

A renal biopsy is rarely required to establish the diagnosis of DN but might be considered in certain circumstances:

- No diabetic retinopathy:
 - Particularly in T1DM (retinopathy is observed in 85–99% of patients with established nephropathy).
 - ~30% of those without retinopathy will have an alternative lesion at biopsy (membranous GN, IgA nephropathy, etc.).
 - T2DM patients have DN without retinopathy more commonly.
 - Note: this implies proper ophthalmic assessment, not just brief fundoscopy.
- Dysmorphic red cells, red cell casts, or macroscopic haematuria:
 - Microscopic haematuria, usually + to ++ only, is seen in ~60% patients with DN. However, it will usually require independent investigation (📖 p. 22).
- Rapid onset, rapidly increasing, or massive proteinuria.
- Conversely, a lack of proteinuria may cast doubt on the diagnosis and make histology desirable, e.g. possible drug-induced TIN (📖 p. 580). Also consider renovascular disease in this situation (📖 p. 586).
- Rapidly deteriorating GFR despite good BP and glycaemic control.
- Symptoms or signs suggestive of a multisystem disorder, e.g. vasculitis, connective tissue disorder, hepatitis C, HIV.

Further investigation and assessment

- Urinalysis (? haematuria); quantify proteinuria (📖 p. 21).
- SCr, eGFR, U&E, serum albumin, HbA1C, lipid profile.
- Consider serum and urine protein electrophoresis in older patients.
- Check visual acuity, fundoscopy, and arrange ophthalmology review, if not already under follow-up.
- Check BP.
- Examine for other evidence of vascular disease (bruits, peripheral pulses, etc.).
- Assess for peripheral neuropathy.
- ECG.
- Consider USS kidneys, esp. if microscopic haematuria (kidneys are often normal-sized in DN despite ↓ GFR).

Diabetic nephropathy: management

Introduction

Treatment goals: prevention of (i) progression from microalbuminuria (incipient DN) to macroalbuminuria (overt DN); (ii) progressive decline in renal function in patients with macroalbuminuria; and (iii) CV events.

Glycaemic control

◆ Unlike prevention, the effects of strict glycaemic control on progression from micro- to macroalbuminuria, as well as benefits for preservation of renal function, are more controversial.

The ADVANCE and ACCORD studies have suggested that intensive treatment of hyperglycemia in T2DM does not necessarily lead to an acceptable risk/benefit ratio. Participants had strong CV risk profiles (including prior events) and were at high risk of future events. Microvascular end points, including renal outcomes, were improved in both studies. However, primary CV outcomes were not improved by intensive glycaemic therapy and, in ACCORD, intensive treatment was associated with a 22% increase in all-cause mortality. So, more aggressive glycaemic management in higher risk T2DM patients (usually later in the course of their disease) delivered only a weak protective effect with respect to CV outcomes.

KDOQI practice guidelines recommend maintaining HbA1c at <7%. However, some authorities suggest a target between 7–8% in patients with longstanding disease who are at higher CV risk.

See 📖 p. 894 for the use of hypoglycaemic drugs in CKD (⚠ metformin!). Patients with T2DM and DN often require conversion to insulin.

Blood pressure

- ↑ BP is proportional to ↑ albumin excretion.
- Numerous studies have demonstrated that treatment of BP, irrespective of the agent(s) used, has a beneficial effect on albuminuria.
- RAS blockade with ACE-I or ARBs confers an additional 'renoprotective' benefit, independent of BP reduction.
 - ACE-I or ARBs reduce the risk of progression of microalbuminuria to macroalbuminuria (by 60–70%), reduce macroalbuminuria, and reduce the rate of decline in GFR.
 - ► ACE-I or ARBs should also be used in normotensive patients with micro- or macroalbuminuria.
 - Strict adherence to evidence would generally see ACE-I used in T1DM and ARBs in T2DM. However, most clinicians are pragmatic and principally guided by tolerability.
 - ACE-I also demonstrably reduce the risk of MI, CVA, and CV death (by ~25% at 2 years). This might be true for ARBs as well.
 - Allow ≥25% change in SCr and eGFR. Greater increases may indicate the presence of renal artery stenosis (a >70% renal artery stenosis is present in ~15% of individuals with T2DM and ↑ BP).
 - Monitor K⁺ after 1 week and then monthly for first 2–3 months. Offer dietary advice if K⁺ elevated 📖 p. 259 (± loop diuretic, e.g. furosemide 40–80mg od).

- A low-salt diet (📖 p. 259) enhances the renoprotective effects of ARBs in T2DM. Furthermore, lower urinary Na^+ excretion, reflecting lower intake, is associated with fewer CV events.
- Target BP:
 - Uncertain. In the UKPDS, a 12% risk reduction in diabetic complications was found with each 10mmHg drop in SBP, with lowest risk at 120mmHg.
 - KDIGO recommend a BP target of $<130/80\text{mmHg}$ if $>30\text{mg}/24\text{h}$ proteinuria.
 - UK Renal Association (and NICE) also recommend $<130/80\text{mmHg}$.
 - Recent guidelines for hypertension from non-nephrological bodies, e.g. ESH-ESC (2013), have suggested the evidence for a target of $<130/80\text{mmHg}$ is not particularly robust and suggested a target SBP of $<140\text{mmHg}$ for most hypertensive groups, including diabetics.
 - Many nephrologists will aim $<125/75\text{mmHg}$ if proteinuria $>1\text{g}/24\text{h}$.
- Add further therapy in a stepwise manner, selecting drugs according to the comorbidity profile of the individual patient.
 - Diuretics may enhance the anti-proteinuric effects of RAS inhibition.
 - Furthermore, volume overload is often an important driver of \uparrow BP in DN with renal impairment.
 - Thiazides may be suitable initially, but loop diuretics are preferred as GFR deteriorates ($<40\text{mL}/\text{min}$).
 - β -blockers if arrhythmias, CCF, coronary artery disease.
 - Evidence favours non-dihydropyridine calcium channel blockers (e.g. diltiazem) over dihydropyridine (e.g. amlodipine), but clinician preference and patient tolerability means this is often overlooked.

Proteinuria

- Proteinuria is itself an important treatment target.
 - Aim $<0.5\text{g}/24\text{h}$ (uACR $<30\text{mg}/\text{mmol}$ or uPCR $<50\text{mg}/\text{mmol}$), as BP allows.
 - ACE-I or ARBs should be used in normotensive patients with proteinuria (micro- or macroalbuminuria).


Box 8.2 ACE-I and ARB combination therapy

- There is no evidence to support combination ACE-I and ARB therapy.
- The ONTARGET study randomized >25,000 patients with either CV disease or DM + microvascular disease to an ACE-I, ARB, or combination therapy.
 - No differences were seen in 1° outcome (composite of CV morbidity and mortality).
 - There were differences in 2° outcomes: K⁺ (>5.5 mmol/L) and renal failure were significantly higher for combined therapy.
 - Subsequent post hoc analysis found doubling of SCr, need for acute dialysis, and death more frequently in the combined therapy group.
 - Limitations: only 38% of subjects had DM, and only 13% microalbuminuria.
- A recent meta-analysis examined 33 randomized trials involving >68,000 patients.¹
 - Dual blockade was not associated with ↓ mortality.
 - It was associated with an 18% decrease in CCF-related admissions (many studies included patients with cardiac failure).
 - Importantly, it was associated with a 55% increased risk of ↑ K⁺, a 66% increased risk of ↓ BP, and 41% increased risk of renal failure.
- The VA NEPHRON-D study of losartan with or without lisinopril in T2DM with overt nephropathy (uACR > 300mg/g and eGFR 30–90mL/min) was stopped early (median 2.2 years follow-up) because of safety concerns involving hyperkalaemia and AKI. This was despite a non-significant trend toward benefit with respect to the primary and secondary end points (relating to progression of renal disease or death). However, there was no demonstrable difference in CV events.
- Overall conclusions, as the evidence currently stands:
 - Combination therapy with an ACE-I and ARB should be avoided.
 - Maximizing the dose of either an ACE-I or an ARB is the best current strategy.


¹Makani H, et al. (2013). Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ*, **346**, f360.

Diabetic nephropathy: management 2

Additional RAS blockade

- There has been much interest in combination therapy for RAS inhibition in DN.
 - For ACE-I + ARB therapy, see Box 8.2,  p. 614.
 - Aldosterone has been associated with progression of renal disease through increased fibrosis and proteinuria.
 - Plasma aldosterone often decreases with ACE-I or ARB therapy, but levels eventually return to baseline in many (~40%)—a phenomenon termed ‘aldosterone escape’.
 - The addition of the aldosterone antagonist spironolactone to a regimen including an ACE-I or ARB has an anti-proteinuric (and variable BP) effect in both T1DM and T2DM.
 - No studies have shown long-term benefit for other endpoints.
 - Δ There is a significant risk of $\uparrow K^+$, particularly in patients with \downarrow GFR, and this often limits the utility of spironolactone in practice.
 - Combination therapy with a direct renin inhibitor has also been studied, with initial studies suggesting a BP-independent anti-proteinuric effect in T2DM.
 - However, the ALTITUDE study (aliskirin + ACE-I/ARB in T2DM) was stopped early because of adverse events in the combination therapy group (renal failure, $\uparrow K^+$, \downarrow BP, CV events).

Other interventions

- Treat dyslipidaemia:
 - Aim fasting LDL <3.0 mmol/L. Statins are usually necessary (and demonstrably reduce cardiac events in diabetic patients).
 - \bullet^* Statins may reduce proteinuria and preserve GFR in overt DN.
- The role of aspirin and other antiplatelet agents for primary prevention of CV events in patients with DN is uncertain. However, if no contraindication, low-dose aspirin (75mg od) is often recommended.
- Smoking cessation.
- Modest dietary protein restriction (0.8g/kg per day,  p. 208) may slow decline in GFR. \bullet^* Some advocate a more stringent restriction to 0.6g/kg/day in selected patients.

Novel treatments for DN

Better understanding of DN has informed novel therapeutic strategies, particularly with respect to the downstream effects of hyperglycaemia (AGE formation, protein kinase C activity, production of pro-fibrotic intermediates, endothelin activity, and inflammatory pathways). Some show promise in both experimental models and clinical trials. In all cases, larger studies will be necessary to determine if short-term improvements (e.g. reduction in albuminuria) translate to overall improvements in DN outcomes.

Pyridoxamine. Is a member of the vitamin B6 family that inhibits AGE formation. It reduces mesangial expansion, decreases albuminuria, and slows SCr rise in animal models. Clinical studies suggest promise for early intervention in DN.

Experimental agents that prevent AGE cross-linkage or inhibit AGE and AGE receptor (RAGE) interaction are also under development.

Ruboxistaurin. Is a selective protein kinase C inhibitor that reduces albuminuria (albeit with no significant difference for other renal outcomes) in T2DM DN.

Pirfenidone. Is an antifibrotic (via ↓ TGF-β production) and a free radical scavenger under investigation in several clinical contexts, including DN. It reduces mesangial expansion and collagen gene expression in animals. Clinical trials suggest it may improve GFR but not albuminuria. **Tranilast** is another antifibrotic agent that has shown beneficial effects in animal models and clinical trials. **Doxycycline** may also have antifibrotic properties and has been shown to reduce proteinuria.

Sulodexide. A glycosaminoglycan, inhibits TGF-β production and causes dose-dependent reductions in albuminuria (persistent after discontinuation). Early clinical trials vs placebo have been disappointing.

Avosentan. Is an ET-1 receptor antagonist that reduces urinary albumin excretion at the expense of increased CV events (CCF and volume overload). Atrasentan also reduces albuminuria and is more selective for the ET-A receptor. It is associated with peripheral oedema but is less likely to cause frank volume overload. Further trials are awaited.

The transcription factor nuclear factor erythroid-related factor 2 (Nrf2) is involved in numerous anti-inflammatory and antioxidant pathways. Nrf2 knockout mice suffer worse nephropathy in experimental diabetes. **Bardoxolone methyl**, a synthetic triterpenoid, induces Nrf2 and improves GFR (but with no change in albuminuria). Unfortunately, the international BEACON trial was stopped early, following excess adverse events in the treatment arm.

Diabetic mice lacking vitamin D receptors demonstrate RAS upregulation, glomerulosclerosis, and increased urinary albumin losses. The administration of an active vitamin D analogue **paricalcitol** has been shown to significantly ameliorate this albuminuria.

Other diabetes-related urinary tract disorders

Papillary necrosis (📖 p. 585)

Occurs in ~1:20 with diabetic nephropathy. May be asymptomatic but can present as pain (recurrent renal colic) or infection. Haematuria, modest proteinuria (<2g/24h), and sterile pyuria are common.

Renovascular disease (📖 p. 586)

Suspect if difficult to control BP, fluid retention, or >20% rise in SCr (or fall in eGFR), following an ACE-I or ARB.

Neurogenic bladder (diabetic cystopathy)

A degree of bladder dysfunction is present in ~40% of patients with long-standing diabetes. It results from peripheral and autonomic neuropathy (characterized by segmental demyelination with impaired conduction). The first manifestation is usually loss of sensation of bladder filling, with subsequent progressive loss of motor function. Incomplete emptying leads to a large-volume bladder, with a significant post-micturition volume and urinary stasis. Recurrent UTIs and urinary incontinence are common.

Investigation: MSU for M,C+S. USS bladder pre- and post-void. Ask the patient to complete a bladder diary. Urodynamic findings include decreased bladder sensation, impaired detrusor contractility, and eventual detrusor areflexia. Detrusor hyperreflexia is also recognized. Screen for other manifestations of autonomic dysfunction, e.g. postural HR and BP. Exclude significant prostatic disease.

Interventions include regular voiding in the absence of urge (e.g. every 2h), anti-incontinence aids to absorb urine losses and protect skin integrity, assisted voiding (e.g. suprapubic manual pressure), drugs (e.g. the parasympathomimetic agent bethanechol) (benefits inconsistent), intermittent self-catheterization, (also ↓ bladder volume and may help partial recovery of detrusor function), long-term catheterization, urinary diversion, and treatment of associated infection.

Urinary tract infection (📖 p. 706)

♀ with diabetes have twice the incidence of UTI, compared to those without diabetes. Diabetes is also a risk factor for UTIs in ♂. There is also a higher incidence of pyelonephritis and renal abscess formation. 90% of cases of emphysematous pyelonephritis (📖 p. 711) occur in patients with diabetes.

Contrast induced-AKI (📖 p. 148)

Patients with diabetes, probably as a result of intrarenal microvascular disease, are more susceptible to CI-AKI.

Considerations in ESRD from diabetic nephropathy

► Patients with T1DM (and selected patients with T2DM) should be considered for combined kidney/pancreas transplantation (📖 p. 446).

Diabetic patients often need to initiate dialysis at an earlier stage than patients with ESRD from another cause, e.g. eGFR in the 10–15 mL/min range, as they are often more symptomatic, tolerate volume overload less well, and have a heightened propensity to hyperkalaemia.

Survival and causes of death in diabetic patients on dialysis

Diabetic patients with ESRD have a 5-year survival rate of ~30% (compared with ~60% in those without diabetes). This is largely a consequence of their comorbidity, particularly CV disease. A higher incidence of withdrawal from dialysis treatment is also reported.

Dialysis modality: peritoneal dialysis vs haemodialysis

No clear difference in outcome between PD and HD has been observed. USRDS data and Canadian studies have offered conflicting results (potentially explained by different patient demographics and comorbidities). Overall, there is a suggestion that older diabetic patients survive longer on HD, and younger patients longer on PD.

Renal transplantation in diabetics

Renal transplantation is safe and effective. In appropriately selected patients, it can offer improved survival and rehabilitation, compared to dialysis. Studies have shown similar 1- and 5-year graft survival in diabetic and non-diabetic patients undergoing transplantation when data are censored for patients dying with a functioning graft. Living donor graft survival is superior to deceased donor grafts (80% vs 64% 5-year graft survival).

Plasma cell dyscrasias

Introduction

In this related group of disorders, bone marrow-derived malignant plasma cells produce abnormal immunoglobulin proteins that can cause renal injury by a number of mechanisms, including tubular blockage (e.g. myeloma cast nephropathy), direct glomerular injury (e.g. light chain deposition disease), immune complex formation (e.g. cryoglobulinaemia), and aggregation + accumulation (e.g. AL amyloidosis).

The four most important syndromes are:

- Myeloma kidney (cast nephropathy) (~30–65%).
- AL amyloid (~20%).
- Monoclonal immunoglobulin deposition disease (MIDD):
 - Light chain deposition disease (LCDD) (~10%).
 - Immunotactoid or fibrillary glomerulopathy (rare).
- Cryoglobulinaemia (rare).

Renal presentations of the plasma cell dyscrasias

- AKI: cast nephropathy, dehydration, \uparrow Ca^{2+} , sepsis, drug-induced.
- CKD: cast nephropathy, AL amyloid, MIDD.
- Proteinuria (or nephrotic syndrome): AL amyloid, MIDD.
- Tubular dysfunction (acquired Fanconi's syndrome, partial proximal and distal tubular defects): cast nephropathy, plasma cell infiltration.

What is in an immunoglobulin (Ig)?

An Ig comprises two heavy chains (with a complement-fixing site) and two light chains (with an antigen-binding site). Plasma cell dyscrasias may produce whole monoclonal Ig, whole light chains or heavy chains, or parts of either. This leads to the slightly confusing terminology surrounding the specific diseases caused by each protein.

Myeloma kidney

Multiple myeloma is a haematological malignancy caused by an excess of plasma cells. It is characterized by aberrant overproduction of monoclonal immunoglobulin (termed paraprotein or 'M' protein) plus associated light chains, either kappa (κ) or lambda (λ). The most common class of whole immunoglobulin is IgG (followed by IgA then IgD). In some cases, only the associated κ or λ light chain will be identified.

The diagnosis of myeloma requires:

- A serum or urine paraprotein.
- Clonal plasma cells occupy $>10\%$ of the bone marrow.
- End-organ damage unexplained by other pathology, e.g. \uparrow Ca^{2+} , \uparrow SCr, anaemia, or lytic bone disease (remember: CRAB (□□ p. 624)).

Incidence ~40 pmp/year. 80% patients present aged >60 (although the diagnosis may need to be considered in much younger patients). ♂ $>$ ♀. Renal involvement is a major complication of myeloma, present at (or preceding) diagnosis in 20–50% of patients, and in 50% of patients during the course of the disease (~10% require RRT).

Myeloma and AKI

Myeloma has a propensity to injure the renal tubules, leaving patients vulnerable to secondary insults that cause ATN, such as volume depletion and hypotension. In addition, reduced tubular flow will increase tubular light chain concentrations and further enhance tubular damage.

Common causes of AKI

- Cast nephropathy (most common).
- ATN from sepsis, ↓ BP.
- ↑ Ca^{2+} causes dehydration and vasoconstriction.
- NSAIDs taken for skeletal pain.
- Contrast-induced AKI.
- Drug-induced: diuretics, toxicity of myeloma therapy.

When to suspect myeloma

Any unexplained ↑ SCr/↓ eGFR, esp. if associated with disproportionate anaemia (or anaemia that is refractory to ESA therapy). Also ↓ Plt or ↓ WCC (marrow failure 2° to plasma cell infiltration), immune paresis (reduction in all Ig classes), skeletal pain (e.g. low back). Urinalysis may be relatively normal (light chains are not detected by dipstick).

Investigations

- FBC (↓ Hb common; ↓ Plt and ↓ WCC less so), ↑ ESR, ↑ SCr, ↑ Ca^{2+} , ↑ urate/LDH (↑ cell turnover).
- Serum protein electrophoresis (SPEP) for paraprotein. Detects intact Ig but only high levels of light chain. Immunofixation is more sensitive but is not quantitative. Immunoglobulins (? immune paresis), β₂ microglobulin (activity monitoring—but accumulates in renal impairment).
- Bence-Jones proteinuria. These are urinary free light chains detected by urinary protein electrophoresis and immunofixation.
- Skeletal survey (osteolytic lesions, osteoporosis, fractures).
- Bone marrow aspirate and trephine.
- Renal biopsy (📖 p. 80).

Serum free light chain (SFLC) assay

- New nephelometric/turbidimetric assays that measure free κ or λ light chains are superseding biochemical methods. They utilize polyclonal antibodies to epitopes that are sequestered when light chains are bound to heavy chains but exposed when they circulate freely.
- A rapid test, with excellent sensitivity and specificity.
- Combine with SPEP, as this characterizes the intact Ig component.
- Can identify most patients with myeloma, amyloidosis, and MIDD.
- Considered abnormal when κ or λ free light chain is increased and the ratio between the two is abnormal.
- SFLC accumulates if ↓ GFR, so normal ranges are adjusted.
- Serial measurements help to monitor therapeutic response.
- Advocated by the International Myeloma Working Group (IMWG) for initial screening of plasma cell dyscrasias.

Myeloma: cast nephropathy

Introduction

The commonest form of renal involvement within the plasma cell dyscrasias (~30–65%) and virtually always the cause (or a contributor) to severe renal impairment. Casts develop when the excess filtered load of light chains reacts with Tamm–Horsfall mucoprotein (THMP) in the more distal tubule and forms an insoluble proteinaceous plug. This obstructs tubular flow, disrupts tubular architecture, and leads to progressive interstitial injury (which becomes rapidly irreversible).

Cast formation is promoted by various properties of the light chain (e.g. charge in relation to tubular fluid pH, binding avidity for THMP, propensity to aggregate), their concentration and promoting factors, such as dehydration. It is possible to have a very high light chain load without AKI.

Pathogenesis and histology

Cast nephropathy is characterized by eosinophilic acellular casts that have a distinctive fractured appearance (see Fig. 8.1). These occur principally in the distal nephron (distal tubules and collecting ducts), leading to tubular epithelial cell death and luminal distortion. Casts are surrounded by inflammatory cell infiltrates (including macrophages and multinucleate giant cells), causing interstitial inflammation, oedema and, inevitably, fibrosis. Casts are polychromatic, with Masson's trichrome positive for monoclonal light chain, and may stain with Congo red (although are not birefringent under polarized light).

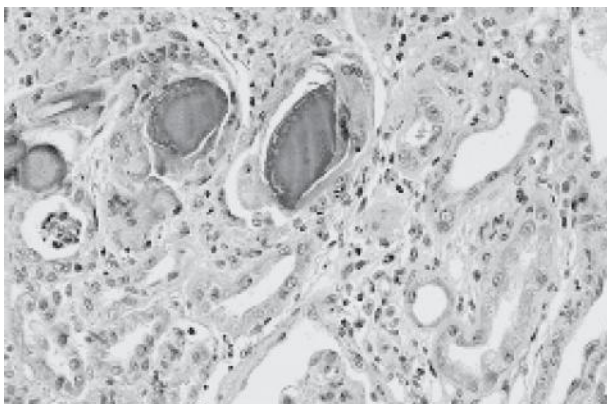


Fig. 8.1 Fractured tubular casts characteristic of myeloma kidney. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P *et al.* (eds) (2005). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford: Oxford University Press.

Management of cast nephropathy

► Correct associated reversible causes of AKI: dehydration, \uparrow Ca^{2+} , sepsis, and hyperuricaemia.

- Rehydrate:
 - Crystalloid IV—may require large volumes (>5L) if \uparrow Ca^{2+} .
 - Δ Sodium bicarbonate can be used if there is a systemic acidosis, but alkaline diuresis does not alter outcomes.
 - Strict monitoring of fluid balance. Encourage to drink 3L/day.
 - Increasing urinary flow will reduce urinary light chain concentration and help prevent further cast formation.
 - Furosemide promotes cast formation, so its use should be avoided.
 - Expect Hb to fall—transfuse, as required.
- Correct \uparrow Ca^{2+} (📖 p. 806).
 - If \uparrow Ca^{2+} persists once euvolaemic, consider IV bisphosphonate (📖 p. 807).
- Appropriate cultures and antimicrobials if concomitant sepsis.
- Correct hyperuricaemia (📖 p. 160):
 - Start allopurinol 100mg daily.
- Stop NSAIDs and other nephrotoxic drugs.
- If anaemic, consider for an ESA (📖 p. 222). High dose usually necessary.
- Renal support:
 - Initiate RRT for standard indication (required in ~10%; recovery in ~20%). Dialysate Ca^{2+} may need reduction.
 - No convincing evidence of a modality benefit for HDF, HF, or PD.
 - \bullet Extended frequent haemodialysis, using a protein-leaking dialyser with very large pores and improved light chain clearance (termed a 'high cut-off' or HCO dialyser), may be of benefit and is currently under further investigation.
- \bullet Plasma exchange (PEX):
 - PEX can reduce plasma light chain load, but rebound is usual.
 - Appears less beneficial than extended dialysis with HCO dialyser.
 - Beneficial in hyperviscosity syndromes (e.g. Waldenström macroglobulinaemia) (📖 p. 635).
- Specific therapy:
 - Myeloma is incurable. The goal is to reduce Ig or light chain burden, induce remission, and increase survival.
 - High-dose corticosteroid, e.g. dexamethasone 20mg PO bd for 4 days, to induce plasma cell apoptosis (as soon as possible).
 - Subsequent chemotherapy is tailored to the individual situation.
 - Bortezomib, a proteasomal inhibitor, appears beneficial in patients with renal disease and does not require dose adjustment (Δ SE: neuropathy). It may be given alone or in combination with thalidomide (or its analogue lenalidomide) (Δ SE: venous thrombosis) \pm doxorubicin.
 - Alkylating agents, such as melphalan and cyclophosphamide, impair haemopoietic stem cell function and may be best avoided if autologous transplantation is feasible.
 - Autologous stem cell transplantation (ASCT) offers the best prospect of complete remission in selected patients.

When myeloma is not myeloma

Finding a paraprotein in serum or urine does not always confirm a diagnosis of myeloma.

Monoclonal gammopathy of uncertain significance (MGUS)

- Paraprotein <3g/dL.
- <10% plasma cells in the bone marrow.
- Usually does not have Bence–Jones proteinuria.
- No evidence of end-organ damage ('CRAB'):
 - Calcium: \uparrow Ca^{2+} >0.25mmol/L (1mg/dL) above the upper limit of normal or >2.75mmol/L (11mg/L).
 - Renal insufficiency: SCr >173 μ mol/L (1.96mg/dL).
 - Anaemia: Hb 20g/L below lower limit of normal or <100g/L.
 - Bone lesions: lytic lesions or osteopenia with compression fractures.

Other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months).

- ~3% of individuals aged >70 have MGUS.
- ~1% progress to symptomatic myeloma each year.
- Risk factors for progression: higher paraprotein level, non-IgG paraprotein, and an abnormal SFLC ratio.

A monoclonal protein that can be characterized as a MGUS is not uncommonly found during the initial work-up of elderly patients with CKD. This mandates surveillance, usually 6–12-monthly, with consideration of either a bone marrow biopsy or a renal biopsy or both if there is diagnostic doubt or evidence of progression. Where renal involvement is the prime clinical concern in this context, the term *monoclonal gammopathy of renal significance* has recently been coined.

Asymptomatic (previously 'smoldering') myeloma

- Refers to asymptomatic patients, with paraprotein >3g/dL and a plasma cell infiltrate >10% but no end-organ damage.
- Evolves to symptomatic myeloma in ~3% patients per year for the first 5 years, and then progression declines in incidence.

Plasmacytomas

- Solid tumours made up of clonal plasma cells found as solitary bone plasmacytoma (SBP) or solitary extramedullary plasmacytoma (EMP) (usually upper respiratory tract).
- <50% produce a (usually low level) paraprotein.
- Renal involvement is rare.
- Progression to myeloma in ~50% (SBP > EMP). Treated with local radiotherapy. Median survival 10 years.

ESRD in myeloma

Mortality on dialysis depends mainly on progression of the underlying myeloma, as patients survive as long as matched myeloma patients without renal failure. Early mortality is high (~20% die within the first 2 months), but mean 3-year survival is ~30%. Patients who respond to chemotherapy do much better.

Both haemodialysis and peritoneal dialysis are feasible modalities. However, the main risk concerns susceptibility to infection (from the disease itself and its treatment), so CAPD-related peritonitis and dialysis catheter-related sepsis can be severe. For this reason, an AVF should be fashioned as soon as recovery of renal function is unlikely (~20% recover renal function with treatment, usually within the 3 months).

The usual indications for commencement of dialysis in CKD/ESRD apply (📖 p. 267), but patients may be symptomatic at a higher GFR in view of their comorbidities and \therefore require an earlier start. In addition, progression to ESRD can be swift, with limited time for RRT education or psychological adjustment.

Monoclonal Ig deposition disease

Introduction

Monoclonal Ig deposition disease (MIDD) describes another clinicopathological variant of abnormal monoclonal light chain (or, less commonly, heavy chain) deposition, termed LCDD and HCDD, respectively. This is a similar condition to AL amyloid, but there are important structural differences, as the proteins do not organize into fibrils. LCDD is more common and usually caused by an abnormal κ chain, while μ or γ chains are usually responsible for HCDD.

The clinical presentations of LCDD and HCDD are similar—usually with nephritic-type glomerular injury: proteinuria (nephrotic range in ~30%), microscopic haematuria, \uparrow BP, and renal impairment (which may rapidly progress). May also present as CKD. Renal involvement is often the finding that prompts a search for an underlying dyscrasia (usually myeloma, but Waldenström macroglobulinaemia, chronic lymphocytic leukaemia, and lymphoma are also associated). However, a malignant process may not fully declare itself despite prolonged follow-up.

Light chain deposition disease (LCDD)

- A plasma cell dyscrasia causes tissue deposition of a monoclonal Ig light chain (κ in 65%).
- Differs from amyloid, as the light chain lacks hydrophilic residues so cannot organize into fibrils (or stain positive for Congo red), forming granular deposits instead.
- The light chains have distinct properties, e.g. variants of the κ light chain variable region (types I and IV), influencing their deposition.
- Associated with overt myeloma in ~50% (myeloma may subsequently develop). Bone marrow plasma cell expansion not always present.
- No monoclonal band on electrophoresis, and immunofixation in ~30% patients, but SFLC assays are significantly more specific.
- Extrarenal features are less common than renal: cardiac (diastolic dysfunction, arrhythmias), hepatic (abnormal LFTs, hepatomegaly), and nerves (neuropathy).
- Histological features on renal biopsy:
 - Extracellular matrix accumulation causes nodular glomerulosclerosis (Congo red *negative*), with glomerular and tubular basement membrane thickening. This appears similar to diabetic Kimmelstiel–Wilson changes (📖 p. 608). Can be an MCGN injury pattern.
 - Immunostaining is positive for monoclonal light chains in capillary walls, basement membranes, and mesangium.
 - EM demonstrates bands of amorphous, granular deposits, without fibril formation, in glomerular and tubular basement membranes.
- Treatment is directed against the underlying plasma cell dyscrasia, generally using the same criteria and regimens as for myeloma.
- Response is monitored through measurement of SFLC.
- Age and CKD are negative prognostic indicators. ~50% will eventually reach ESRD. Renal transplantation contraindicated unless complete remission. ~25% 10-year survival.

Heavy chain deposition disease (HCDD)

A rare disorder. Abnormal heavy chains deposit in the glomerulus and cause a similar disease to LCDD. Underlying myeloma is identified in ~25%. Extrarenal disease is less common.

Monoclonal Ig-derived material in the kidney

Can arise from any part of an immunoglobulin (📖 p. 620) and can be classified (see Table 8.3) according to the appearance of the deposits on biopsy (including EM).

Immunoglobulin and Ig-derived fragments have an affinity for basement membranes, perhaps explaining the strong association with renal disease (particularly as ~20% of cardiac output passes through the kidneys).

Table 8.3 Classification

Organized	Crystalline	Cast nephropathy Fanconi's syndrome (📖 p. 825)
	Fibrillar	AA or AL amyloidosis
	Microtubular	Immunotactoid GN Cryoglobulinaemia
Disorganized	Granular	LCDD
		HCDD

Immunotactoid and fibrillary glomerulonephritis

Rare disorders characterized by the deposition of non-amyloid (i.e. Congo red negative) proteinaceous fibrils derived from immunoglobulin. Usually very similar glomerulopathic presentation to that of MIDD. They are almost always confined to the glomeruli, with no extrarenal disease. Progression to ESRD is frequent.

No specific diagnostic test, so renal biopsy (with EM) is key. Investigate for paraprotein, HCV, haematological malignancy, and autoimmune disease.

Fibrillary GN. Does not usually associate with a paraprotein. Deposition of polyclonal IgG in mesangium and glomerulus. Appears as mesangial proliferation or MCGN on light microscopy. EM: randomly arranged fibrils, usually ~20nm in diameter.

There is no treatment proven to slow progression. Small trials of immunosuppressive therapy have been disappointing (except in patients with crescentic changes on renal biopsy where prednisolone + cyclophosphamide may be effective).

Immunotactoid GN. Often associated with haematological disease (esp. CLL, B cell NHL). Whole monoclonal IgG and C3 deposits. Light microscopy appears as an atypical membranous or lobular MCGN. EM: rod-like, hollow, microtubular structures, usually >30nm in diameter, ordered in parallel. Treat underlying disease.

Renal amyloid: AL amyloid

Introduction

Amyloidosis is a multisystem disorder caused by extracellular deposition of abnormal (misfolded and insoluble) fibrils resulting from the aggregation of an aberrant protein. When this aberrant protein is an immunoglobulin or light chain (usually λ), it is known as primary or AL amyloidosis. In secondary amyloidosis, the protein is serum amyloid A (SAA), which is overproduced in chronic inflammation. In less common hereditary forms, a variety of proteins are involved, including fibrinogen A α chain, transthyretin, and apolipoproteins AI and AII.

Amyloid fibrils of all types are 8–12nm in diameter and always bound to the normal plasma protein serum amyloid P (SAP). SAP appears to render the fibrils extremely resistant to degradation. Classically, amyloid deposits appear an apple-green colour on Congo red staining if viewed under birefringent light.

AL amyloid

The fibrils in AL amyloid are derived from either whole monoclonal Ig or, more commonly, from light chain (usually λ). There is an underlying plasma cell dyscrasia, but this will be clinically overt in only 25% (usually myeloma—amyloid deposits will be found in 10–20% myeloma patients).

AL amyloid may be deposited in virtually any tissue in the body, depending, to an extent, on the particular physicochemical characteristics of the involved Ig or light chain.

Annual incidence ~10 pmp. Median age at diagnosis ~65.

Clinical features

Depend on specific organ involvement, but systemic symptoms, such as malaise and weight loss, are common.

- **Cardiac:** restrictive cardiomyopathy (~30%) and arrhythmias (these are the main cause of death).
- **Liver:** hepatomegaly (and splenomegaly) from infiltration. Hyposplenism causes susceptibility to sepsis (the other main cause of death).
- **Gut:** motility disorders, GI bleeding, macroglossia (tongue infiltration).
- **Nerves:** sensorimotor neuropathy (may be painful), autonomic neuropathy (e.g. orthostatic hypotension, bladder dysfunction), and compression syndromes (e.g. carpal tunnel).
- **Haematological:** bleeding diathesis, associated with factor X or IX deficiency. May manifest as easy bruising—but measurement of PT, APTT, and often bleeding time are necessary prior to organ biopsy (Δ esp. renal).
- **Skin:** purpura (esp. recurrent periorbital), papules.
- **Joints:** synovitis and polyarthropathy.
- **Adrenal:** hypoadrenalism.
- **Thyroid:** hypothyroidism.
- **Renal:** involvement in ~50%. Normally proteinuria (often nephrotic range, with severe oedema) and variable degrees of renal impairment. Microscopic haematuria is uncommon. Tubular defects, including RTA, may occur. ~20% develop ESRD. Kidneys often appear large on USS.

Renal histology

- *Light microscopy*: widespread amorphous extracellular amyloid deposits are seen in the mesangium, along the glomerular basement membrane and in blood vessels. They appear less frequently in the tubules and interstitium. Characteristic Congo red staining.
- *Immunostaining*: for λ (occasionally κ) and SAP may be positive, but is unreliable. Other types of amyloid deposits are differentiated with special stains, e.g. to SAA.
- *EM*: demonstrates fibrils (see Fig. 8.2) but will not distinguish types.

Investigations

- Tissue biopsy to confirm diagnosis. If no renal involvement, then salivary gland, subcutaneous abdominal fat, or rectum are favoured sites (positive in >80%).
- Serum and urine protein electrophoresis \pm immunofixation. Positive in ~90% and 75%, respectively. Δ Beware a coincidental MGUS, and consider other, including hereditary, forms.
- Serum free light chains (electrophoresis + SFLC positive in ~99%).
- Bone marrow examination (\uparrow plasma cells in ~50–60%).
- Echocardiography.
- ^{125}I SAP scintigraphy: not widely available. Radiolabelled SAP protein is injected to locate areas of amyloid deposition. Demonstrates distribution and extent of deposits and can be used to monitor response to treatment.

Prognosis

Very poor outlook without treatment—usually progressive and fatal within 1–2 years. Cardiac involvement is a particularly poor prognostic indicator. Diagnosis of renal AL amyloid is associated with a median time to RRT of ~1 year (with median time to death within a further year).

Happily, the prognosis is greatly improved with effective therapy of the underlying plasma cell dyscrasia—with amyloid regression in many cases. For renal involvement, resolution of the nephrotic syndrome, with stabilization of renal function and retarded progression to ESRD, is the goal of treatment.

Management

Treatment aims to decrease, or eliminate, the culpable plasma cell clone. Patients are often elderly, so therapy must be tailored accordingly. Regimens include cyclophosphamide, thalidomide, and dexamethasone (CTD), or melphalan plus dexamethasone (M/Dex). Responses in ~30–50%. Lenalidomide and bortezomib are increasingly used, based on experiences in myeloma. High-dose chemotherapy with autologous stem cell transplantation in selected patients.

Dialysis for standard indications. Renal transplantation is only possible if the plasma cell dyscrasia is in complete remission (recurrence in the graft is inevitable otherwise) and cardiac function remains acceptable.

Renal amyloid: AA amyloidosis

AA amyloidosis

AA amyloidosis results from the sustained elevation of the acute phase reactant serum amyloid A protein (SAA). In developing countries, chronic infections account for the majority of cases. In developed nations, chronic inflammatory autoimmune conditions, particularly rheumatoid arthritis, are now much more important.

Prevalence is linked to that of underlying conditions, which vary according to geography. The overall post-mortem incidence of AA amyloidosis in western nations is 0.5–0.86%.

Pathogenesis

There are several isoforms of SAA: SAA1 and SAA2 appear to be most important for acute phase responses. They are HDL-bound apolipoproteins that ↑ macrophage HDL uptake during inflammation (through the displacement of apolipoprotein A1). The persistence of SAA is probably 2° to pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α. Proteolytic cleavage of SAA then generates peptide fragments that aggregate into misfolded AA fibrils via an interaction with the glycosaminoglycan heparan sulphate. It remains unknown why only ~5% of patients with persistent inflammation develop AA amyloidosis; other factors (e.g. genetic, including SAA1 polymorphisms) are clearly important.

Causes

- Chronic inflammatory disease:
 - Rheumatoid arthritis and juvenile rheumatoid arthritis (~40%).
 - Psoriatic arthropathy, ankylosing spondylitis (~30%).
 - Reiter's syndrome.
 - Behçet's syndrome.
 - Inflammatory bowel disease.
- Chronic infections:
 - TB, leprosy.
 - Osteomyelitis.
 - Cystic fibrosis, bronchiectasis.
 - Chronic ulceration.
- Malignancies:
 - Renal cell carcinoma.
 - Lymphoma, Castleman's disease.
- Familial:
 - Familial Mediterranean fever (FMF).

Clinical features

- *Renal*: unlike AL amyloid, renal involvement is universal. Proteinuria (often nephrotic range) is typical, although a minority (<10%) present with progressive CKD, with no proteinuria (predominantly vascular amyloid deposition). Renal biopsy demonstrates both glomerular and tubulointerstitial involvement. Note: microscopic haematuria is present in ~30% so is a much more common feature than in AL amyloid.
- *Spleen*: always involved (→ hyposplenism → infection).
- *Adrenals*: abnormal adrenal function in ~50%.

- *Liver*: hepatomegaly.
- *GI tract*: present in more advanced disease (→ motility disorders, malabsorption, bleeding).
- *Cardiac (~10%), skin, tongue, and nerve*: much less common than in AL.

Investigations

- Tissue biopsy is necessary to confirm diagnosis. This is often a renal biopsy, but less invasive alternatives include salivary gland, subcutaneous abdominal fat, or rectum (positive in >80%).
- Immunostaining tissue for SAA protein differentiates AA from other forms of amyloidosis in virtually all cases.
- CRP and ESR were used to monitor disease and response to treatment, but SAA is increasingly used for this purpose.
- ¹²³I SAP scintigraphy (📖 p. 629).

Prognosis

Outcomes depend heavily on the control of underlying disease processes. Prognosis is better than AL amyloid but still guarded: ~40% survival at 3 years, overall. Infection is the major cause of death. SAA concentration helps predict outcomes, as risk of death rises with the median SAA (10-year survival ~90% if median SAA <10mg/L and only ~40% if >10mg/dL).

Outcomes have improved for those with ESRD (previously a significant cause of death), although patients still have worse dialysis outcomes than those with unrelated conditions. Renal transplantation can be considered if underlying disease is consistently controlled, as recurrent amyloid is surprisingly uncommon in this context. However, 3-year patient survival post-transplant is reduced (principally 2° to infectious and CV causes).

Treatment

Treat the underlying inflammatory or infectious condition to prevent further amyloid deposition. Existing amyloid appears to regress in ~50%, especially if SAA is maintained <10mg/L.

- *Infectious disease*: antimicrobials and or surgical intervention, as indicated.
- *Chronic inflammatory disease*: several treatments have shown efficacy in the inflammatory arthritides and may be applicable to other situations.
 - Alkylating agents, such as cyclophosphamide and chlorambucil, have been shown to improve survival.
 - Anti-TNF therapy, with infliximab, etanercept, and adalimumab, are effective at lowering SAA production.
 - Experience is growing with the anti-IL6 receptor antibody tocilizumab.
 - Colchicine has demonstrable efficacy in FMF, reducing febrile episodes and renal involvement. Mechanism of action is unclear but appears related to suppression of inflammatory responses. 🌟 It has also been used, with variable success, in non-FMF patients with renal disease.
 - Novel approaches: there is increasing interest in therapies that can interfere with fibril aggregation and deposition, e.g. agents that disrupt the interaction of SAA with glycosaminoglycan or induce dimerization of SAP to provoke improved systemic clearance.

Renal amyloid: other forms

Other forms of amyloidosis with renal involvement

Inherited fever syndromes

Familial Mediterranean fever (FMF): causes AA amyloidosis and is the most common inherited form. Inheritance is autosomal recessive, most commonly affecting Sephardic Jews, Armenians, and Turks. It is caused by a mutation in the *MEFV* gene encoding pyrin, a regulator of transcription for inflammatory mediators, including IL-1. Periodic acute attacks (of variable frequency) present before the age of 20, with fever (~25% have fever alone) and serositis (→ peritonitis, pleurisy, synovitis) lasting 48–72 hours before spontaneous resolution. During the flare: ↑ WCC and ↑ CRP. AA amyloid complicates ~60% (Turks are at highest risk), and renal involvement is common. Colchicine 1–2mg/day is highly successful at reducing both flare frequency and AA amyloidosis risk. It may also stabilize already established renal disease.

Others: TNF receptor-associated periodic syndrome (TRAPS) is autosomal dominant, with onset in childhood. Colchicine is less effective. Muckle Wells syndrome presents soon after birth, with daily episodes of rash, red eyes, and fever.

Hereditary amyloidosis

These are much less common than the AL or AA types. The inheritance of an abnormal gene leads to lifelong production of a potentially amyloidogenic protein. Most forms do not present until middle age or later. They can be difficult to identify and may potentially be mislabelled as AL amyloid, particularly if there is a concomitant MGUS (common in this age group). Characterization of the amyloid type with immunohistochemistry is helpful, but genetic testing at specialist centres is diagnostic.

Familial amyloid polyneuropathy: the commonest. Caused by mutations in transthyretin. Multiple mutations have been identified, producing different clinical phenotypes. Predominantly a neurological disorder, but renal involvement is described.

Fibrinogen A α -chain: the hereditary form with most renal involvement (almost exclusively glomerular). Presents >age 50. Combined liver–renal transplantation is a potential treatment option.

Apolipoprotein A1: may present with hypertension and CKD in middle age (\pm cardiac and nerve involvement). Again, combined liver–renal transplantation is a potential treatment option.

β 2 microglobulin-related dialysis amyloid

- β 2 microglobulin (β 2-M) is a component of the MHC class I complex and is produced by all cells that express MHC I. It is freely filtered at the glomerulus and reabsorbed (and metabolized) in the proximal tubule. Consequently, it accumulates in patients with ESRD, and these accumulations are amyloidogenic.
- β 2-M is incompletely cleared by dialysis treatments (~1,500mg is produced each week, only ~1/3 of which is removed). β 2-M clearance on dialysis depends on several factors:

- Residual renal function.
- Modality (clearance on HD < PD < daily HD < nocturnal HD).
- Characteristics of the dialysis membrane (high flux is better than standard. Biocompatible is better than bioincompatible).
- Duration of treatment and ultrafiltration volumes.
- A degree of deposition is universal and begins early after reaching ESRD. However, clinical presentation takes much longer; usually occurring after >5 years' dialysis treatment. Clinical features:
 - Generally, a disorder of soft tissue and joints.
 - Carpal tunnel (very common in patients on dialysis >10 years).
 - Chronic tenosynovitis of finger flexors. Generalized joint pain, stiffness, and restricted movement (particularly shoulders, but also hands, feet, and spine). Progresses to destructive arthropathy. Contributes to an increased fracture risk.
 - Organ deposits occur (esp. GI), but clinical issues are rare.
- Diagnosis:
 - Generally made on clinical grounds. Radiological appearances (bone cysts and periarticular lucency) are characteristic (see Fig. 8.2). If tissue is available (e.g. after joint replacement), it will stain with Congo red. Specific anti- β 2-M immunostains are available.
- Treatment:
 - Modify dialysis prescription (📖 p. 288): increase treatment hours; use a high-flux, biocompatible dialyser; consider HDF.
 - Analgesia and orthopaedic intervention, as needed.
 - Renal transplantation is the treatment of choice but is often not possible in the group of long-standing, often elderly, dialysis patients who are most severely affected. Deposits are slow to resolve post-transplant, but symptoms often significantly improve.

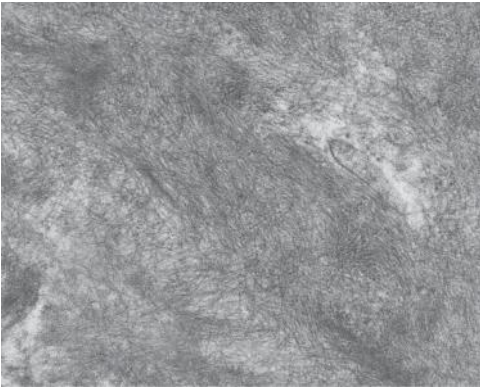


Fig. 8.2 Amyloid fibrils on electron micrograph of renal biopsy tissue. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P et al. (eds) (2005). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford: Oxford University Press.

Cryoglobulinaemia

Introduction

Cryoglobulins are single or mixed immunoglobulins that precipitate below 37°C and re-dissolve on warming. Several types have been described and may be encountered in different clinical scenarios—and with different clinical consequences.

Cryoglobulinaemia implies that circulating cryoglobulins are causing tissue damage. This may be 2° to hyperviscosity, immune complex deposition (with complement activation), or precipitation in small vessels, with thrombosis and downstream ischaemia (typically in cooler extremities).

The overall prevalence of cryoglobulinaemia is unknown but strongly tied to that of hepatitis C (HCV) (📖 p. 686). It is more common in ♀.

Cryoglobulins may be present in otherwise healthy individuals, so prognosis will depend on both disease activity and disease associations. Renal manifestations are associated with a worse outcome.

Classification

Classified according to their constituents.

Type I cryoglobulinaemia (<20%)

The result of a monoclonal immunoglobulin (usually IgM, then IgG > IgA > light chain) and often associated with lymphoproliferative disease (myeloma, lymphoma, CLL, Waldenström macroglobulinaemia).

Type II (or mixed essential) cryoglobulinaemia

Usually monoclonal IgM, complexed with the Fc portion of polyclonal IgG. This monoclonal IgM autoantibody is a type of rheumatoid factor (any antibody directed against another antibody is termed anti-idiotypic and possesses rheumatoid factor activity). Associated with HCV (📖 p. 686) and other infections (including HIV, HBV, and syphilis) as well as autoimmune disease (e.g. SLE, Sjögren's syndrome). Also described with B cell non-Hodgkin's lymphoma.

HCV enters host cells (hepatocytes and CD5+ B cells) via the LDL receptor—infected B cells are resistant to apoptosis and exhibit increased production of autoantibodies.

Type III cryoglobulinaemia

Similar to type II, but this time polyclonal IgM is directed against IgG. Type III is also associated with viral infections and autoimmune disease and may evolve into type II over time.

Clinical features

Type I cryoglobulins do not fix complement so may present with a hyperviscosity syndrome (acrocyanosis, retinal occlusions, Raynaud's, digital ulceration, livedo reticularis, purpura, arterial and venous thrombosis).

Type II and III cryoglobulins cause systemic inflammation. Consider cryoglobulinaemia in any patient with unexplained renal disease and a rash (skin involvement is virtually universal—often a cutaneous vasculitis, with infarcts and ulceration), particularly if systemic symptoms, such as fatigue and myalgia, are present. Also neuropathy, arthralgia, GI involvement, and lung involvement (pulmonary infiltrates and haemorrhage).

Renal involvement occurs early in up to 60% cases, usually presenting as the nephritic syndrome with AKI. Renal biopsy reveals an MCGN-type pattern of injury (📖 p. 550).

Investigation

- Complement components (📖 p. 41).
- ► Screening test for types II and III: high titre of rheumatoid factor plus low C4.
- Cryoglobulins: the blood sample needs to be transported at 37°C, ideally in a water bath. Speak to your laboratory.
 - Type I cryoglobulins may precipitate within 24–48h, but II and III can take up to 7 days.
 - Result is generally reported as ‘cryocrit’ (the volume of precipitate as a percentage of original serum volume) and can be helpful for disease monitoring.
 - The specific constituents of the cryoglobulin can be confirmed by immunochemistry.
- Tissue biopsy, e.g. renal.
- Investigate for underlying condition, particularly hepatitis serology, HIV testing, autoimmune serology (ANA, dsDNA, ENAs, etc.), FBC, blood film, serum and protein electrophoresis, SFLC, appropriate imaging ± bone marrow examination for haematological disease.

Treatment

- Treat underlying condition, e.g. pegylated IFN- α and ribavirin for HCV.
- Immune suppression, typically corticosteroids and cyclophosphamide, but increasing interest in rituximab (trials in progress).
- Plasma exchange: for hyperviscosity or severe disease, e.g. rapidly progressive AKI.

Waldenström's macroglobulinaemia

- A clonal lymphoid and plasma cell disorder with overproduction of IgM monoclonal protein.
- Multiple presentations: systemic symptoms (fever, weight loss, night sweats), anaemia, lymphadenopathy, hepatosplenomegaly, neuropathy, hyperviscosity syndrome (📖 p. 634), and cryoglobulinaemia.
- Renal involvement is uncommon but is glomerular (not cast nephropathy) when it occurs (microscopic haematuria, proteinuria, \uparrow SCr). Histologically: GN with intracapillary thrombi and deposits from IgM aggregation. These stain for μ and κ chains. Cryoglobulinaemic features, MCGN, and amyloid may also be seen.
- Diagnosis rests on finding a monoclonal IgM protein and $>10\%$ lymphoplasmacytic cell infiltration of bone marrow.
- Treatment: plasma exchange for hyperviscosity, rituximab, alkylating agents (cyclophosphamide, chlorambucil), purine analogues (e.g. fludarabine), and stem cell transplantation are all possibilities.

Sickle cell nephropathy

Introduction

Renal involvement occurs in ~60% of patients with sickle cell disease (HbSS) at some point during their life, although only 10–15% of these patients will develop ESRD. These figures are halved in individuals with the HbSC form of the disease. Heterozygous patients (HbSA) may develop tubular defects later in life, although they do not appear to be at a greater risk of developing CKD.

Pathophysiology

The relatively hypoxic and hyperosmolar environment of the inner medulla promotes polymerization of deoxygenated haemoglobin S and subsequent sickling of erythrocytes. This results in impaired renal medullary blood flow, microinfarcts, and papillary necrosis. Alongside this, persistent anaemia and high cardiac output lead to glomerular hypertrophy and hyperfiltration. Over time, the fine network of vasa recta is destroyed; the enlarged glomeruli become sclerosed, and CKD ensues.

Clinical presentation (and underlying cause)

- Polyuria and nocturia:
 - Hyperfiltration and poor medullary perfusion → hyposthenuria (inability to concentrate urine under water-deprived conditions). This is reversible (with blood transfusions) until age 10 but becomes irreversible in later life, causing polyuria and dehydration.
- Metabolic abnormalities:
 - SCN patients often have a partial form of distal RTA and a primary defect in the tubular secretion of K^+ , resulting in a hyperchloraemic metabolic acidosis and $\uparrow K^+$.
 - In contrast, proximal tubular function appears to be supranormal, associated with $\uparrow PO_4$ and β_2 microglobulin reabsorption and \uparrow uric acid and creatinine secretion.
- Proteinuria:
 - In the majority of patients, prolonged hyperfiltration leads to microalbuminuria, progressing to overt proteinuria over time.
 - Although proteinuria is rare in individuals with HbSS disease aged <20, ~60% aged >40 have an elevated uACR or uPCR.
- CKD:
 - GFR begins to fall from the 3rd decade onwards, leading to CKD in a significant number of patients (ESRD in ~5–10%).
- Haematuria and renal colic:
 - Medullary infarction and papillary necrosis can cause visible haematuria. This is usually self-limiting but can be painful and persistent.
- Hypertension:
 - Uncommon in most patients with SCD (presumably the result of persistent vasodilation and dehydration).
 - However, in patients with SCN and CKD, \uparrow BP is more prevalent and may contribute to a rapid decline in renal function.
- AKI:
 - Occurs in ~10% of those hospitalized with crises.

Renal medullary carcinoma

This aggressive malignancy is extremely rare but is found exclusively in patients with sickle cell disease or, more commonly, sickle cell trait. It can occur at any age from childhood onwards and presents with loin pain, haematuria, and weight loss. Although patients are treated with surgery and chemotherapy, these are essentially palliative, as the disease is usually metastatic at presentation and fatal within a year.

Investigations

Although SCN is relatively common in patients with SCD, it is not the only cause of haematuria, proteinuria, or CKD in these patients. Other conditions, such as lupus nephritis, HIVAN, or hepatitis B- or C-associated nephropathy, need to be excluded.

- *Routine, outpatient investigations:* U&Es, SCr, urinalysis and uACR/uPCR, FBC, reticulocytes, LFTs.
- *New-onset haematuria:* renal tract USS, urine cytology; and consider CT-IVU. Cystoscopy may be necessary in older patients as in the general population (📖 p. 67).
- *Heavy proteinuria or new-onset nephrotic syndrome:* immunological and serological screen (📖 p. 40). Parvovirus serology (may cause nephrotic syndrome after the acute infection). Renal biopsy may be necessary (particularly if rapid onset).

Management

There is no specific management for SCN, so treatment can be divided into the management of SCD and the management of proteinuric CKD.

- *SCD.* Many of the complications of SCD, such as frequent crisis and severe anaemia, can be improved with regular hydroxycarbamide (HC) (also known as hydroxyurea). There is limited evidence from studies in children that early signs of SCN can be improved with HC therapy. Similarly, regular transfusion (\pm exchange transfusion) can help mitigate many complications of the disease, although evidence for impact on renal disease is lacking. Bone marrow transplantation in childhood will cure SCD but carries significant risks (not currently widely available).
- *CKD.* Patients with proteinuria (uACR $>50\text{mg}/\text{mmol}$) should be treated with an ACE-I or ARB. Start at low dose because of the risks of $\uparrow K^+$ and \downarrow BP in this group. When taken at night, these drugs often also reduce nocturia. EPO can improve Hb and reduce transfusion requirement in some patients (target Hb 80–100g/L), although high doses are often necessary. Heavy, visible haematuria should be treated with analgesia and IV hydration. It is usually self-limiting, but embolization may be considered for persistent, heavy bleeding.

Dialysis and transplantation should be considered for all patients with ESRD. There appears to be a survival disadvantage on dialysis for sickle patients (when age-matched to non-sickle patients). USRDS data show comparable graft function at 1 year but reduced patient survival ($\sim 60\%$ at 3 years). Recurrent transfusions may lead to sensitization with anti-HLA antibodies. Recurrent disease is common but usually mild.

The kidney in systemic vasculitis

Introduction

The term 'vasculitis' reflects the underlying process: inflammation and leucocyte infiltration of blood vessel walls. This may lead to local inflammation (e.g. purpura), vessel wall damage (→ aneurysm formation or haemorrhage), or vessel occlusion (→ ischaemia and infarction).

It is an autoimmune condition, but the precise causes are unclear. Both genetic (e.g. association with α 1-antitrypsin deficiency and certain tyrosine phosphatase polymorphisms) and environmental factors (nasal *S. aureus* carriage, silica exposure, and certain drugs, e.g. propylthiouracil) appear important.

The systemic vasculitides are classified as small, medium, and/or vessel, according to the size of the smallest vessel affected (see Fig. 8.3). The forms that most commonly involve the kidneys are discussed here (or elsewhere as indicated).

Vasculitis: classified according to the smallest vessel involved

- *Large vessel:*
 - Takayasu's arteritis affects the thoracic aorta and its branches, presenting with \uparrow BP, pulse deficits, and ischaemic limbs or viscera (brain, heart, lungs, gut).
 - Giant cell arteritis (temporal arteritis) presents in older patients with headache, jaw claudication, visual symptoms, and myalgia.
- *Medium vessel:*
 - Polyarteritis nodosa (📖 p. 652).
 - Kawasaki disease affects children, presenting as a febrile illness with lymphadenopathy, skin rash, conjunctivitis, and mucositis (lips, tongue).
- *Small vessel:*
 - Without immune complex deposition:
 - ANCA-associated vasculitis (📖 p. 640).
 - Eosinophilic granulomatosis with polyangiitis (Churg–Strauss).
 - With immune complex deposition:
 - Henoch–Schönlein purpura (📖 p. 650).
 - Cryoglobulinaemia (📖 p. 634).
 - Cutaneous leucocytoclastic vasculitis.
- Other forms of vasculitis may be associated with autoimmune diseases, such as SLE, RA, Sjögren's, and Behçet's.

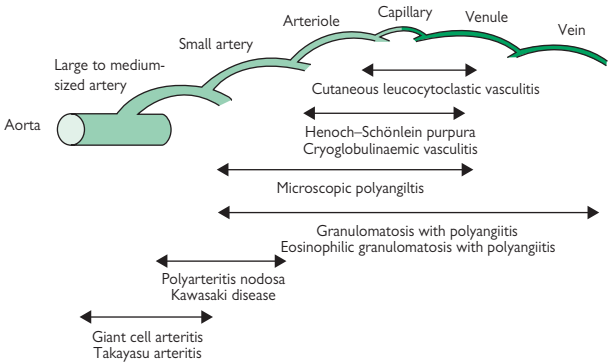


Fig. 8.3 Chapel Hill classification of vasculitis, based on the size of vessel. Modified from Jeanette JC, Falk RJ, Andrassy K, et al. (1994) Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum*, **37**: 187–92. with permission from John Wiley and Sons.


ANCA-associated vasculitis

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis includes granulomatosis with polyangiitis (GPA—previously known as Wegener’s granulomatosis), microscopic polyangiitis (MPA), and renal-limited vasculitis (RLV).

GPA is differentiated pathologically by the presence of granulomatous inflammation, but this may not always be apparent if a biopsy for histological examination is not undertaken. Clinical surrogates that point towards GPA, rather than MPA, include upper airways symptoms or lower respiratory tract nodules and cavitation.

Classification

Two classification systems are used: (i) the Chapel Hill Consensus Conference (CHCC) criteria, and (ii) The European Medicines Agency (EMA) algorithm. Neither is perfect. The categorization of patients remains imprecise (and often clinically unnecessary). It has been suggested that a more simple classification, based on anti-PR3 or anti-MPO positivity, may be more expedient (see ANCA,  p. 642).

Does discriminating GPA from MPA matter?

Perhaps not—treatment is similar, and the clinical and serological presentations overlap, often enough to suggest that they may represent a disease spectrum, rather than distinct entities (see Table 8.4). In the relevant literature, many studies group them together as a small vessel vasculitis.

Table 8.4 GPA and MPA discrimination

	GPA	MPA
ENT involvement	Yes	No
ANCA specificity	c-ANCA (PR3)	p-ANCA (MPO)
Granulomata	Yes (<i>but not in the kidney</i>)	No
Likelihood of relapse	Higher	Lower

Incidence

The incidence of MPA/GPA/RLV is 10–20 pmp per year (in Europe). This increases with age (peak age 65–74). It is rare in childhood. More common in Caucasians. Slightly more common in ♂ vs ♀.

Prognosis

Without treatment, mortality is ~80%. However, this prognosis was dramatically improved by treatment with cyclophosphamide and steroids. Even so, 1- and 5-year survival (in patients with renal involvement) remain ~85% and ~75%, respectively—in part, 2° to considerable treatment-related morbidity (Δ death in the first year is 3× more likely to be 2° to treatment

than the disease itself on traditional regimens. In addition, >40% of morbidity is related to therapy).

- *Poor prognostic indicators*: older age, pulmonary haemorrhage, and severe renal disease.
- *Poor renal prognostic indicators*: severe disease at presentation, age >65 years, resistance to cyclophosphamide therapy, and fibrotic changes on renal biopsy. Δ ESRD will result in up to 25%.

Clinical presentation

- ▶ Extremely variable and the early stages of the disease often missed.
- Systemic symptoms are common: fever, weight loss, malaise, myalgia, and polyarthralgia.
- Other systems or organs that can be affected include:
 - *Upper respiratory tract* (~80% GPA, uncommon MPA): nasal discharge, epistaxis, sinusitis, oral or nasal ulcers, otitis media, deafness, cartilaginous involvement (collapse of nasal bridge and subglottic stenosis).
 - *Lung* (~70% GPA, ~30% MPA): capillaritis, causing pulmonary haemorrhage (may present as frank haemoptysis but can be incipient),
 - ▶ Pulmonary haemorrhage is exacerbated by even mild pulmonary oedema, so any degree of fluid overload should be avoided. Also lung nodules and cavities, pleuritis, and pleural effusions.
 - *Kidney* (~80% GPA, ~90% MPA): scenarios include:
 - Microscopic haematuria or haematoproteinuria with a normal GFR. Proteinuria is usually subnephrotic range. \uparrow BP (~30%).
 - Grumbling deterioration in GFR.
 - Fulminant AKI.
 - Patients with renal-limited vasculitis may develop additional organ involvement at a later stage.
 - *Skin*: vasculitic rash, palpable purpura, ulceration.
 - *Nervous system*: mononeuritis multiplex, peripheral neuropathy.
 - *Eyes*: conjunctivitis, episcleritis, uveitis, retro-orbital mass.
 - *Gut*: abdominal pain, haemorrhagic ulceration, bloody diarrhoea.
 - *Cardiac*: pericarditis, coronary vasculitis.
 - *Circulation*: venous thromboses are more common.

Birmingham vasculitis activity score (BVAS)

This is a validated clinical tool that quantifies disease activity in systemic vasculitis. It has been adopted internationally and is now a staple in clinical vasculitis trials.

The BVAS form is divided into nine sections. Eight are organ-based, each including symptoms and signs typical for involvement of that particular organ in vasculitis, e.g. haematuria, proteinuria, and different categories of SCr in the renal section. The ninth section is for systemic symptoms. The clinician only scores features they consider to be the result of active vasculitis. Completion of the form provides a numerical score (0–68) that can be used to assess disease severity and response to treatment.

Online BVAS calculators are available, although some training prior to their use is desirable.

ANCA-associated vasculitis: investigations

ANCA

- During testing for ANCA, the patient's serum is tested for IgG binding to ethanol-fixed neutrophils.
- Binding occurs in either:
 - A *cytoplasmic* pattern (c-ANCA) (antibody usually confirmed as anti-proteinase 3).
 - A *perinuclear* pattern (p-ANCA) (antibody usually confirmed as anti-myeloperoxidase).
- In fact, both PR3 and MPO are found in the same intracellular granules, so these staining patterns are actually useful artefacts of ethanol fixation.
- Positive ANCA staining is then followed by specific assays for IgG binding to MPO or PR3 antigens (via ELISA or bead assay).
- **⚠** ANCA may also be positive in other inflammatory and infective diseases, so always interpret in clinical context.
 - This is particularly true of p-ANCA.
 - Anti-MPO and anti-PR3 assays are usually negative or low titre (other neutrophil antigens, e.g. lactoferrin or cathepsin, are the source of binding).
 - *Inflammatory*: SLE, rheumatoid arthritis, inflammatory bowel disease, interstitial lung diseases, autoimmune liver disease.
 - *Infective*: HIV, TB, infective endocarditis.
- ~10–15% of patients with clinical and/or histological evidence of GPA/MPA/RLV are ANCA-negative at presentation (although some will become positive over time).
- The positive predictive value of a positive ANCA is dependent on the clinical situation:
 - GPA: ANCA-positive in 80–90% (~75% c-ANCA or anti-PR3).
 - MPA: ANCA-positive in 80–90% (~70% p-ANCA or anti-MPO).

Other investigations

- ► Urinalysis for haematuria (microscopic haematuria almost universal) and proteinuria, microscopy for red cells and red cell casts, uPCR.
- FBC (anaemia common, thrombocytosis, leucocytosis), SCr, U&E, LFTs, CRP (often raised). Consider blood cultures.
- ABGs if suspected lung involvement.
- *Other autoimmune serology*:
 - Anti-GBM: 'double positive' ANCA and anti-GBM disease is well recognized and behaves like anti-GBM disease (📖 p. 656).
 - Anti-dsDNA, ENAs, C3, C4, rheumatoid factor to help exclude alternative diagnoses (📖 p. 40).
- *Imaging*:
 - Renal USS for renal sizes and to exclude obstruction.
 - CXR or CT may show patchy or diffuse alveolar shadowing. This could represent infection, pulmonary oedema, or pulmonary haemorrhage. Nodules, cavitation, pleural involvement, and reticulonodular shadowing may also be present in GPA.
 - Transfer factor may be raised in pulmonary haemorrhage.

- *Bronchoscopy* may be desirable if pulmonary haemorrhage suspected but no definite haemoptysis. Bronchoalveolar lavage may reveal frank blood or haemosiderin-laden macrophages.
- *Renal biopsy* is usually indicated. However, a positive anti-MPO or anti-PR3, in the context of rapidly progressive AKI, may mandate the immediate commencement of treatment prior to histological diagnosis.

Renal histology

A focal and segmental necrotizing crescentic glomerulonephritis is characteristic (see Fig. 8.4). If small vessels, e.g. interlobular arteries, are sampled, they may show inflammation and necrosis. Associated interstitial inflammation is often present. Immunostaining reveals no, or very few, immune complex or complement deposits, ∴ referred to as 'pauci-immune'. Granulomatous inflammation is not present in the kidney in GPA (but often found in the upper airways and other tissues).

Chronicity, particularly the degree of irreversible glomerulosclerosis and tubulointerstitial fibrosis, will offer useful prognostic information. This may help to guide therapy. For example, aggressive and sustained induction therapy is not warranted in a patient with principally kidney limited disease where a biopsy has suggested that renal recovery is improbable.

ANCA and pathogenesis


There is now a large literature confirming that ANCA can activate neutrophils *in vitro*, leading to: (i) tethering and migration across endothelium; (ii) degranulation → proinflammatory cytokines → recruitment of monocytes and macrophages; (iii) augmentation of inflammation and endothelial cell injury through free radical generation.

This suggests that ANCAs are not an epiphenomenon (providing a useful clinical test), but that they contribute to pathogenesis. *In vivo* confirmation of this has been obtained with the demonstration of anti-MPO antibodies causing focal necrotizing crescentic GN following injection into mice. In addition, neonatal disease following placental transfer of anti-MPO antibodies has been described.

It is likely that T cells specific for MPO and PR3 also contribute. Unanswered questions include: (i) how antibodies to MPO or PR3 arise; and (ii) how tolerance to self-antigens is broken. Transient induction of anti-PR3 antibodies has been shown during infection, and a possible infective association has been reinforced by the link between GPA and persistent *S. aureus* nasal carriage.

ANCA-associated vasculitis: treatment

Both the disease and toxicity of therapy are associated with significant morbidity and mortality. Risk vs benefit should be assessed in each individual case and discussed with the patient. There has been a recent expansion in the literature regarding treatment of ANCA-associated vasculitis (see Table 8.5).

For a full discussion on starting immunosuppression, particularly the necessary monitoring and preventative and protective measures (e.g. bone protection and PJP prophylaxis) that must be undertaken, see  p. 540.

Induction therapy (to achieve remission)

Corticosteroids: high-dose oral steroids (usually starting at around 1mg/kg prednisolone but rarely exceeding 60mg). Tapering regimens vary in different centres; possible regimens are shown in Table 8.5.

Table 8.5 Suggested regimen for steroid reduction



Week	Dose	Week	Dose	Month	Dose
0	60mg	6	20mg	3	12.5mg
1	45mg	7	20mg	4	12.5mg
2	30mg	8	15mg	5	10mg
3	25mg	9	15mg	6	10mg
4	25mg	10	15mg	12	7.5mg
5	20mg	11	15mg		

Cyclophosphamide: in addition to steroids. Daily oral therapy or intravenous or oral pulsed therapy. Pulsed therapy is as effective at inducing remission but may be associated with a higher risk of relapse. Switch to maintenance therapy between 3 and 6 months when remission achieved (minimum 3 months' therapy recommended).

- Oral: 1.5–2mg/kg/day (1.5mg/kg if age >60) to a maximum of 200mg (round the dose to the nearest 25mg).
- Intravenous. Possible regimens:
 - Ten pulses (15mg/kg) over 25 weeks, with age and GFR adjustments, or
 - 0.75g/m² every 3–4 weeks (initial dose to 0.5g/m² if age >60 years or GFR <20mL/min/1.73m²).
 - Doses are adjusted accordingly to maintain 2-week nadir leucocyte count >3,000/mm³.

Rituximab: provides an alternative to cyclophosphamide and has been shown to be as effective at inducing remission. Adverse events (perhaps surprisingly) appear comparable. The risk of relapse is yet to be clearly defined. It has the attraction of not affecting fertility. Note: much more expensive. Dose: 375mg/m² weekly × 4.



Additional therapy for severe disease

- Severe disease may be defined (arbitrarily) as rapidly ↑ SCr, SCr >500µmol/L (or dialysis-dependent), or pulmonary haemorrhage.
-  Pulsed methylprednisolone:
 - Three doses of 0.5–1g IV over 3 days given initially.
 - No direct evidence of benefit and may increase complications.
- The MEPEX trial suggested that plasma exchange is more effective than pulsed corticosteroids in severe disease (increased survival at 3 months, increased independent renal function at 3 months, less ESRD at 1 year), but the additive effect of both treatments is not known.
- Plasma exchange:
 - Indications: severe disease or coexisting anti-GBM antibodies.
 - MEPEX regimen: seven exchanges (60mL/kg) over 14 days with 5% albumin. FFP or Octaplas® may be needed at the end of the exchange if there has been a recent renal biopsy or there is pulmonary haemorrhage ( p. 72).
 - Ongoing PEXIVAS study should define dosing/duration further.

Resistant disease

- Failure to induce remission occurs in ~10%.
- Therapeutic options: add rituximab to steroids and cyclophosphamide (or cyclophosphamide to steroids and rituximab). Commence plasma exchange. Consider IVIg (0.5mg/kg/day). Polyclonal ATG or alemtuzumab (Campath®) have been used but lack an evidence base.

Maintenance therapy (to maintain remission)

- Induction therapy usually moves to maintenance between 3–6 months.
 - Low-dose prednisolone (see Table 8.5).
 - Convert cyclophosphamide to azathioprine 1.5mg/kg/day (max 200mg).
 - MMF 1g bd is an alternative in patients intolerant of azathioprine (but is associated with higher rates of relapse). It is not yet known whether MMF offers an alternative for induction therapy (MYCYC trial ongoing).
 - The role of rituximab in maintenance therapy is not yet defined.
 - Methotrexate may also be used but has a higher relapse rate and is generally not favoured for patients with renal or lung disease.
- Co-trimoxazole may reduce upper respiratory tract relapses in GPA and is used, in addition to standard immunosuppression.
- Most clinicians continue maintenance therapy for at least 2 years, often longer in GPA, but the optimal duration is unknown. The risks and benefits of ongoing treatment will depend on the individual clinical scenario and should be discussed with the patient.
-  Maintenance therapy is not recommended in patients who are dialysis-dependent and have no extrarenal disease manifestations. Relapse rates are lower in patients with ESRD on dialysis ( but infection rates are higher).

ANCA-associated vasculitis: monitoring response and predicting relapse

See Table 8.6 for recent trials.

Successful achievement and maintenance of remission may be monitored by:

- Clinical assessment: see Clinical presentation in ANCA-associated vasculitis (📖 p. 641), but note that patients may not just have a recurrence of previous features—they may develop new ones.
- Changes in BVAS score (📖 p. 641).
- Presence/absence of urinary abnormalities: particularly haematuria (note: persistent proteinuria may not indicate persistent disease, rather irreversible glomerular damage).
- CRP: useful but non-specific. Poses a common clinical dilemma when raised; does it represent relapse or infection? ⚠ Both must be taken seriously.
- Stable or improving renal function.
- ANCA and anti-MPO or anti-PR3 levels.
 - 📈 Rising anti-MPO or anti-PR3 level may predict relapse, but this has not been consistent in all studies.
 - There is currently no role for presumptively increasing immunosuppression in the absence of a change in clinical disease activity (although rising titres will usually mandate an increase in surveillance intensity).

See Fig. 8.4 for renal biopsy.

Treating relapse

- Severe relapses should be treated, as per induction therapy. However, any decision to re-institute cyclophosphamide should be based, at least in part, on the cumulative dose to date, as there is evidence of a higher malignancy risk for cumulative doses over 36g. The preservation of fertility may also be a prime concern. Rituximab may be preferred in this situation.
- Less severe relapses require careful clinical judgement. Most clinicians will opt to avoid repeat cyclophosphamide therapy where possible. If relapse has occurred off maintenance therapy, then the re-institution of steroids and azathioprine (or MMF) may be sufficient.

Renal replacement therapy

Standard AKI indications for IHD or CRRT apply during the treatment of vasculitis (📖 p. 172). The development of irreversible ESRD will influence treatment choices (see Treating relapse, 📖 p. 646).

Transplantation: it is generally recommended that patients wait for 6–12 months post-remission prior to transplantation. Ongoing ANCA positivity per se is not significantly associated with reduced graft survival. Recurrent disease can be expected in 15–20% but causes graft loss in a minority. A recent series of ~100 patients suggested 70% graft survival at 10 years. Rejection rates are similar to the general transplant population, but there is an increased infection risk, presumably reflecting cumulative immune suppression.

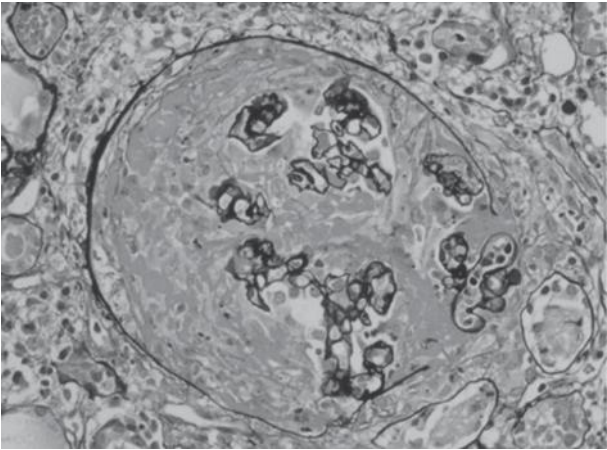


Fig. 8.4 Renal biopsy in ANCA-associated vasculitis. The glomerulus is outlined by Bowman's capsule, which is highlighted by the silver stain (as are the capillary loops). Most of the glomerulus has been obliterated by a crescent, with just a few remnant capillary loops remaining open.

Table 8.6 Recent trials in systemic vasculitis

Trial	Year	Treatment	n	In brief
CYCAZAREM	2003	Cyclophosphamide (CyC) vs Aza (maintenance)	144	RCT. Renal patients. Aza as good
SOLUTION	2003	ATG (refractory disease)	15	Case series. Possible benefit. Δ in pulmonary haemorrhage
WGET	2005	Etanercept vs placebo (maintenance)	174	RCT. Etanercept had worse outcomes and \uparrow malignancy
MEPEX	2007	Plasma exchange (PEX) (induction)	137	RCT. PEX improved mortality and GFR (see text)
CYCLOPS	2009	Daily oral CyC vs intermittent pulsed (induction)	160	RCT. No difference
RITUXVAS	2008	Rituximab (RTX) vs CyC (induction)	44	RCT. RTX safe and comparable
IMPROVE	2010	MMF vs azathioprine (Aza) (maintenance)	156	RCT. MMF less effective
RAVE	2010	RTX vs CyC (induction)	197	RCT. Excluded pulmonary haemorrhage and severe renal disease. Comparable outcomes
CycLowVas	2011	RTX x2 doses, CyC x6 doses (induction)	23	Case series. Excluded pulmonary haemorrhage and severe renal disease. Good remission, less steroid
MYCYC	Ongoing	MMF vs CyC (induction)		RCT
PEXIVAS	Ongoing	PEX (induction)		RCT. Further info re dosing/timing of PEX and steroids
RITAZAREM	Ongoing	RTX vs Aza (maintenance in relapsing disease)		RCT

Henoch–Schönlein purpura

Introduction

- Small vessel systemic vasculitis predominantly affecting children (20 per 100,000 population in the UK).
- Peak incidence age 4–5 (range generally 2–11).
- 2:1 ♂:♀ ratio. Caucasian > black patients.
- More common in winter and early spring—associated with an upper respiratory tract infection (with accompanying fever and malaise) in ~2/3.
- IgA plays a critical role in the pathogenesis of HSP (→ circulating IgA containing immune complexes, IgA deposition in vessel walls and renal mesangium). These abnormalities are associated with IgA1, not IgA2.
- IgA complexes and complement deposit in target organs → release of inflammatory mediators.
- Serum IgA elevated in ~50%. A small number are ANCA-positive.

Clinical presentation

- Presents as a tetrad of skin rash, abdominal pain, arthralgia, and renal involvement.
 - *Rash*: skin manifestations usually dominate the clinical picture. Purpuric (usually symmetrical) rash, affecting legs, buttocks (and, less frequently, arms). Abdomen, chest, and face are typically spared. New lesions may develop over several months. Histology: leucocytoclastic vasculitis with vascular IgA and C3 deposition. Urticaria may also occur.
 - *Abdominal*: GI manifestations in ~3/4 patients. Nausea, vomiting, diarrhoea (may be bloody), colicky pain (which may be severe), GI bleeding, ileus, infarction, perforation, intussusception, pancreatitis, cholecystitis.
 - *Arthralgia*: joint manifestations in ~2/3 patients. Usually symmetrical polyarthralgia, mainly involving knees and ankles, wrists and fingers less common. True arthritis and permanent damage extremely rare.
 - *Renal involvement*: focal and segmental mesangial proliferative GN presenting as haematuria, proteinuria (which can be nephrotic range) ± renal impairment and ↑ BP. A renal biopsy is usually reserved for nephritic/nephrotic presentations, renal impairment, and persistent or heavy proteinuria. The severity of renal sequelae is often not related to the severity of other manifestations
 - *Other*: pulmonary haemorrhage, cerebral vasculitis (→ headache, irritability, seizures, focal weakness, altered mental state), neuropathies, and orchitis.

Prognosis

- Usually self-limiting (usually <1 month; rarely >2 months).
- Follow-up is recommended.
 - Isolated microscopic (and intermittent macroscopic) haematuria may persist, but the prognosis is good in this situation.
 - ↑ BP is also probably more common.
 - The presence of proteinuria is an adverse prognostic sign.

- Nephritic and mixed nephritic/nephrotic presentations have the worse prognosis (~1/3 will progress to ESRD).
- Estimated as the cause of ESRD in ~1.5–3% children overall.
- In adults, renal involvement is more common. Complete resolution is the norm, but persistent urinary abnormalities (Δ proteinuria) predict a worse prognosis and mandate follow-up.
- Recurrence in ~1/3 cases, particularly if renal involvement (usually within 6 months).

Treatment

- Usually symptomatic only, e.g. analgesia for arthralgia.
- Severe skin or GI manifestations may require corticosteroids.
- Nephritis (●^o no strong evidence base):
 - Steroid treatment does not prevent renal involvement.
 - Heavy proteinuria, impaired renal function, and crescents on renal biopsy often precipitate steroid treatment, e.g. 3 \times doses of IV methylprednisolone, followed by 4 weeks of PO prednisolone. If the response is favourable, they are continued and weaned over ~6 months. Some advocate the use of cyclophosphamide in this group.
 - RPGN with >50% crescentic change is often treated as per other causes of systemic vasculitis (e.g. steroids, cyclophosphamide, and plasma exchange).
 - ACE-I for persistent proteinuria.

HSP and IgAN: similar but (probably) not the same

Whether HSP and IgA nephropathy are different faces of the same clinicopathological entity remains a matter for debate.

- Similarities:
 - The extrarenal manifestations of both are similar.
 - IgAN can occur in patients with a history of HSP and the two have occurred in the same family.
 - Patients with HSP who subsequently receive a kidney transplant may develop IgA deposits in the graft.
 - Similar changes in the IgA system, e.g. aberrant glycosylation of circulating IgA, can be demonstrated in both.
- Differences:
 - Age of onset is much younger in HSP.
 - Extrarenal manifestations, especially cutaneous, are much more common in HSP.
 - Glomerular, particularly mesangial, sclerosis is more common in IgAN, while endothelial proliferation is more common in HSP.
 - On EM, deposits are mostly limited to the mesangium in IgAN but more widely distributed in HSP.
 - IgA deposits may be relatively weak in HSP, compared to IgAN.
 - IgG immune deposits are found more commonly in HSP.
 - Persistent haematuria, proteinuria, and CKD are more common in IgAN.

Polyarteritis nodosa

Introduction

Polyarteritis nodosa (PAN) is a rare (<10 PMP) medium-vessel necrotizing transmural arteritis, involving principally the skin, nerves, gut, and kidney. Most cases are idiopathic, but ~30% may be secondary (hepatitis B, hepatitis C, SLE, RA, Sjögren's, hairy cell leukaemia). Onset is usually age 40–60.

Symptoms and signs

Usually presents with systemic symptoms (fever, weight loss, arthralgia, and myalgia). Skin disease includes nodules, livedo reticularis, or purpura (indicating small vessel involvement). Medium vessel involvement in the gut presents as abdominal pain (often postprandial), perforation, or bloody stool. Other features include testicular pain (epididymo-orchitis), mononeuritis multiplex (peripheral neuropathy), stroke, and myocardial ischaemia.

Renal ischaemia causes \uparrow BP \pm renal impairment. There may be loin pain from segmental renal infarcts. Unlike the ANCA-associated vasculitides, glomerular disease is not a feature of PAN.

Investigations

Urinalysis

Inactive—generally no microscopic haematuria (as no glomerular inflammation), although proteinuria may be present (\uparrow BP). An exception might be the haematuria (often visible) that occurs with renal infarction with PAN).

Routine laboratory tests

FBC, biochemistry profile with muscle enzymes. CRP is usually raised and may be used to monitor disease.

Tests to exclude an underlying cause or alternative diagnosis

Hepatitis B and C serology, C3, C4, RhF, ENAs, anti-dsDNA, cryoglobulins, blood cultures (exclude infection).

► PAN is not associated with ANCA.

Diagnostic tests

Diagnosis is made, following tissue biopsy or angiography. The classical finding is of microaneurysms or beading, with vascular occlusion in the renal or mesenteric vascular tree (see Fig. 8.5). Renal biopsy may show segmental transmural fibrinoid necrosis in medium-sized arteries \pm downstream ischaemic changes or frank infarction.

Management and natural history

- The prognosis of untreated disease is extremely poor.
- Treat underlying cause in secondary disease.
- In primary PAN, mild disease is generally treated with corticosteroids alone.
- Moderate to severe disease is treated with corticosteroids and cyclophosphamide for at least 3–6 months, followed by azathioprine in a similar manner to ANCA-associated vasculitis.
- Relapses are infrequent.



Fig. 8.5 Medium-vessel aneurysms in the kidneys at ateriography. Reproduced with permission from Wu K and Throssell D (2006) *Nephrol Dial Transplant*, 21(6): 1710–12.

Takayasu's disease

- Chronic inflammatory condition associated with granulomatous arteritis, intimal proliferation, and medial and adventitial fibrosis (→ arterial occlusion, post-stenotic dilatation, and frank aneurysm formation). Atherosclerosis supervenes as patients age.
- Affects large vessels—principally the aorta (and branches) and pulmonary vessels. Aetiology unknown.
- Most common in young ♀. Relatively common in Asia (esp. Japan). Rare in Caucasians (<3 pmp).
- Classically described as a triphasic disease: (i) 'pre-pulseless' phase with systemic symptoms; (ii) a vascular inflammatory phase; and (iii) a quiescent occlusive phase.
- Presentation: systemic symptoms (weight loss, fatigue, fever), claudication, angina, CVA, vertebrobasilar insufficiency, steal syndromes, aneurysms, asymmetrical BP in limbs, bruits, aortic incompetence (if ascending aorta involved). ~50% develop renovascular ↑ BP.
- Investigations: acute phase response (↑ CRP, ESR) and normochromic anaemia. Autoantibodies, including ANCA, are negative.
- Angiography is diagnostic (MR angiography and PET scanning may identify areas of active inflammation).
- Treatment: steroids are the mainstay, but many patients relapse as they are tapered. Evidence base for 'steroid-sparing' agents is poor. Methotrexate, azathioprine, and anti-TNF therapy have been used.
- Revascularization is often necessary. Relatively poor results from angioplasty (reocclusion) and stenting (restenosis). Surgery may be necessary (but high incidence of graft restenosis).

Churg–Strauss syndrome

Introduction

Now referred to as eosinophilic granulomatosis with polyangiitis (EGPA). This is an ANCA-associated vasculitis (50% positive), but patients are generally younger patients than MPA/GPA/RLV (mean age 40). ♂ = ♀.

Characterized classically by rhinitis, asthma, and eosinophilia and primarily affects the lung and skin. However, it may affect any organ. The incidence of renal involvement in EGPA is difficult to estimate (probably ~30%).

Symptoms and signs

Disease typically evolves in stages (with some overlap):

- Atopic prodrome:
 - 2nd/3rd decade.
 - Allergic rhinitis or other atopic conditions.
 - Asthma (often severe/steroid-requiring).
- Eosinophilic stage:
 - Peripheral eosinophilia ($>1.5 \times 10^9/L$).
 - Eosinophilic infiltration of organs (esp. lung and gut).
- Vasculitic stage:
 - 3rd/4th decade.
 - Severe systemic vasculitis/extravascular granulomatosis.
 - Presents as fever, malaise, weight loss.
 - Widespread organ involvement includes:
 - Lungs: ↑ severity of asthma, dyspnoea, haemoptysis, pulmonary opacities/nodules, pleural effusions.
 - Kidneys (~30%): 50% with rapidly progressive AKI, 50% with isolated proteinuria/haematuria. ↑ BP is common (presumably renal ischaemia).
 - Gut: eosinophilic gastroenteritis, ischaemic bowel, abdominal pain, bloody diarrhoea.
 - Skin: tender subcutaneous nodules, palpable purpura, urticaria.
 - ENT: nasal obstruction, polyps, otitis media, hearing loss.
 - Cardiac: coronary vasculitis (angina), myocarditis (LVF), or pericarditis (Δ tamponade).
 - Neuro: mononeuritis multiplex, painful polyneuropathy.
 - Musculoskeletal: myalgia, migratory polyarthritis.
 - Lymphadenopathy: eosinophilic LN seen in 30–40%.

Investigations

- Urinalysis, (microscopic haematuria, proteinuria), microscopy for red cells and red cell casts, uPCR.
- FBC (↓ Hb) and prominent eosinophilia (often >10% total WCC, or absolute count $>1.5 \times 10^9/L$).
- ↑ ESR, ↑ CRP, immunoglobulins (↑ IgE—common and may vary with disease activity, polyclonal hypergammaglobulinaemia). U&E, Alb, LFT, CK.
- ANCA (usually anti-MPO) positive in ~50% (particularly during vasculitis phase). RhF often positive at low titre.

- CXR (flitting, patchy infiltration) \pm ABG.
- ECG, echo (consider cardiac MR with gadolinium if either abnormal).
- Lung—transfer factor, HRCT, PFT (obstructive picture with \downarrow lung volume), BAL/lung biopsy.
- Tissue biopsy classically shows eosinophil-rich granulomatous inflammation. If sampled, vessels show a small to medium vessel necrotizing vasculitis.
- Renal biopsy may show vasculitis \pm focal and segmental necrotizing GN though usually with an eosinophilic infiltrate and granuloma formation throughout the interstitium. A large series of \sim 115 patients (all ANCA-positive) showed $>50\%$ had necrotizing GN on biopsy.

Diagnostic criteria

Lanham criteria (three criteria) vs American College of Rheumatology criteria (six criteria) from:

- Asthma.
- $>10\%$ eosinophils.
- Mono-/polyneuropathy.
- Migratory/transient CXR opacities.
- Paranasal sinus abnormalities.
- Biopsy containing a blood vessel, with eosinophils in extravascular areas.

Treatment

Assess for severity using the five factor score (FFS): (1) cardiac involvement; (2) SCr $>141\mu\text{mol/L}$ (1.6mg/dL); (3) proteinuria $>1\text{g/day}$; (4) GI disease; (5) CNS involvement. Score 0 (no factors), 1 (1 factor), or 2 (2+ factors).

- *Prednisolone*: PO 1mg/kg/day for 6–12 weeks (or until remission (consider initial pulsed IV if multi-organ involvement). Treat asthma and \uparrow BP with standard therapy. $>90\%$ remission with steroids alone if FFS score 0. Eosinophilia is exquisitely steroid-sensitive and may resolve rapidly on treatment.
- *Cyclophosphamide*: PO or IV for 3–6 months, followed by maintenance therapy similar to ANCA-associated vasculitis (📖 p. 640). Use for refractory disease or if FFS 2+, FFS 1 plus cardiac involvement, or FFS 0 but ANCA-positive.
- *Other*: azathioprine and methotrexate (not if GFR $<50\text{mL/min}$) have been used to maintain of remission. Limited data for MMF, rituximab, and others. Plasma exchange appears to confer no additional benefit.

Monitor for relapse using clinical symptoms, eosinophil count, and acute phase reactants (ESR, CRP). ANCA positivity does not predict disease activity. Relapse can be expected in $\sim 25\%$ of cases. Survival is 70% at 5 years. Most deaths occur during the vasculitic phase.

Anti-GBM (Goodpasture's) disease

Introduction

A rare disease (<1 pmp) that presents as RPGN ± pulmonary haemorrhage. Occurs in older children and adults of all ages but with peaks at age 20–30 and 60–70. More common in Caucasians. ♂ > ♀ (slightly).

Pathogenesis

Caused by antibodies (usually IgG) against two adjacent regions in the NC1 domain of the α3 chain of type IV collagen ('Goodpasture's epitopes'). This α3 chain is limited to the BM of the glomerulus and alveolus (also choroid plexus, testis, and cochlear—although clinically irrelevant). The epitopes are usually structurally sequestered and ∴ protected but become more accessible in the disease.

It is now recognized that cell-mediated immunity is also important, with strong evidence from animal models and clinical studies that T cells reactive with type IV collagen contribute to inflammatory responses.

Genetic (e.g. HLA DR15, particularly the DRB1*1501 allele) and environmental (e.g. hydrocarbon exposure) factors influence susceptibility.

Others risk factors include smoking and membranous GN (anti-GBM disease can occur before, during, or after this GN). Such factors appear to damage either the glomerular or alveolar BM → epitope exposure and autoimmune responses. There is no strong association with infection.

Symptoms and signs

- Usually presents acutely with rapidly progressive AKI (with haematuria and subnephrotic proteinuria) ± pulmonary haemorrhage (~60%).
- Some patients report loin pain and haematuria during early stages.
- No renal involvement is very rare.
- Pulmonary haemorrhage may present as frank haemoptysis but is often more incipient, e.g. cough, dyspnoea, blood-flecked sputum.
- Pulmonary haemorrhage occurs almost exclusively in smokers and, more commonly, in younger patients.
- ► Note: pulmonary haemorrhage is exacerbated by even mild pulmonary oedema, so fluid overload must be avoided.
- Systemic symptoms, such as fever and weight loss, are usually absent and may suggest an alternative diagnosis, such as vasculitis.

Investigations

Routine laboratory tests

- Urinalysis for blood and protein, uPCR (proteinuria usually non-nephrotic). FBC, U&E, SCr, CRP (often raised).

Autoimmune serology

- Anti-GBM antibodies: request urgently if suspected. Titres broadly correlate with disease activity. False positives: viral infections, esp. HIV, hep C. False negatives unusual (diagnosis then rests on biopsy).
- ANCA: important differential diagnosis, and 25% are 'double positive' for both anti-GBM and ANCA (usually anti-MPO). Such patients usually behave like anti-GBM disease but may have rashes and arthralgia.

Imaging and investigation of pulmonary haemorrhage


- CXR ± CT (diffuse alveolar shadowing). ABGs.
- Renal USS to measure renal sizes and exclude obstruction.
- Transfer factor (KCO) may be raised if pulmonary haemorrhage.
- Bronchoalveolar lavage: frank blood or haemosiderin-laden macrophages.



Renal biopsy

- ► Usually indicated but should not delay treatment if anti-GBM positive in the appropriate clinical context.
- Histology: focal and segmental necrotizing, crescentic GN. The light microscopic findings are similar to those in ANCA-associated vasculitis, except that all crescents are usually at the same stage of development (termed 'synchronous'). Immunostaining demonstrates linear capillary wall staining for IgG and C3 (also seen in diabetic nephropathy and fibrillary GN). EM will show frequent breaks in the GBM.
- The biopsy may also yield helpful prognostic information. Significant potentially reversible acute tubular injury may suggest a good chance of recovery despite advanced renal failure.

Management

Initial treatment is similar to ANCA-associated vasculitis, although maintenance therapy is generally not necessary, as relapse is very rare (anti-GBM is often referred to as a 'one-hit' disease).

For a discussion on starting and monitoring immunosuppression, see  p. 540.

- **Corticosteroids:** prednisolone (1mg/kg to max 60mg/day), and taper over 6 months, then stop (regimen will vary between centres). Initial pulsed methylprednisolone (three doses × 0.5–1g IV) although limited direct evidence of benefit.
- **Cyclophosphamide:** given in combination with steroids. Usually 3 months daily oral therapy ( p. 541). If anti-GBM remains positive, some clinicians then favour switching to azathioprine for a further period.
- **Plasma exchange:** should be given to all patients. Usually daily for 2–3 weeks, but duration can be tailored to clinical response and anti-GBM titre (aim: undetectable) ( p. 950).

Once dialysis-dependent, renal recovery is very unusual. Potentially toxic treatment may not be warranted in this situation (unless there is pulmonary haemorrhage), but features on the renal biopsy (see 'Investigations') should also inform this decision, as should potential future transplantation (see 'Prognosis').

Prognosis

Almost uniformly fatal if untreated. Independent renal function in >90% at 1 year when presenting SCr <500µmol/L (5.6mg/dL); 82% when SCr >500µmol/L (5.6mg/dL), and just 8% if dialysis-dependent. Pulmonary haemorrhage significantly increases early mortality.

Transplantation is not recommended until anti-GBM antibodies have been absent for 6 months. If they persist, then further treatment (e.g. rituximab) may be contemplated.

Lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous multisystem disease characterized by autoantibody production and a diverse range of clinical manifestations, as outlined in Table 8.7. SLE is more common in black patients, Hispanics, and Asians. It principally occurs in young adults and is more common in ♀ by a factor of ~10.

Lupus nephritis should form part of the differential diagnosis in any patient presenting with an active urinary sediment ± renal dysfunction. The diagnosis of SLE will not already be established in many patients.

Renal disease is common in SLE, developing to some degree in ~50% of patients and usually occurring within the first 5 years of diagnosis. Surveillance is ∴ important (and often performed by non-nephrologists).

Pathogenesis

The pathogenesis of SLE is multifactorial, involving genetic, hormonal, and environmental factors. The strong genetic element is shown by ~25–50% concordance in monozygotic twins and the fact that ≥10% of patient relatives are affected. Numerous abnormalities of the immune system have been described, although it is not universally understood whether these are epiphenomenon or causative.

The hallmark of SLE is the production of a range of autoantibodies, in particular, to self-antigens that contain DNA and RNA. Factors that may promote autoimmunity include ↑ IFN-α, increased levels of the B cell survival factor Blys (BAFF), and stimulation of nucleic acid-binding receptors TLR7 and TLR9. Immune complexes containing autoantibody cause tissue injury by stimulation of leucocyte Fc receptors and complement activation. However, complement appears to play a dual role, as it can also be protective—genetic deficiency of the early classical pathway components C1q and C4 strongly predisposes to SLE, perhaps through a defect in the clearance of apoptotic cells. Faulty apoptotic processes are a general feature of the disease, with early autoantibody responses directed against the nucleosome (which arises from apoptotic cells).

Common clinical manifestations

- *Systemic*: fever, weight loss.
- *Skin*: malar rash, photosensitivity, alopecia.
- *Joints/hands*: arthralgia, arthritis, Raynaud's.
- *Serositis*: pleural effusion, peritonitis, pericarditis.
- *CNS*: headaches, stroke, seizures, psychosis.
- *Renal*: ↑ SCr, haematuria, proteinuria (nephrotic syndrome), ↑ BP.
- *Haematological*: anaemia, leucopenia, thrombocytopenia.
- *Cardiovascular*: myocarditis, pericardial effusion, sterile endocarditis, venous and arterial thromboses (antiphospholipid syndrome).

Investigations

Routine laboratory tests

- Urinalysis for blood (→ suggests active glomerular disease) and protein, microscopy for red cell casts, uPCR or uACR.
- FBC, U&E, SCr, LFTs, CK, ESR (typically raised), ↓ serum albumin (if nephrotic).
- CRP (typically not raised unless serositis; can be a useful discriminator).

Immunological tests in patients suspected of having SLE

- ANA (>95%; sensitive but not specific) Anti-dsDNA (increased specificity), C3 and C4 (reduced), ENAs (including anti-Ro, anti-La, anti-Sm) (📖 p. 42).
- Anti-C1q antibodies have reasonable sensitivity and even better specificity for active nephritis (particularly in combination with anti-DNA).
- ANCA (positive in a proportion; usually anti-MPO) (📖 p. 642).
- Anticardiolipin antibodies and lupus anticoagulant (📖 p. 664).

Radiology

Renal USS: renal sizes; exclude obstruction, and investigate possible renal vein thrombosis (esp. if nephrotic ± antiphospholipid syndrome) (📖 p. 590).

Renal biopsy

A renal biopsy is indicated in most patients with suspected lupus nephritis. ► Note: severe disease may be seen histologically with a 'mild' clinical phenotype (e.g. normal SCr, mild proteinuria, and microscopic haematuria). Histology is crucial for planning of treatment and also yields important prognostic information. A complex range of light microscopic findings may be present and classified as shown in Table 8.7. In all cases, immunostaining shows a 'full house', i.e. it is positive for IgG, IgM, IgA, C3, and C1q. Other renal pathologies also occur in SLE, including thrombotic microangiopathy (📖 p. 574), AIN (📖 p. 580), minimal change (📖 p. 558), and ischaemic nephropathy from renal artery stenosis (📖 p. 665).

Table 8.7 ISN 2004 classification of lupus nephritis

I	Normal light microscopy with immune deposits
II	Mesangial proliferation with immune deposits
III	Focal lupus nephritis: endo- or extracapillary GN in <50% of glomeruli
IV	Diffuse lupus nephritis: endo- or extracapillary GN in >50% of glomeruli, either segmentally (IV-S) or globally (IV-G)
V	Membranous change (subepithelial deposits)
VI	Advanced sclerosis with >90% glomeruli obsolete
Class III and IV are additionally labelled as active (a), chronic (c), or both (a/c).	

Signs of activity: endocapillary hypercellularity with or without leucocyte infiltration, karyorrhexis, fibrinoid necrosis, GBM rupture, cellular or fibrocellular crescents, subendothelial deposits on light microscopy, intraluminal immune aggregates.

Signs of chronicity: segmental or global glomerulosclerosis, fibrous adhesions, fibrous crescents.

Lupus nephritis: initial treatment

Initial therapy


For a discussion on starting and monitoring immunosuppression, see  p. 540.

Classes I and II

Usually presents as mild renal disease, such as microscopic haematuria ± proteinuria that does not usually warrant specific therapy.

Classes III and IV (or III + V and IV + V)

- Immunosuppression is required for these categories.
- Class III typically presents as mild to moderate renal disease, with microscopic haematuria, moderate proteinuria, and (in a significant number) deteriorating renal function. Extrarenal SLE is often active (see Fig. 8.6).
- Class IV typically presents as severe renal disease: ↑ BP, oedema, active urinary sediment, deteriorating renal function (Δ often rapid), and nephrotic range proteinuria (extrarenal SLE is usually active).
- Class V typically presents as the nephrotic syndrome. The prognosis is worse if class V is found in combination with class III or IV.
- In the past, large doses of pulsed IV cyclophosphamide were used in addition to steroids (based on NIH evidence).
- More recent evidence has shown that: (i) low-dose IV cyclophosphamide is just as effective, and (ii) MMF is as efficacious as cyclophosphamide for most patients.
- Standard initial therapy for most with classes III and IV disease is: . . . high-dose oral steroids and oral MMF. Cyclophosphamide is generally reserved for patients who have failed initial treatment.

Corticosteroids Most centres start with a high dose of oral prednisolone (~1mg/kg, max 60mg od). Protocols for subsequent tapering will vary. See  p. 540 for possible regimen. Pulsed IV methylprednisolone (0.5–1g IV × 3) is often given initially, although there is no direct evidence of benefit—although it may allow a lower dose of prednisolone to be used initially (e.g. 0.5mg/kg—the ‘EuroLupus protocol’).

Mycophenolate Given at a total dose of 2–3g/day and normally continued at the maximum dose for at least 6 months. It is important to titrate the dose to these levels, as tolerated.

Cyclophosphamide Usually reserved for patients who have failed MMF, although some clinicians still favour as initial therapy in more fulminant disease. Usually given as 6 × IV doses of 500mg at 2-weekly intervals.

Rituximab Reserved for patients who have not responded to MMF or cyclophosphamide. Clinical trials in both extrarenal and renal lupus disappointing, but clinical experience suggests benefit in selected patients.

Belimumab (Anti-BLyS) Clinical trials have shown benefit in extrarenal lupus. Studies in lupus nephritis are ongoing.

Class V

- The optimal therapy for pure membranous lupus nephritis is uncertain, as most trials have included only small numbers of such patients.

- If renal function is normal and proteinuria subnephrotic, immunosuppression may not be indicated initially.
- Spontaneous remission of class V disease may occur.
- Patients should be treated with ACE-I or ARBs, as for any proteinuric renal disease.
- If nephrotic range proteinuria, most clinicians would institute similar therapy to classes III and IV, as described previously.
- Calcineurin inhibitors are an alternative.

Additional therapy

- All patients with lupus nephritis should receive ACE-I/ARBs, if significant proteinuria, plus BP treatment, as needed (aim <130/80mmHg).
- Treat complications of CKD, e.g. anaemia and SHPT (Δ often neglected).
- SLE patients have high incidence of CV disease, so CV risk factors much be given appropriate attention.
- Hydroxychloroquine (200–400mg PO od) for all patients, unless contraindicated (demonstrably lowers disease flare rates).

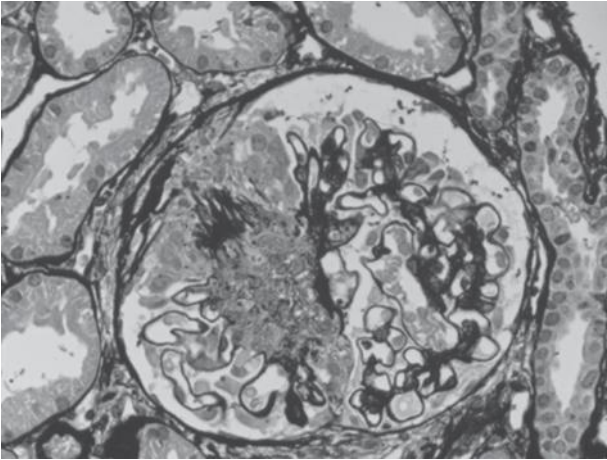


Fig. 8.6 Image from a renal biopsy of a patient with lupus nephritis. The glomerulus shows segmental proliferation and is outlined by Bowman's capsule, which picks up the silver stain, as do the capillary loops. The left hand half of the glomerulus shows endocapillary proliferation, and the right half is almost normal. This biopsy would be classified as class III or class IV, depending on the percentage of glomeruli affected (see Table 8.7).

Lupus nephritis: further treatment

Maintaining remission

There is no clear demarcation between induction and remission phases. Evidence of an initial response to treatment, with improving renal function and reducing proteinuria, can continue for many months. Nonetheless, although it is somewhat arbitrary, patients are categorized after 6 months' treatment:

- Complete remission:
 - uPCR <50mg/mmol, with a normalized or stable SCr.
- Partial remission:
 - uPCR improved 50% on baseline and <300mg/mmol, with a normalized or stable SCr.
- Non-responders.

Complete remission

- If MMF has been used, the dose may be reduced, although it is advisable to maintain a dose of around 2g/day for at least 2 years.
- Low-dose prednisolone (e.g. 5–10mg daily) is often continued.
- Azathioprine can be an alternative to MMF for remission maintenance if the latter is not tolerated (although recent trial evidence suggests that MMF is superior).

Partial remission or non-responders

- The clinical decision-making process in partial responders can be challenging; options include continued observation (especially if parameters are improving), a further renal biopsy, or an escalation in therapy.
- Cyclophosphamide or rituximab may be considered.

Cessation of immunosuppression

There is no strong evidence to guide the decision to withdraw maintenance therapy. Case series suggest that the risk of relapse is inversely proportional to length of prior treatment. Therapy for at least 5 years is advisable.

Monitoring

Patients require close long-term surveillance.

Monitoring for renal disease

- Urinalysis (particularly microscopic haematuria), uPCR or uACR.
- SCr, serum albumin. If there is significant proteinuria, serum albumin can be a more precise marker than uPCR and uACR (providing no other factors that depress albumin, such as infection, are present).
- Repeat renal biopsy.

Monitoring lupus serology

- Anti-dsDNA, C3, C4, ESR, anti-C1q are useful for disease activity.
- One or more may be known to be particularly useful in an individual patient, but no single marker, or combination, has sufficient sensitivity or specificity to be used in isolation.

- Δ Some patients may have active serology but no clinical disease activity. However, those in whom the serological markers are negative are unlikely to have significant activity (especially if previously positive).

Prognosis

Outcomes are variable and depend on disease severity and response to treatment. Overall mortality ~10% at 10 years for lupus nephritis (approximately double that of non-renal disease). Chronic inflammation, organ damage, toxicity of therapy, and increased CV disease all contribute to this.

Renal replacement therapy

SLE represents ~1–2% of patients on an ESRD programme. Survival is comparable to patient without SLE. Lupus is generally quiescent once on dialysis (a state of relevant immune suppression), although extrarenal disease flares may occur and require treatment. Interestingly, the better the quality of dialysis (e.g. longer hours), the higher the risk of relapse.

Patients are usually good candidates for transplantation. It is recommended that disease has been inactive for 3–6 months at the time of transplantation. There is conflicting evidence concerning graft outcomes, with a historical suggestion that these may be poorer. However, this is probably not the case. Recurrent disease is relatively uncommon. Concurrent antiphospholipid antibody syndrome with graft loss from thrombotic events may contribute to the inferior outcomes seen in some series.

Antiphospholipid syndrome (APS)

Introduction

Antiphospholipid antibodies may occur as a primary entity (~50%) or in association with connective tissue diseases, e.g. SLE (~30–40%), Sjögren's (~40%), RA (~30%), systemic sclerosis (~25%). They are also present in ~5% of the normal population.

As well as autoimmune diseases, antiphospholipid antibodies are associated with infections (e.g. HIV, hepatitis C, and syphilis) and drugs (e.g. hydralazine, procainamide, IFN- α).

APS is defined as antiphospholipid antibodies plus one or more clinical episodes of arterial, venous, or small vessel thrombosis in any organ (confirmed on imaging or histologically).

APS occurs at all ages and is more common in ♀. It is more frequent in relatives of affected patients.

APS and fetal loss

Definition used in pregnancy is antiphospholipid antibodies plus:

- One or more spontaneous abortion (>10 weeks).
- One or more births <34 weeks, with severe pre-eclampsia, eclampsia, or placental insufficiency.
- Three or more unexplained, consecutive, spontaneous abortions <20 weeks' gestation.

Pathogenesis

Dysregulation of coagulation → thrombosis. Exact mechanisms are unclear. However, it appears that aberrant apoptosis may expose membrane phospholipids for binding by plasma proteins. These complexes then stimulate autoantibody production.

Thrombosis is initiated by antibodies to coagulation factors (e.g. protein C and S) ± platelet and endothelial activation ± complement activation.

Clinical features

Some patients are asymptomatic. In others, an associated disease will dominate clinical presentation, e.g. SLE. The presentation of APS essentially reflects a multi-organ disorder, characterized by hypercoagulability and recurrent thrombosis:

- *Vascular*: DVT, PE, pulmonary hypertension, MI, digital ischaemia.
- *Obstetric*: fetal loss, pre-eclampsia.
- *Neurological*: CVA, sinus thrombosis.
- *Haematological*: thrombocytopenia (~30%), haemolytic anaemia.
- *Skin*: livedo reticularis, cutaneous infarcts, ulceration.
- *Eyes*: retinal vein thrombosis, amaurosis fugax.
- *Other*: adrenal infarction, avascular necrosis, Libmann–Sacks endocarditis.

Catastrophic APS (CAPS) is a rare, fulminant form, with rapid multisystem involvement and organ infarction. Mortality is high.

Renal involvement

- Thrombotic microangiopathy (📖 p. 574).
- Renal artery thrombosis and ischaemic nephropathy (📖 p. 586).
- Hypertension (including accelerated phase).
- Proteinuria.
- Increased risk of vascular thrombosis post-transplantation.
- Increased risk of vascular access thrombosis in haemodialysis patients.

Laboratory tests for antiphospholipid antibodies

- Elevated levels of antibodies against anionic membrane phospholipids or their associated plasma proteins.
- Persistence is important for diagnosis of APS—one or more of the following must be present on at least two occasions, at least 12 weeks apart:
 - IgG ± IgM anticardiolipin antibody (IgG more commonly associated with thrombosis). Causes false positive syphilis serology.
 - Anti-β₂GP-I.
 - Lupus anticoagulant (⚠️ strongest risk for thrombosis).

The lupus anticoagulant (LA) is directed against various plasma coagulation molecules and results in prolongation of clotting assays, including APTT, kaolin clotting time, and dilute Russell viper venom time (DRVVT). The presence of LA is confirmed by mixing normal plasma with patient plasma. If there is a clotting factor deficiency, mixing should correct the clotting time; when it does not, it suggests an inhibitor is present.

Treatment

Tailored according to presentation and prior history of thrombotic events. Asymptomatic individuals who are found to have antiphospholipid antibodies do not require specific treatment. However:

- Prophylactic therapy:
 - Modify other risk factors: smoking, ↑ BP, ↑ lipid. Avoid oral contraceptive.
 - 📖 Aspirin 75mg daily. Widely used in this context but benefit unproven. Clopidogrel is an alternative if aspirin-intolerant.
 - If SLE, consider hydroxychloroquine 200–400mg daily.
- Thrombosis:
 - Full anticoagulation with IV or SC heparin, followed by (lifelong) warfarin therapy (target INR 2.0–3.0 for venous and 3.0–4.0 for arterial thrombosis or recurrent thrombotic events).
 - Consider warfarin plus aspirin if refractory.
- APS in pregnancy:
 - Aspirin and LMWH prophylaxis for those with no previous history of thrombosis or prior fetal loss. Continue 6–12 weeks post-partum.
 - Full anticoagulation with LMWH for those with thrombosis history.
- CAPS: meticulous anticoagulation. Plasma exchange, corticosteroids, and IVIg may be of benefit. Consider immune suppression (e.g. cyclophosphamide, esp. if associated connective tissue disorder).

Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a heterogeneous autoimmune connective tissue disorder characterized by inflammation, fibrosis, and vasomotor abnormalities. It is ~5× more common in ♀, with peak age 30–40.

On the basis of clinical presentation, organ involvement, and outcomes, it is subclassified as follows.

Diffuse cutaneous systemic sclerosis

Skin involvement is proximal to elbows and knees, and solid organ involvement is frequent. Characteristic autoantibodies: anti-Scl-70 and anti-RNP. More equal sex distribution.

Limited cutaneous systemic sclerosis

Skin involvement is more distal, and solid organ involvement is unusual. CREST syndrome is an example. Characteristic autoantibodies: anti-centromere.

Pathophysiology

Dysregulated collagen synthesis and degradation, associated with multiple immunological (e.g. anti-endothelial cell antibodies) and vascular (e.g. aberrant vasomotor control) irregularities, leads to collagen accumulation and fibrotic cutaneous and visceral damage. Many cell types (including endothelial, fibroblasts, T and B cells, and macrophages), as well as cytokines (particularly pro-fibrotic IL-4, TGF- β , and PDGF), contribute to progressive changes in the extracellular matrix and its constituents, including fibronectin, proteoglycans, and various forms of collagen.

Clinical presentation

Patchy skin oedema, with eventual fibrosis and calcinosis, digital ulceration, periorbital tethering and microstomia, nasal beaking and tapering of the fingers (sclerodactyly), Raynaud's phenomenon, facial and limb telangiectasia, non-erosive arthritis, myalgia, oesophageal (and intestinal) dysmotility, pulmonary fibrosis, and pulmonary hypertension.

Renal involvement

Clinical presentations: \uparrow BP and scleroderma renal crisis, CKD (relatively common—2° to fibrotic renal change), drug-related, e.g. NSAIDs, systemic vasculitis (<2%), SSc + SLE overlap with lupus-type nephritis.

SCr, eGFR, urinalysis (\pm uPCR), and BP should be regularly monitored in patients with SSc (e.g. 3–6 months). Patients should be encouraged to undertake home BP monitoring.

Scleroderma renal crisis

A syndrome of AKI and accelerated \uparrow BP in the context of SSc. It occurs in 5% of all SSc patients (15% diffuse disease; 1–2% limited disease). It is the first presentation of SSc in ~20%.

Pathogenesis

Remains poorly understood, but endothelial injury with intimal thickening of intrarenal arteries \rightarrow \downarrow renal perfusion and hyperreninaemia. Subsequent changes (including epithelial to mesenchymal transdifferentiation) within the glomeruli and tubulointerstitium promote renal injury. Endothelin-1 receptor dysregulation has also been observed.

Risk factors

Recent onset of diffuse disease, active skin disease, steroid use, positive anti-RNA polymerase.

Clinical features and investigation

- New-onset significant ↑ BP (e.g. >150/80mmHg) or BP that is significantly higher than a patient's own baseline. Can be asymptomatic, but accelerated BP with multisystem involvement may be present (📖 p. 518).
- Urinalysis, urine microscopy, and uPCR. Urinalysis is surprisingly bland but may reveal mild proteinuria ± microscopic haematuria.
- ↑ SCr, ↓ Hb, ↓ Plt, film (? fragments), ↑ LDH, ↓ haptoglobins (microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia in ~50%).
- Autoantibodies: ANA (~60% +ve in speckled pattern), anti-RNA polymerase antibodies.
- USS kidneys, ECG ± echocardiogram (pericardial effusion in ~5%).

Renal histology

May be necessary if the diagnosis is in doubt. Also yields important prognostic information. ► BP must be controlled prior to biopsy (📖 p. 80).

Characteristic findings are 'onion skin' intimal proliferation and thickening, fibrin thrombi, fibrinoid necrosis, thrombotic microangiopathy, ischaemic and collapsed glomeruli, variable degrees of ATN.

Management (see also Hypertensive emergency 📖 p. 518)

- Admit to a high dependency environment.
- Continuous cardiac monitoring, and consider invasive monitoring, particularly invasive arterial BP monitoring.
- Meticulous fluid balance. Chart input and output. Catheterize. Patients have ↑ vascular resistance, so cautious fluid challenges, as appropriate.
- ► Antihypertensive treatment. Aims: reduce SBP by 20mmHg and DBP by 10mmHg every 24h. ⚠ Avoid ↓ BP.
- ACE-I are the mainstay of therapy—they have been shown to significantly reduce mortality (from 80% to 15%). Good BP control can prevent further renal deterioration and assist renal recovery. However, there is no evidence that ACE-I prevent renal crises.
 - Captopril (12.5–50mg PO tds) has a short half-life and is easy to titrate to BP. Switch to a longer-acting agent as soon as stable.
 - Add an ARB as second line. Additional agents, e.g. calcium channel blockers, may be required.
- ~25% will require renal replacement therapy at presentation.
- Unproven interventions include: epoprostenol infusion for 24–48h (→↑ renal perfusion), fish oils (📖 p. 547), and plasma exchange if severe TMA.

Prognosis

Progression to ESRD in ~20–50%. However, ~50% will discontinue RRT within 1–2 years (transplantation should ∴ rarely be considered during this period). The degree of irreversible damage on renal biopsy may provide useful prognostic information to aid decision-making. Mortality remains significant (~30% at 3 years). Poor prognostic features include: permanent ESRD, older age (age >55), and low or normal BP at presentation (presumably a marker of significant cardiac involvement). Recurrence is rare, but compliance with treatment is crucial.

Rheumatoid arthritis



Introduction

RA is a chronic multisystem autoimmune disorder of unknown aetiology, characterized by synovial hypertrophy, joint inflammation, joint erosion, and many extra-articular manifestations. The annual incidence of RA is ~3 cases per 10,000 population, with a prevalence of ~1%. Incidence increases with age (peaking at age 35–50), and the disease is more common in ♀.

Renal conditions complicating RA

- Drug toxicity (esp. NSAIDs).
- Renal amyloidosis (AA amyloid).
- Secondary membranous nephropathy (MN).
- Other glomerular lesions.
- Rheumatoid vasculitis.

Drug toxicity

- NSAIDs: see  p. 902.
- *Methotrexate* (see  p. 899): now the most commonly prescribed disease-modifying anti-rheumatic drug (DMARD). Usually not nephrotoxic per se at the doses used for RA. However, it is primarily renally excreted, and the need for dose adjustment is often underestimated. Best avoided if GFR <30mL/min.
- *Gold (sodium aurothiomalate)*: now rarely used. Caused proteinuria in ~10% and associated with membranous GN.
- *Penicillamine*: now rarely used; associated with membranous GN in ~15%.
- *Anti-TNF biological agents* (e.g. *etanercept*): use has rapidly expanded. They appear safe, but case reports of an association with glomerular lesions and vasculitis have emerged.

Renal amyloidosis (p. 628)

Usually a long history of poorly controlled active RA, with joint deformities. Often seropositive (RHF +ve), with a grumbling acute phase response. Presentation is with proteinuria—often in the nephrotic range.

Membranous GN

Presents with proteinuria (less commonly, nephrotic syndrome) and historically associated with DMARDs, particularly gold and penicillamine. Usually occurred within 6–12 months of commencement of therapy. Drug withdrawal usually leads to remission, but this may take up to a year. There are reports of MN in association with *etanercept* therapy.

Other glomerular lesions

Mesangioproliferative GN is the most common renal lesion in RA patients who have undergone a renal biopsy (~35%). An association with IgAN is also well recognized. These present with an active urinary sediment and (less commonly) renal impairment. A crescentic proliferative GN has been described in association with anti-TNF therapy.

Rheumatoid-associated vasculitis

A small and medium vessel vasculitis, usually in RhF and anti-CCP (cyclic citrullinated) antibody +ve patients with long-standing disease. Other risk factors include ♂ sex and smoking. About 1 in 10 ♂ and 1 in 40 ♀ with RA developed vasculitis, although it is thought that this incidence is decreasing with improved treatment of severe RA. It is a severe multisystem disorder, associated with a high mortality. Clinical presentation may be with cutaneous leucocytoclastic vasculitis, mononeuritis multiplex, digital ischaemia, and ulceration, or with gut, cardiac, or cerebral vasculitis.

Renal involvement manifests as an active urinalysis with a rising SCr. The renal lesion is a pauci-immune necrotizing GN (📖 p. 643). Investigations include ↑ CRP, ↑ RhF, ↑ anti-CCP antibodies, and ↓ C3, ↓ C4. ~30% are p-ANCA-positive. Anti-TNF therapy has been successfully used for treatment, although it has also been implicated as a trigger in some cases (mechanisms unclear). Many clinicians treat as for ANCA-associated vasculitis (📖 p. 644).

Renal disease in other connective tissue disorders

Renal disease is not uncommon, and monitoring of urinalysis, SCr, eGFR, and BP are an important consideration during follow-up.

Sjögren's syndrome

A multisystem autoimmune disorder that may be primary or arise in association with other connective tissue disorders, e.g. SLE, RA, or systemic sclerosis. Lymphocytic infiltration of exocrine glands, particularly the lacrimal and salivary glands, causes sicca symptoms, such as dry eyes and dry mouth. Anti-Ro and anti-La antibodies are typical. Renal involvement in ~20%. Manifestations:

- Distal (type 1) renal tubular acidosis (📖 p. 824):
 - May be partial or complete, with a tendency to nephrolithiasis.
- Impaired concentrating ability, with polyuria.
- AKI 2° to acute interstitial nephritis (📖 p. 580):
 - Generally steroid-responsive. CKD (and ESRD) rare.
- Glomerular disease is uncommon.

Mixed connective tissue disorder

Associated with:

- Membranous nephropathy (📖 p. 564) and MCGN (📖 p. 550).
- Lupus nephritis or scleroderma renal crisis may develop.

Polymyositis and dermatomyositis

- Myositis and myoglobinuria may lead to false positive haematuria or, less commonly, AKI 2° to rhabdomyolysis (📖 p. 152).
- Glomerular disease associations, e.g. mesangial proliferation, have been reported.

Sarcoidosis

Introduction

A multisystem granulomatous disease of unknown cause, usually affecting the respiratory system of young adults and characterized by non-caseating granulomas in involved organs. Renal disease complicates up to 40% of cases, although it is often subclinical.

Pathogenesis


Remains esoteric, although unidentified antigen(s) appear to fuel dysregulated immune responses in susceptible individuals. Genetic predisposition is suggested by ↑ incidence in monozygotic twins, family aggregation, and race distribution (↑ African Americans + Scandinavians). Many immune response genes have been incriminated (e.g. cytokine polymorphisms), with specific alleles associated with particular clinical phenotypes.

The culpable antigens remain anonymous, although several environmental and infectious precipitants have been proposed. In particular, mycobacterial species (with mycobacterial DNA isolated from ~25% of sarcoid specimens), propionibacteria, and viruses. Various environmental triggers have also been postulated. It is unclear how this exposure results in such varied abnormalities of the immune response. CD4+ Th cell activation and cytokine production (esp. IFN- γ , IL-2, IL-12, and TNF- α) appear crucial (patients with sarcoidosis who acquire HIV do not progress their granulomatous disease). T cells exhibit a restricted TCR repertoire, suggesting oligoclonal expansion in response to a specific antigen. In addition, paradoxical peripheral immune anergy is evident during active disease, e.g. reduced delayed type hypersensitivity reactions.

Histology

Characteristic, irrespective of site: non-caseating epithelioid granulomas, comprising a central area of macrophages that differentiate into epithelioid cells before fusion into multinucleate giant cells. These are surrounded by CD4+ T cells, with CD8+ cells and B cells located peripherally. Unlike TB, necrosis is minimal. The nidus for granuloma formation may be partly processed antigenic material (e.g. microbial debris), and they are an attempt to 'seal off' such material to limit tissue injury.

Symptoms and signs

- Protean: sarcoidosis is the great clinical mimic of the post-syphilis era.
- Classically presents with ≥ 1 of the following four: bilateral hilar adenopathy, pulmonary infiltrates, skin lesions, and ocular involvement.
- Other:
 - *General*: lymphadenopathy, fevers, weight loss, malaise.
 - *Chest*: stage I—bilateral hilar adenopathy; stage II—adenopathy and infiltrates; stage III—interstitial disease with regressing adenopathy; stage IV—pulmonary fibrosis.
 - *Eyes*: uveitis, keratoconjunctivitis sicca, retinal vasculitis.
 - *Skin*: pigmentary changes, lupus pernio, erythema nodosum.
 - *Cardiac*: conduction defects, arrhythmias, cardiomyopathy.
 - *Neuro*: mononeuritis multiplex, aseptic meningitis, pituitary infiltration (\rightarrow cranial DI); neurosarcoid may present as an MS-like illness.
 - *Liver*: granulomatous hepatitis.
 - *Kidney*: see  p. 671.

Investigations

Usually rests on combined clinical, imaging, and histological findings. 50% of cases are found incidentally on chest imaging. Serum ACE +ve in ~75% cases and useful for disease monitoring.

Renal involvement

Exact prevalence unknown. CKD occurs in ~1% of patients.

Calcium metabolism

- Common. Activated macrophages within granulomas express 1α -hydroxylase and convert 25-(OH) vitamin D_3 to active $1,25$ -(OH) $_2$ vitamin D_3 (calcitriol), particularly during sunny months (increased substrate availability). This leads to \uparrow gut Ca^{2+} uptake and \rightarrow :
 - Hypercalcaemia (10–20%). More common in older patients (esp. σ^7).
 - Hypercalciuria (~50%).
 - Calcium oxalate nephrolithiasis (~15%).
 - Nephrocalcinosis (which is associated with CKD).
- *Management*: rehydrate. Steroids \downarrow macrophage calcitriol production. Consider \downarrow calcium (and oxalate) intake (📖 p. 723). Avoid calcium and vitamin D supplements. Bisphosphonates inhibit osteoclastic release of skeletal calcium. Ketoconazole inhibits the conversion of 25-(OH) vitamin D_3 to $1,25$ -(OH) $_2$ vitamin D_3 .

Tubular dysfunction

2° to \uparrow Ca^{2+} or granulomatous TIN. Defective concentrating ability with polyuria common. Other defects: RTA, Na^+ wasting, and Fanconi's.

Glomerular disease

Uncommon. Various histological patterns described, including FSGS, membranous, mesangioproliferative, MCGN, IgAN, and crescentic GN (all may be steroid-responsive). Immunoglobulin and complement deposition is usual. Underlying mechanisms unknown but presumably a consequence of altered immune responses.

Obstruction 2° to retroperitoneal lymphadenopathy and fibrosis

(See 📖 p. 738.)

Granulomatous interstitial nephritis

~20% sarcoid patients have renal granulomatous inflammation, although it is symptomatic in a minority only. More common in σ^7 . ~50% have an abnormal CXR and ~50% an elevated serum ACE. Concomitant \uparrow Ca^{2+} may be present (and contribute to \uparrow SCr). Presentation is variable: asymptomatic \uparrow SCr, active disease in other organs, loin pain. Urinalysis is typically bland, with proteinuria mild, if present.

- *Diagnosis*: renal biopsy (see Histology). Ca^{2+} deposition not uncommon.
- *Differential diagnosis*: AIN of any cause, esp. drug hypersensitivity (📖 p. 580), infection, TINU (📖 p. 581) and Sjögren's syndrome (📖 p. 669).
- *Management*: rehydrate if \uparrow Ca^{2+} . Prednisolone 20–40mg daily: SCr and Ca^{2+} may improve rapidly. Taper once SCr stabilized—generally slowly (over >1 year). Many clinicians maintain a long-term maintenance dose, at the lowest possible dose. Monitor SCr and Ca^{2+} (serum and urine), but predicting relapse is difficult, so maintain high index of suspicion.

Fabry's disease

Introduction

Fabry's disease is a rare, multisystem, X-linked lysosomal storage disease, resulting from a deficiency of the enzyme α -galactosidase A (α -Gal A). This results in the widespread lysosomal accumulation of the glycosphingolipid substrates of α -Gal A, particularly globotriaosylceramide (GL-3).

Progressive GL-3 accumulation in vascular endothelial lysosomes leads to extensive and progressive occlusive small vessel disease.

Genetics

The second most common lysosomal storage disorder (after Gaucher's disease), with a prevalence of ~ 1 in 100,000. The gene for α -Gal A is located on the long arm of the X chromosome (Xq22).

More than 500 α -Gal A mutations have been identified. Many lead to little, if any, α -Gal A activity (classic Fabry's disease), whilst others allow for residual enzyme activity (typically late-onset disease).

The sons of affected σ will not have the disease, whereas all their daughters will be heterozygotes. 50% of the sons of heterozygotes will then be affected (whilst 50% of their daughters will also be heterozygotes).

Heterozygous f have a wide range of clinical manifestations, from asymptomatic to severely affected (although symptoms tend to manifest later in life). Genetic counselling should be offered.

Clinical features

Often begin in childhood and adolescence.

- **Skin:** petechial-like angiokeratomas (appear as clusters of small red spots; classically umbilical, swimsuit region, and on extremities). Histologically, these are small, dilated veins of the upper dermis, covered by hyperkeratotic epidermis.
- **Cardiac:** occlusive coronary disease, conduction abnormalities, valvular disease, LVH. Lower extremity oedema (lymphatic glycosphingolipid accumulation).
- **Neurological:** painful acroparaesthesias (tingling, numbness, and stiffness of distal extremities—particularly during a febrile illness), neuropathic pain, autonomic dysfunction, hyperhidrosis, TIAs, stroke, vertebrobasilar insufficiency (ataxia, memory loss), tinnitus, hearing loss, depression.
- **Ocular:** corneal opacities (called verticillata) and dystrophy (visible on slit lamp examination).
- **Pulmonary:** cough, obstructive airways disease.
- **Renal involvement:** glomerular damage with proteinuria \pm microscopic haematuria. Progressive CKD and ESRD (typically age ~ 30 – 50). Renal abnormalities may be milder in heterozygote f , e.g. isosthenuria, asymptomatic proteinuria—however, 10% will progress to ESRD.

The underdiagnosed 'renal variant'

There is evidence that Fabry's disease is an underestimated cause of progressive CKD and ESRD. Measurement of α -Gal A activity in ♂ dialysis patients suggests 0.2–1.0% have unrecognized disease.

The majority of these patients do not exhibit current or historical 'hallmark' Fabry's symptoms, esp. angiokeratomas, acroparaesthesias, or corneal opacities, which might have drawn attention to the diagnosis sooner. Many other features of classical disease remain absent, although cardiac involvement can often be found on closer scrutiny.

These individuals tended to have residual α -Gal A activity and \therefore to have developed clinically overt disease later in life.

Renal histology

As well as in vascular endothelium, glycosphingolipid accumulation occurs in podocytes, mesangial cells, and, to a lesser extent, tubular cells (lipid-laden distal tubular cells are shed and can be seen on urine microscopy). In later-onset variants, podocytes are more dominantly affected than other cell types.

On microscopy, foamy inclusions may be seen in most cell types. Arteriolar sclerosis, glomerular atrophy and sclerosis, and tubulointerstitial fibrosis are common. Electron microscopy reveals characteristic lysosomal lamellar cytoplasmic (termed myelin or zebra bodies).

Investigation

- Slit lamp examination.
- Lipid-laden epithelial cells on urine microscopy.
- Reduced or absent plasma α -Gal A activity.
- Elevated serum GL-3 level.
- α -Gal A mutation analysis in equivocal cases.

Treatment

Enzyme replacement therapy (ERT) with recombinant α -Gal A has transformed management. Two preparations are available: agalsidase alfa (Replagal®) and beta (Fabrazyme®). Usually delivered as an IV infusion at 2-weekly intervals. ⚠ Extremely expensive. Infusion reactions are not uncommon. Neutralizing antibodies develop to the recombinant enzyme but do not usually appear to decrease efficacy.

Treatment demonstrably stabilizes and slows progression of disease, with clearance of accumulated GL-3 from capillary endothelial cells in kidney, skin, and heart. Progression of CKD is slowed.

Initiate ERT at the time of diagnosis in adult ♂ patients. Timing will depend on clinical symptoms and evidence of organ involvement in heterozygote ♀.

ERT should be continued in ESRD patients for its non-renal benefits. Transplantation is feasible, as recurrent disease is also ameliorated by therapy.

HIV and renal disease

Introduction

Almost 40 million people worldwide are infected with HIV-1, and ~30% of patients with HIV infection have a degree of renal dysfunction. As a result, HIV-associated kidney disease has emerged as a relatively common cause of ESRD and HIV-associated mortality.

HIV is associated with almost every described renal lesion (as well as many electrolyte and acid–base disorders), either as a direct consequence of infection or as a result of the nephrotoxic profile of highly active antiretroviral therapy (HAART) medications (see Table 8.8). HIV-related renal lesions can be classified according to histopathological findings. The most frequent are: classic HIV-associated nephropathy (HIVAN), HIV immune complex kidney disease (HIVICK), and HIV-associated thrombotic microangiopathy (HIV-TMA). However, many more glomerular lesions can occur that sit outside this framework. In addition, patients may develop glomerular disease related to concomitant HCV or HBV infection.

► Patients with HIV infection are also more vulnerable to episodes of AKI (which has a higher mortality risk than non-HIV-associated AKI) as well as HIV-associated malignant lesions of the kidneys.

Epidemiology

Historically, HIVAN was the most common lesion associated with HIV infection in the developed world. However, the incidence has decreased with HAART. The true prevalence of HIVAN is unknown, as many patients do not undergo a renal biopsy. In one series, HIVAN was seen in 40–60% of biopsies. In another, the following lesions were found: HIVAN 27%; HIVICK 21%; membranous GN 13% (\pm hep B); post-infectious diffuse proliferative GN 8%; mesangial hyperplasia (pure mesangial changes, immunostaining negative) 6%; IgAN 5%; others—malignant \uparrow BP, TMA, TIN, ATN, diabetic nephropathy, hep C-associated MCGN.

The incidence of renal associated neoplasms is ~4–8% in patients with AIDS. Neoplastic processes include lymphomas and Kaposi's sarcomas and usually occur as part of widespread disease.

Table 8.8 Causes of renal failure in HIV

AKI	<ul style="list-style-type: none"> Sepsis Rhabdomyolysis Drug toxicity: <ul style="list-style-type: none"> Rifampicin Co-trimoxazole Aminoglycosides Acute glomerulonephritis Pyelonephritis Renal TB
Acute on chronic	<ul style="list-style-type: none"> HIVAN (\pm HIVICK) with: <ul style="list-style-type: none"> ATN Drug nephrotoxicity Granulomatous disease Malignant \uparrow BP Lymphoma
CKD	<ul style="list-style-type: none"> HIVAN Other GN: <ul style="list-style-type: none"> Membranous MCGN IgAN Mesangioproliferative Idiopathic FSGS Hypertensive nephrosclerosis Diabetic nephropathy

Adapted from Swanepoel, C, *Am J Kidney Dis*, 2012;**60**(4):668–678.

HIV and renal disease: HIVAN

Introduction

As HIV infection has burgeoned globally, HIVAN has become a significant cause of CKD and ESRD. It is almost exclusive to black adults. The University of Cape Town has developed a HIVAN classification to enable standardization of terminology (see Table 8.9). Prognostic indicators and outcomes have been evaluated using this classification.

Pathogenesis

Transgenic mouse models suggest that expression of HIV genes alone is not sufficient to cause HIVAN. Genetic factors (*MYH9*, *ApoL1* genes—two variants in the *ApoL1* gene have been identified as the susceptibility alleles responsible for most of the increased risk in black patients), unknown environmental factors, and host factors (e.g. RAAS activation) are also important. Viral proteins, such as Nef, induce podocyte dysfunction—characterized by increased proliferation, apoptosis, and dedifferentiation. Others, including Vpr, induce apoptosis of renal tubular epithelial cells. As renal cells do not express classical CD4 HIV-1 receptors, it is unclear how virus enters the cells, although direct cell–cell transmission appears important for infection of renal tubular epithelial cells.

Histopathology

HIVAN is characterized by the so-called collapsing variant of FSGS (the capillary tuft literally crumples), with microcystic tubular dilatation, tubular atrophy, interstitial infiltrates (often CD8+ cells), interstitial oedema, and fibrosis. Immunostaining is non-specific. EM often reveals endothelial cell tubuloreticular inclusions and nuclear bodies.

► These findings should prompt serological testing for HIV.

Symptoms and signs

Proteinuria—often with the nephrotic syndrome clinically. Renal impairment (usually superadded ATN). BP is characteristically normal (~80%), perhaps 2° to relative vasodilatation and renal salt loss. Oedema may be less marked than in other cause of the nephrotic syndrome, a phenomenon that is unexplained.

Investigations

- Urine microscopy—may show broad, waxy casts.
- uPCR—proteinuria often heavy.
- ↑ SCr, U&E (SIADH), ↓ albumin.
- CD4+ T cell count:
 - Usually <200 cells/μL (but HIVAN has been reported in patients with higher counts).
 - Renal prognosis is worse in patients with AIDS, especially if their CD4 count <50 cells/μL.
- HIV viral load: typically high (>400 copies/mL).
- Hepatitis B and C serology.
- USS—often shows normal or large echogenic kidneys.
- Renal biopsy: owing to diversity of potential lesions, biopsy is recommended in virtually all cases.

Table 8.9 The University of Cape Town classification of HIVAN

Glomerulus	Glomerular variants of HIVAN <ul style="list-style-type: none"> – FSGS collapsing variant – FSGS non-collapsing variant with additional features – Global sclerosis with epithelial cell involvement ('fetal' variant) Additional features to glomerular variants of HIVAN: <ul style="list-style-type: none"> – Parietal \pm visceral epithelial cell hypertrophy and hyperplasia – Presence of pseudocrescents
Interstitial	Fibrosis Lymphocytic infiltrate Plasma cells within the lymphocytic infiltrate Diffuse inflammatory lymphocytic syndrome
Tubules	Presence of microcysts Epithelial cell hyperplasia and hypertrophy
HIV and immune complex GN	With additional features of HIVAN (as described above): <ul style="list-style-type: none"> – MCGN – Ball in cup: very large subepithelial immune deposits – Any other GN Without additional features of HIVAN (immune complex alone)
Others	Diseases unrelated to HIV, e.g. granulomas, ATN, drug reactions, lymphoma

Adapted from Swanepoel, C, *Am J Kidney Dis*, 2012;60(4):668–678.

Management of HIVAN

HAART, a three-drug regimen of two reverse transcriptase inhibitors plus a protease inhibitor, has completely transformed the outlook for HIV-infected individuals. A diagnosis of HIVAN is considered as an indication for HAART, regardless of CD4 count. Continuous therapy is important to gain maximal benefit: there is a high incidence of ESRD in patients whose treatment is interrupted through poor compliance.

HAART exerts the following effects on HIVAN:

- Reduced proteinuria—with full or partial remission of nephrotic syndrome.
- Delayed progression of renal impairment.
- Potential renal recovery and dialysis independence

ACE-I/ARBs should be prescribed, as for any proteinuric renal disease (note: avoid calcium channel blockers if on protease inhibitors).

Prednisolone has been used with some success, particularly when prominent interstitial inflammation and \uparrow SCr, but there is an absence of well-controlled trials. Ciclosporin has been studied in children.

HIV and renal disease: other lesions

HIVICK

Immune complex-related lesions are gathered under the term HIVICK. These resemble IgA nephropathy and diffuse proliferative glomerulonephritis (lupus-like).

Pathogenesis

As the immune complexes are generated by an HIV-induced immune response, an active viraemia is required. It is not clear why some patients develop HIVICK and some patients develop HIVAN, but both appear to be the consequence of a dysregulated immune response to HIV infection. In IgA type, IgA and viral antigen complexes deposit in the kidney.

Histopathology

Mesangial change with mild/moderate hyperplasia and immune deposits. Large subepithelial deposits are seen with a 'ball-in-cup' appearance. The diffuse proliferative GN (described as 'lupus-like') has IgG, IgM, C3, and C1q immune deposits.

Symptoms and signs

Presentation can vary, although haematuria and low-grade proteinuria are most common. Rapidly progressive glomerulonephritis and nephrotic syndrome are also recognized. Unlike HIVAN, the vast majority of patients are Caucasian or Hispanic, although affected Asians and black patients are described.

Investigations

Investigations, such as ANA and ANCA, must be interpreted with caution because false positives are more common in HIV-infected patients.

Management

Whilst HAART is established as the main treatment for HIVAN, it is unclear if other types of HIV-related kidney disease derive as much benefit from its use. The Strategic Timing of Antiretroviral Treatment (START) study is an ongoing trial investigating the impact of early HAART therapy on AIDS and non-AIDS conditions, including CKD, and should help to answer this question in the near future.

HIV-associated thrombotic microangiopathy

HIV-TMA is associated with more advanced HIV disease and AIDS. It is another example of a renal lesion that has declined in incidence in the HAART era (<1% of HIV-infected patients).

The pathogenesis of HIV-associated TMA is poorly understood. ADAMTS-13 levels are generally not decreased, suggesting an unconventional mechanism for TMA in this group (□ p. 576). However, with adequate treatment, it generally carries a better prognosis than idiopathic TMA.

Suspect if AKI, thrombocytopenia, and evidence of microangiopathic haemolytic anaemia. Definitive diagnosis requires a renal biopsy. Patients with a high viral load (VL) require longer PEX therapy, compared to patients with a lower VL.

HAART-related renal side effects

There has been a definite reduction in the incidence of HIVAN since the introduction of HAART medications; however, significant evidence of nephrotoxicity associated with HAART has emerged.

Common problems include:

- Protease inhibitors:
 - Examples: indinavir, nelfinavir, ritonavir.
 - Problems: crystalluria (may cause microtubular obstruction and ATN or lead to nephrolithiasis), interstitial nephritis.
- Nucleotide reverse transcriptase inhibitors:
 - Examples: zidovudine, didanosine, adefovir, tenofovir.
 - Problems: proximal tubular cell injury (→ Fanconi-like syndrome), lactic acidosis (often severe—probably the consequence of mitochondrial DNA damage), AKI (ATN). Also associated with CKD (itself the consequence of interstitial fibrosis).

ESRD in patients with HIV infection

In the USA and elsewhere, HIV-associated ESRD is an epidemic among black patients. The risk of ESRD in black HIV-infected individuals is ~3–6× higher than in Caucasian HIV-infected patients. Concomitant IVDU and HCV infection are important additional risk factors for ESRD. Despite the successes of HAART, longer overall survival in both black and Caucasian patients with HIV-associated CKD has meant that the prevalence of ESRD is still increasing—and remains associated with poorer survival (although this is improving).

Dialysis

Survival on either HD or CAPD appears comparable. HIV-infected patients undergoing haemodialysis do not require isolation.

Transplantation

Transplanting patients with HIV infection is a challenge in terms of infection rates, rejection rates, and attaining therapeutic and non-toxic levels of immunosuppression. However, in appropriate cases, it is thought to improve survival in comparison to dialysis.

Patient selection is crucial. Criteria: stable disease and antiviral regimen, compliant with medication, undetectable viral load, and preserved CD4 counts >200 cells/μL. In addition, drug interactions and toxicities are a major challenge.

The largest series of HIV kidney transplantations was published in 2010, with 150 performed over a 6-year period (including both live-related and deceased donor). Regimens were tacrolimus- or ciclosporin-based, and some patients had ATG induction; 3 years' follow-up. Rejection rates were high—31% at year 1, 41% at year 3. Graft survival was worse in comparison to the non-HIV transplant population, and increased numbers of neoplasms were seen.

Hepatitis B

Introduction

Approximately 1/3 of the world's population have been infected with HBV, and ~350 million are chronic carriers. The majority of these are in the developing world, especially Africa and South East Asia where perinatal transmission is the dominant route of infection. The prevalence in the USA and Western Europe is ~0.1–0.5% (placing them in the lowest WHO category), although this will vary considerably between particular communities. In the USA, it is estimated that there are ~1.3 million carriers (some estimates are much higher). The majority of these infections are acquired as adults, principally via sexual activity or IVDU. Although acute HBV infection rates have fallen (→↓ IVDU, needle exchanges, behavioural change in the HIV era, vaccination of the at-risk), the frequency of chronic infection is actually increasing because of migration from areas of high prevalence.

The virus

The HBV genome comprises partially double-stranded circular DNA linked to a DNA polymerase and surrounded by nucleocapsid and lipid envelopes. Embedded within these outer layers are the numerous antigens familiar from serological identification of the disease.

The illness

In adults, an acute seroconversion illness follows 1–6 months after exposure. This ranges from asymptomatic (usual), through a non-specific viral illness, to a more severe illness with frank jaundice. Most adults develop immunity and clear the virus. The remainder become chronic carriers. Patients may alternate between active disease, where the immune responses cause liver inflammation, and an inactive carrier state. Carriers are at risk of hepatic (chronic hepatitis, cirrhosis, and hepatocellular carcinoma) and extra-hepatic (e.g. GN, vasculitis, and reactive arthritis) complications. If HBV is acquired in childhood, chronic carriage is the norm (~90%). This falls to ~5–10% in adults (higher in the elderly).

HBV serology explained

- The diagnosis and monitoring of HBV is based on the collective interpretation of several serologic markers (+ HBV DNA + liver enzymes) (see Table 8.10).
- HBsAg may appear ≥ 1 week post-exposure but usually ≥ 4 –6 weeks.
 - HBsAg positivity indicates that an individual is infected (Δ and \therefore potentially infectious).
 - HBsAg persistence (> 6 months) separates acute infection from chronic 'carrier' status.
 - Quantitative HBsAg testing is available, with lower levels associated with better host immune HBV control. Its utility for monitoring of therapy (esp. nucleoside/nucleotide analogues) is increasing.
- The immune response to HBsAg produces *anti-HBs* (as does vaccination). This usually persists indefinitely.
- The first antibody identified is actually anti-HBc. IgM anti-HBc indicates acute infection—and it may be the evidence of HBV acutely, before HBsAg and anti-HBs appear. Subsequent IgG anti-HBc persists indefinitely (signifying either historical or ongoing infection).

- HBeAg is a marker of viral replication (Δ and \therefore infectivity).
 - Although HBeAg is often present acutely (suggesting \uparrow infectivity), that is not its main clinical utility.
 - HBV within liver cells may be in a replicating (i.e. virus-producing) and non-replicating (host DNA-integrated) form. As HBeAg is produced only during viral replication, it is an extremely useful marker of viral activity during surveillance of chronic HBV carriers.
 - HBeAg disappearance and appearance of anti-HBe is termed seroconversion. This may occur during acute HBV or years later in chronic carriers. Seroconversion is good news—associated with \downarrow HBV replication, HBV clearance, clinical improvement, and favourable response to treatment.
- \blacktriangleright General rule: +ve HBeAg = infectivity; +ve anti-HBs = immunity.
- HBV DNA estimates viral burden and viral replication. It can be quantitatively measured via sensitive PCR assays.
 - HBV DNA helps: (i) to determine recovery from acute infection; (ii) to distinguish inactive carriers from those with active disease; and (iii) to assess the appropriateness of antiviral therapy.

Table 8.10 Interpretation of HBV serology

Serology	Status	Implication	
HBsAg	Negative	Susceptible	
Anti-HBc	Negative		
Anti-HBs	Negative		
HBsAg	Negative	Immune due to natural infection	
Anti-HBc	Positive		
Anti-HBs	Positive		
HBsAg	Negative	Immune due to HBV vaccination	
Anti-HBc	Negative		
Anti-HBs	Positive		
HBsAg	Positive	Acutely infected	
Anti-HBc	Positive		
IgM anti-HBc	Positive		
Anti-HBs	Negative		
HBsAg	Positive	Chronically infected	
Anti-HBc	Positive		
IgM anti-HBc	Negative		
Anti-HBs	Negative		
HBsAg	Negative	Interpretation unclear; four possibilities	
Anti-HBc	Positive		1. Resolved infection (most common)
Anti-HBs	Negative		2. False positive anti-HBc, \therefore susceptible 3. 'Low level' chronic infection 4. Resolving acute infection

Adapted, with permission, from the CDC. See

www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf.

HBV-related renal disease

Introduction

Three common nephropathies are described: membranous GN, MCGN, and polyarteritis nodosa (PAN). An association between HBV and IgAN has also been reported but may be coincidental, as IgAN is common in many populations. Minimal change, FSGS, and amyloid are also described.

Pathogenesis

Direct HBV renal tissue invasion does not occur (unlike HIV). Instead, viral and host factors (including genetic predisposition) play a role in glomerular immune complex deposition. These complexes comprise viral antigens and host antibodies, either forming *in situ* in the kidney or becoming trapped after circulation. The location of the immune deposit depends on its size, which, in turn, depends on the involved antigen.

Investigations

Full HBV serology and HBV DNA PCR (📖 p. 680). HCV and HIV serology. U&E, Scr, LFT. uPCR or uACR. FBC, INR. Full immunological screen may be required (📖 p. 40). USS liver and kidneys. Renal biopsy.

Membranous glomerulonephritis (MN)

HBeAg–antibody immune complexes are small enough to pass through the capillary basement membrane and deposit in the subepithelial space and cause MN. The clinical course of HBV-associated MN differs between children and adults. MN is common in children aged 2–12 years ($\sigma^{\text{♂}} > \text{♀}$), presenting with proteinuria. Usually HBeAg +ve. Tends to remit spontaneously with seroconversion (i.e. clearance of HBeAg and development of anti-HBe). Proteinuria may persist for >1 year. Adults often present with a more chronic nephrotic syndrome and progressive CKD in association with liver disease. >50% will reach ESRD in 3 years.

Mesangiocapillary glomerulonephritis (MCGN)

Immune complexes involving HBsAg are too large to traverse the basement membrane so settle in the subendothelial space. MCGN is more common in adults (>MN in that age group), presenting with ↑ BP, heavy proteinuria, microhaematuria, and progressive CKD (i.e. a more nephritic presentation than MN). Histology is similar to type I MCGN (📖 p. 550), with a ‘tram track’ pattern—some normal capillary loops with thin BM, others with split BM. Unlike MCGN with HCV, cryoglobulins are not present.

Polyarteritis nodosa (PAN)

Occurs within 4 months of HBV infection in adults, presenting as a medium-vessel vasculitis attributed to immune complex deposition (📖 p. 652). ANCA –ve. Relapse rare—never once viral replication has stopped/seroconversion has occurred. Incidence appears to be falling along with the incidence of acute HBV.

IgAN

The liver metabolizes IgA, so serum IgA levels increase in hepatic disease of any cause, potentially ending up secondarily deposited within the renal mesangium and capillary loops. Clinically significant disease is rare.

Treatment of HBV-associated disease in adults

Cessation of immune complex formation requires treatment of HBV. Remission should follow seroconversion from HBeAg to anti-HBe and a reduction in, or disappearance of, HBV DNA. Long-term nucleoside analogues are often used for this purpose (see below). Response rates are higher in MN than MCGN. Standard treatment of proteinuric disease with ACE-I/ARB to achieve BP <130/80mmHg and reduce urinary protein excretion also applies. Immunosuppression should be avoided (\rightarrow ↑ viral replication \pm hepatic decompensation—may occur on treatment withdrawal). PAN is a possible exception where severity of disease may necessitate steroid and cytotoxic therapy, with concomitant antivirals.

Treatment of HBV-related liver disease: a primer

- Decisions are based on HBV DNA, serum ALT, and assessment of liver disease (including histology). Some guidelines have slightly different criteria, according to HBeAg status (with lower HBV thresholds in HBeAg -ve individuals).
- In general, patients should be considered for treatment when HBV DNA levels are above 2,000IU/mL (~10,000 copies/mL) \pm serum ALT is above the upper limit of normal, with evidence of active liver inflammation or fibrosis.

Anti-HBV therapy

Δ Much of the long-term data exclude renal patients. Treatment includes antivirals and immune modulators (to enhance host responses). Response rates are modest.

Interferon alfa

5 million U \times 6/week or 10 million U \times 3/week SC for 4 months leads to undetectable HBV DNA levels and HBeAg clearance in 30–40%. 5–10% of patients relapse after treatment. SE: fatigue, flu-like illness (can be severe and debilitating), depression, leucopenia, thrombocytopenia, GI upset, alopecia, transient liver 'flare' at outset.

Peginterferon alfa

A 48-week regimen has similar efficacy to interferon alfa. Peginterferon alfa 2a has an \uparrow half-life and a more stable plasma concentration, allowing fewer injections and better patient tolerability.

Nucleoside/nucleotide analogues

Associated with lower rates of HBe and HBs seroconversion. Most evidence for extra-hepatic manifestations lies with lamivudine. This inhibits viral polymerase, but efficacy is limited by the emergence of drug-resistant mutants (~15% per year). Usual dose 100mg PO daily, but Δ dose reductions for \downarrow GFR. Adefovir is also associated with resistance, and renal toxicity is recognized. Entecavir and tenofovir are potent antivirals, with good safety profiles and a low resistance rates thus far. Entecavir requires a dose adjustment, according to GFR, but has not been associated with renal toxicity so may be the treatment of choice in renal disease.

Nucleoside analogues are usually continued indefinitely, unless anti-HBe seroconversion is achieved. There is currently no strong evidence that combination therapy is superior.

HBV and ESRD

Introduction

There were multiple documented HBV outbreaks on haemodialysis units in the 1960s and 70s, and they occur sporadically to this day (usually because of poor infection control practices). Such historical outbreaks were associated with considerable morbidity and mortality among both staff and patients alike. By definition, blood contact is not uncommon in this setting, and HBV is a tenacious virus *ex vivo*, remaining infectious on surfaces, even after drying, and requiring potent disinfection to inactivate.

Prevention

▶▶ The best means of controlling HBV-related renal disease is to prevent it. Offer immunization against HBV early in CKD (📖 p. 685). Household contacts and family members of HBsAg-positive patients should also be immunized. Avoid sharing potentially blood-contaminated items (tooth-brushes, etc.). Protected intercourse.

Haemodialysis

Haemodialysis patients are usually screened annually for HBV (and HCV) as well as on return from dialysing abroad. In the UK, <1% of the HD population are HBV-infected. HBV patients require isolation on haemodialysis units, in addition to standard universal precautions. Dedicated machines are used and dialyser re-use avoided. Peritoneal dialysis is an option.

Transplantation in patients with hepatitis B infection

Transplantation is thought to offer a survival benefit over remaining on dialysis, but patient selection is crucial. Patients with evidence of active viral replication (HBeAg +ve or HBV DNA +ve) must be treated prior to transplantation and should remain on a nucleoside/nucleotide analogue post-transplant. IFN- α is an immune modulator and can provoke rejection if used after transplantation. In addition, patients who are HBsAg and/or anti-HBc +ve should be considered for nucleoside/nucleotide analogue prophylaxis post-transplant. Most data in this context concern lamivudine (the dose of which should be adapted to GFR). HBsAg +ve patients have about twice the mortality of non-HBsAg patients 5–15 years post-transplantation (probably partly due to reactivation of latent disease). Cirrhosis is a contraindication to renal transplantation. New acquisitions of HBV post-transplant can present with severe disease on immune suppression. HBV-related GN can recur/occur in transplants.

HBsAg-positive kidney donors

It is acceptable practice to use HBsAg +ve donor to HBsAg +ve recipient, with using antiviral prophylaxis. However, the safety profile is less clear when using an HBsAg +ve donor for a recipient who is anti-HBs +ve (i.e. potentially immune—either as the result of prior infection or of immunization), as pre-existing immunity may not be sufficient to overcome the viral load transferred with the transplanted kidney in the presence of immunosuppression. 🌐 Small case series suggest that outcomes may be favourable.

HBV vaccination in CKD

Patients who are likely to require renal replacement therapy (RRT) should be immunized against HBV—a strategy that has been associated with a reduced incidence of HBV infection in dialysis units.

Despite the lower probability of HBV infection in peritoneal dialysis patients (and patients destined for pre-emptive transplantation), there is sufficient potential they may require haemodialysis at some point in their life that they should also be offered immunization.

Patients should be immunized early in the course of progressive CKD, as the proportion of patients achieving adequate anti-HBs antibody titres is lower, compared with the general population (and lower in advanced, compared with early, CKD).

Although it is desirable to know a patient's anti-HBc status beforehand (to prevent unnecessary immunization), HBV prevalence is so low in many populations that pre-immunization screening may not be warranted. Local protocols will apply.

Most HBV immunization schedules typically involve high doses or frequent doses (or both). Vaccines are generally administered IM (deltoid muscle), but the intradermal route may be more effective.

Examples:

- Engerix B[®] 40 micrograms at 0, 1, 2, and 6 months.
- HBvaxPRO[®] 40 micrograms at 0, 1, and 6 months.
- Fendrix[®] 20 micrograms at 0, 1, 2, and 6 months (● possibly more immunogenic).

Response is assessed through measurement of anti-HBs antibody 8 weeks after course completion.

>100mIU/mL was conventionally regarded as immunity ('responder'), but there is evidence that patients who have a lower (partial) response (10–100mIU/mL) are less likely to become chronic HBV carriers. Such partial responders (and those in whom anti-HBs titres diminish over time) should receive a further booster dose if the annual anti-HBs titre is <100mIU/mL.

'Non-responders' (<10mIU/mL) generally receive no further immunization, although some protocols give a further full course before accepting this status.

Hepatitis C-related renal disease

Introduction

HCV is an RNA virus with six different genotypes, causing hepatitis, cirrhosis, hepatocellular carcinoma, and various extra-hepatic disorders. 150–170 million people are HCV-infected worldwide, with large geographical variation. Transmission is parental and associated with IVDU, accidental infection during healthcare (e.g. needle or multidose vial re-use, contaminated blood products, or poorly sterilized instruments), and regional cultural practices. Perinatal and sexual transmission also occur but are less important than for HBV and HIV.

Infection is mild (often subclinical), following an incubation period (6–9 weeks). 70–85% fail to clear acute infection and become chronic carriers.

Hepatitis C-related glomerulonephritis

HCV is associated with several types of renal disease, predominantly: MCGN with mixed (type II) cryoglobulinaemia, membranous nephropathy (MN), and polyarteritis nodosa (PAN). Also recognized: FSGS, proliferative GN, fibrillary and immunotactoid GN, IgAN.

Chronic HCV and associated mixed cryoglobulinaemia are now known to be the principal cause of type I MCGN (previously thought to be idiopathic).

Renal involvement in some may be mild or clinically silent; in others, there is a significant risk of progression to ESRD (worse if co-infected with HBV/HIV).

HCV-related type I MCGN 2° to type II (mixed) cryoglobulinaemia

Cryoglobulins are one (monoclonal) or more (polyclonal or mixed) immunoglobulins in serum that reversibly precipitate at <37°C (📖 p. 634).

Pathogenesis

HCV-induced clonal expansion of rheumatoid factor (RhF)-expressing B cells in the liver, lymph nodes, and circulation causes excess secretion of immunoglobulins (predominantly IgM kappa (κ) directed against IgG, which is itself directed against HCV). These proteins (IgM κ , IgG, and viral antigens) aggregate into large cryoglobulins. HCV may also be responsible for type III mixed cryoglobulinaemia comprising polyclonal immunoglobulins (see 📖 p. 634). The cryoglobulins deposit in small and medium-sized vessels in the skin, joints, and glomeruli, where they fix complement and cause local inflammation and injury. Prolonged clonal expansion of B cells can eventually lead to B cell lymphoma (~5%).

Pathology

Renal biopsy shows a type I MCGN pattern of injury (📖 p. 550).

- *Light microscopy*: glomerular hypercellularity, lobular accentuation of glomerular tuft, increased matrix and mesangial proliferation, splitting of capillary basement membranes (termed double contouring), intracapillary thrombosis (from cryoglobulin deposition), vasculitis, and fibrinoid necrosis.
- *Immunostaining*: deposits of IgG, IgM, and C3 in the mesangium and capillary walls.

- EM demonstrates large subendothelial deposits that may have a tactoid distribution/size pattern, characteristic of cryoglobulin deposition (measuring 15–30 microns, distinct from smaller fibrillary deposits measuring 12–25 microns). These are so large they may protrude into the capillary lumen, causing thrombosis. This appearance is different from idiopathic MCGN where the subendothelial deposits are much smaller (and more commonly encountered in children and young adults).

Symptoms and signs

► Usually a systemic disease.

- **Extrarenal:** fatigue, weight loss, episodic purpuric rash (leucocytoclastic vasculitis on biopsy), arthralgia, myalgia, mononeuritis multiplex, Raynaud's phenomenon. Hepatosplenomegaly and stigmata of liver disease.
- **Renal:** the kidney is affected in 60%. Manifestations include haematuria, proteinuria (often nephrotic range), (↑ BP, renal impairment (often progressive), and AKI (5%). In general, HCV-associated MCGN has a nephritic presentation, whilst MN is usually nephrotic.

Investigations

- Urinalysis (haematuria, proteinuria) and microscopy (red cells casts).
- U&E, SCr, eGFR, Alb, LFT (i ALT/AST), FBC, ESR, CRP.
- Rheumatoid factor (RhF) may be +ve.
- Complement (normal C3, low C4) (📖 p. 41).
- Cryoglobulins (📖 p. 634). The cryocrit may be surprisingly low.
- Anti-HCV antibody, HCV RNA PCR (in serum and cryoprecipitate).
- If HCV viral load is low, an alternative diagnosis should be considered, so a full immunological screen may be helpful (📖 p. 40).
- HCV genotyping (types 2 and 3 associated with ↑ sustained remission).
- HBV and HIV.
- USS liver and kidneys.
- Renal biopsy (📖 p. 80).

Other HCV-related glomerulopathies

- Non-cryoglobulinaemic MCGN occurs. It will still be associated with HCV antibodies and HCV RNA.
- Membranous nephropathy is uncommon. Presentation, pathology, and outcomes are similar to idiopathic MN. It is thought to result from HCV-containing immune complexes depositing in the glomerular basement membrane (HCV can be demonstrated by *in situ* hybridization). Cryoglobulins are not detected, and complements are normal. Antiviral treatment is usually recommended.
- HCV-associated PAN is well described (📖 p. 652). It tends to be an acute, severe illness, presenting >2 years post-HCV diagnosis (with no cryoglobulins). Remission rates with treatment are high.
- Diabetic nephropathy: HCV infects pancreatic islet cells, causing reduced insulin production, and a post-insulin receptor defect also operates. Diabetic renal disease is ∴ a consideration in long-standing HCV patients.

HCV-related disease: management

Introduction

Before the link between HCV infection and cryoglobulinaemia MCGN was discovered, treatments were similar to those used for other small to medium-vessel vasculitides—namely corticosteroids, alkylating agents, and plasma exchange (to remove circulating cryoglobulins). Insight into the relationship between HCV and cryoglobulinaemia has led to direct treatment of HCV, with immune suppression now reserved for severe or refractory presentations.

Several issues need to be considered prior to treatment: (1) viral genotype (some respond better than others); (2) degree of viraemia; (3) presence of chronic liver disease; (4) severity of CKD (and if dialysis or transplantation is being considered); (5) extra-hepatic manifestations; and (6) other comorbidities (e.g. CV disease).

If liver status does not warrant antiviral therapy, then parameters favouring treatment for renal involvement are nephrotic syndrome, \uparrow SCr, new \uparrow BP, and the nature and severity of the injury on renal biopsy. If HCV viraemia is not present, the renal diagnosis should be reconsidered.

No known therapy specifically alters renal outcome in MCGN, although antiviral therapy may clear HCV and have modest effects on proteinuria and renal function. Relapse of HCV RNA and cryoglobulins on cessation of treatment is common.

Antiviral treatment

The aim is to reduce or eliminate viraemia and decrease the formation of immune complexes. Patients with HCV infection are generally treated with peginterferon alfa (e.g. 180 micrograms/week) \pm the oral antiviral agent ribavirin (e.g. 1,000–1,200mg/day) for 24–48 weeks. Δ However, ribavirin is not recommended if GFR <50 mL/min, and most studies have \therefore excluded renal patients. There is some evidence that it is safe in haemodialysis patients.

Treatment efficacy is measured in terms of sustained virologic response (SVR)—HCV RNA levels should be undetectable for a minimum of 6 months after cessation of therapy. Of the six known HCV genotypes, types 2 and 3 are more responsive than types 1 or 4, with SVR rates of 80% vs 45%, respectively. SE are common: for interferon alfa, see \square p. 683); ribavirin: haemolysis and anaemia.

KDIGO guidelines for HCV treatment in CKD

- CKD stage 1–2: peginterferon alfa and ribavirin.
- CKD stages 3–4: peginterferon alfa monotherapy.
- Haemodialysis: standard interferon alfa.
- Ribavirin (\pm ESA support) may be considered for all stages in specialized centres.
- See $\text{\textcircled{R}}$ <http://kdigo.org/home/guidelines/>.

Additional treatments

Adjunctive therapy should be considered for severe active disease (e.g. rapidly progressive GN, severe neuropathy, widespread cutaneous vasculitis with ulceration). Antivirals will not deal with the circulating cryoglobulins already formed (PEX), and there may be an urgent need to target B cell production (rituximab) and attenuate tissue injury (steroids). Commencement of antivirals may need to be delayed until these goals have been achieved.

Options

- Plasma exchange $\times 3$ /week for 2–3 weeks to remove cryoglobulins.
- Rituximab $375\text{mg}/\text{m}^2$ weekly for 4 weeks to stop further B cell production (also an option if intolerant/resistant to interferon alfa/ribavirin).
- Corticosteroids as methylprednisolone $0.5\text{--}1\text{g}/\text{day}$ for 3 consecutive days, then oral.
- Cyclophosphamide $1.5\text{--}2.0\text{mg}/\text{kg}$ daily orally for 2–4 months.
- Two novel direct-acting antivirals—boceprevir and telaprevir—have recently been licensed for use in combination with PEG-IFN- α and ribavirin to increase the viral response in genotype 1 HCV infection. Use currently limited to patients with normal renal function.
- Low-dose IL-2 is another potential future treatment. Patients with HCV-induced vasculitis have reduced regulatory T cells (Tregs) function. IL-2 promotes Treg survival. Additional studies awaited.

Other considerations

- ESA to maintain Hb $>110\text{g}/\text{L}$ (ribavirin causes red cell fragility). Anaemia can be very problematic.
- ACE-I/ARB to reduce proteinuria (aim uPCR $<50\text{mg}/\text{mmol}$).
- Aim BP $<130/80\text{mmHg}$ (esp. if proteinuria).
- Recommend alcohol avoidance.
- Avoid sharing potentially blood-contaminated items (toothbrushes, etc.). Protected intercourse.
- Screen for hepatocellular carcinoma (liver USS and serum α -fetoprotein) at 12-monthly intervals.

HCV and ESRD

Introduction

As a result of potential exposure to blood-contaminated equipment, haemodialysis patients are at risk of acquiring blood-borne viruses (BBV). The prevalence of HCV infection in HD patients varies widely (5–60%), influenced by factors, such as regional HCV prevalence, infection control techniques, and historical blood transfusion screening.

Standard universal precautions should always be undertaken, but HCV-infected patients do not require isolation on haemodialysis (unlike HBV) or to be dialysed on dedicated machines, as there is no convincing evidence that this affects transmission rates (although the European Best Practice Work Group have suggested it should be considered in centres with high HCV prevalence). ALT should be checked 6-monthly, with annual screening for hepatocellular carcinoma (USS and serum α -fetoprotein).

Hepatitis C-infected patients and transplantation

Renal transplantation may offer selected HCV+ ESRD patients superior survival and quality of life, compared to maintenance HD or CAPD.

It is important to assess the degree of liver damage (usually with a liver biopsy), and those patients with advanced disease, e.g. cirrhosis or portal hypertension, should be considered for combined liver–kidney transplantation (single renal transplantation is contraindicated).

Patients with active HCV will require antiviral therapy prior to transplantation, although treatment in CKD and dialysis patients is associated with low sustained virologic response rates (~20%) and significant drug intolerance (~30–50% of dialysis patients stop treatment). Δ IFN- α treatment post-transplant is strongly associated with acute rejection (~50%).

Post-transplantation, HCV+ transplant recipients have inferior short- and long-term outcomes, compared to HCV- patients. There is a significant increase in early (first 6 months) infection-related deaths. Patient survival at 3 years is ~70%. 10–20% progress to cirrhosis within ~5 years.

The incidence of new-onset diabetes post-transplant (NODAT) is higher in HCV+ recipients.

HCV-related glomerular disease can recur/occur post-transplantation and is extremely difficult to treat (see Table 8.11).

HCV-positive kidney donors

● Rejecting organs from all HCV seropositive (potential) deceased donors will mean discarding organs from many who do not actually have active viral replication at the time.

Limited experience suggests these kidneys may actually be acceptable for viraemic HCV+ recipients, although this risks superinfection with an HCV genotype from the donor that is different from the genotype of the recipient.

Table 8.11 Glomerular disease related to viral infection

Acute GN	
Parvovirus B19	MCGN ± endocapillary GN
Hepatitis A	Mesangial proliferative GN IgA type GN AKI
Dengue fever	Mesangial proliferative GN
Measles	
Yellow fever	
Epstein–Barr virus (EBV)	
Chronic GN	
Hepatitis B virus (📖 p. 682)	Membranous GN MCGN PAN Mesangial proliferative GN Minimal change disease IgAN
Hepatitis C virus (📖 p. 686)	MCGN ± cryoglobulinaemia Membranous GN Mesangial proliferative GN FSGS Fibrillary and immunotactoid GN Minimal change disease IgAN PAN
HIV (📖 p. 676)	HIVAN HIVICK Thrombotic microangiopathy
Parvovirus B19	Collapsing glomerulopathy FSGS

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The kidney in infective endocarditis

Introduction

Infective endocarditis (IE) is defined as infection of the endocardial surface of the heart. If left untreated, valvular insufficiency develops and is generally fatal. IE is mainly an infection of the left side of the heart, involving the mitral or aortic valve (or both). Right-sided endocarditis is often associated with IVDU, but other risk factors include pacemakers, other cardiac devices, and central venous catheters. Common causes include *S. aureus* in acute IE or viridans streptococci and coagulase-negative staphylococci in more chronic IE.

Renal dysfunction occurs due to a variety of mechanisms, including:

- Immune complex-mediated GN.
- Aminoglycoside-induced AKI.
- Drug-induced AIN.
- Emboli (from infected valves).
- Renal abscess formation.

Epidemiology

In the era of effective antibiotic therapy for IE, the incidence of renal complications has been variably reported (ranging from 2 to 60%). The severity of IE-associated GN is related to the duration of infection prior to the institution of antibiotics. Control of infection usually leads to rapid resolution, with recovery of renal function. However, irreversible renal damage may occur if appropriate therapy is delayed. Mortality is higher in those who develop renal disease.

Symptoms and signs

The manifestations of IE are not always classical—and they are often very similar to those found in many other systemic diseases.

- ► Suspect IE if fever, new murmur, splenomegaly, and haematuria (especially if known to have a valvular abnormality or prosthesis).
- Careful examination may reveal splinter haemorrhages (fingers and/or toes), although classical stigmata of IE are often absent.
- Microscopic haematuria points towards GN. A bland urinalysis is unusual—suggesting an alternative diagnosis, e.g. aminoglycoside toxicity.
- Rash, eosinophilia, and a new fever after starting antibiotics may indicate AIN.
- Acute (unilateral) flank pain and frank haematuria suggest emboli. This should prompt a search for evidence of emboli in other organs (check extremities). Infarction at the site of embolization is common; abscess formation is rare. Cerebral emboli occur in ~33% of patients. Emboli may occur after microbiological ‘cure’.

Investigations

- Repeated blood cultures (and sensitivity testing) are the key to management.
- Use CRP to monitor treatment response.
- Echocardiography: transthoracic echo (TTE), but transoesophageal echo (TOE) has superior sensitivity.
- Daily ECG if suspected aortic root abscess.

- Urinalysis + microscopy.
 - Microscopic haematuria ± proteinuria, ? GN.
 - Sterile pyuria or eosinophiluria, ? AIN.
- FBC: anaemia common. If eosinophilia, ? AIN.
- SCr, U&E, albumin.
- Diligent therapeutic monitoring of aminoglycosides if used (📖 pp. 880–1).
- Complement components: C3, C4 (often low) (📖 p. 41).
- RhF and cryoglobulins in ~50% (type III).
- Renal USS. CT or DMSA if emboli suspected (focal perfusions defects).
- Renal biopsy if diagnosis unclear or response to therapy suboptimal.

Pathogenesis

S. aureus IE: staphylococcal enterotoxins are ‘superantigens’ that bind directly to MHC class molecules of antigen-presenting cells and the specific V β chain of the T cell receptor (TCR), causing T cell activation and T cell-derived cytokine release (e.g. IL-1, IL-2, IL-6, TNF, and IFN- γ). Cytokines cause polyclonal B cell activation and immune complex formation, resulting in GN.

Histology

Table 8.12 shows the different histological patterns of renal disease associated with IE. Immune complex-driven GN has a spectrum of presentation from mild focal proliferative glomerulonephritis (\rightarrow urinary abnormalities) to diffuse crescentic necrotizing glomerulonephritis (\rightarrow AKI). It may be similar to post-streptococcal GN (📖 p. 548) or MCGN (📖 p. 550), with hypercellularity (due, in part, to the influx of circulating inflammatory cells) and immune deposits in the glomerular capillary wall.

Fibrinous thromboemboli within arteries, with inflammation of the adjacent renal tissue, may also occur as a consequence of septic emboli—renal abscesses can form at these sites. Thrombotic microangiopathy with cortical necrosis can complicate severe sepsis. Acute tubular injury is a consequence of haemodynamic compromise (as well as nephrotoxic drugs (aminoglycosides or others)).

Treatment

- If GN, cure IE, using appropriate antibiotics. There is no role for adjunctive treatments, even if crescentic change on biopsy.
- If ATN, tailor aminoglycoside doses to levels or change antibiotic.
- If AIN, change antibiotic. No role for steroids.
- Valve surgery may be required.

MRSA glomerulonephritis

MRSA glomerulonephritis presents either as rapidly progressive glomerulonephritis (RPGN) and/or as nephrotic syndrome with various degrees of proteinuria, usually in the context of a severe MRSA infection. Normal complement levels and polyclonal elevation of serum IgG and IgA are often seen. Histological changes are described in Table 8.12.

Table 8.12 Clinicopathological features of renal disease associated with infective endocarditis


	Urinalysis	Complement	Immunoglobulins	Histology	Outcome
Immune-complex GN	Red cell casts	↓	↑IgG, IgA, IgM	Focal or diffuse glomerulonephritis May be crescents	Improves with antibiotics
Acute tubular injury	Granular casts Epithelial cell casts	↔	↔	See  p. 107	Improves with supportive care
Acute interstitial nephritis (AIN)	Eosinophiluria	↔	↑IgG, IgA, IgM	Tubulointerstitial infiltration	Worsens with antibiotics
MRSA glomerulonephritis	Nephrotic range proteinuria	↔	↑IgG, IgA	Mesangial/endocapillary proliferative glomerulonephritis ± tubulointerstitial nephritis as part of the disorder	Improves with antibiotics
Embolic renal infarction	Haematuria	↔	↔	Arterial fibrinous thromboemboli	Variable

Table 8.13 Bacterial infection-related glomerular disease***Mycobacterium leprae***

Amyloidosis (AA):

- Glomerulonephritis
- Diffuse proliferative GN
- Focal proliferative GN
- MCGN
- Mesangial proliferative GN

Mycobacterium tuberculosis

Amyloidosis (AA)

MCGN type II

Treponema pallidum

Congenital syphilis:

- Membranous nephropathy

Acquired syphilis:

- Membranous nephropathy
- Diffuse endocapillary GN
- MCGN
- Mesangial proliferative GN
- Amyloidosis (AA)

Salmonella typhi

Mesangial proliferative GN

IgA nephropathy

Streptococcus pneumoniae

Mesangial proliferative GN

Diffuse proliferative GN

Others reported in association with GN*Brucella melitensis**E. coli**Klebsiella pneumoniae**Yersinia enterocolitica**Mycoplasma pneumoniae**Legionella**Bartonella henselae*

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Renal tuberculosis

Introduction

Tuberculosis is caused by *Mycobacterium tuberculosis* and affects 8–10 million people every year, usually presenting as pulmonary disease. The global burden of TB has risen sharply as a result of HIV infection and the increased number of patients with solid organ transplants taking long-term immunosuppressive medication. Δ Data from the World Health Organization (2010) suggests that one-third of the world population has been exposed to TB and has at least latent disease.

After lymph node involvement, the most common site of extrapulmonary TB is the genitourinary system (15–30% all cases). Renal dysfunction can occur through a variety of mechanisms, including direct infection of the kidney or lower urinary tract, obstructive uropathy, tubulointerstitial nephritis, and secondary amyloidosis.

Genitourinary TB (GUTB)

Pathogenesis

Mycobacterium tuberculosis bacilli are inhaled into the alveoli. Initially, the bacilli are locally contained by leucocytes and macrophages, but, over time, they are carried to regional lymph nodes and the thoracic duct before delivery into venous blood and seeding of distant organs.

In the kidneys, multiple granuloma form at the site of metastatic foci. These are typically bilateral, cortical, and adjacent to the glomeruli. They can remain inactive for decades. Active granulomas may grow to invade the calyceal systems, resulting in the spread of bacilli to the renal pelvis, ureters, bladder, and other genitourinary organs, including the epididymis and prostate.

The renal medulla is preferentially affected, but subsequent papillary and pelvic involvement causes progressive scarring, calcification, fibrosis, and chronic abscess formation. Extensive lesions will result in ESRD.


Ureteral TB may cause strictures (can be extensive), hydronephrosis, and obstruction. Often unilateral.

Symptoms and signs

Classical TB symptoms, e.g. fever, weight loss, and night sweats, are uncommon. Pulmonary symptoms may be absent (although ~30% will have an abnormal CXR). Symptoms are often non-specific, with >25% asymptomatic. It is \therefore essential to maintain a high index of suspicion in those at risk.

Abdominal (particularly back and flank) pain, LUTS, recurrent UTIs that are poorly antibiotic-responsive, macro- and microscopic haematuria, incontinence (bladder fibrosis), infertility in both sexes.

Investigation

- Sterile pyuria (WCC on microscopy but negative culture) is characteristic ( p. 24).
- Three consecutive early morning urine samples (EMUs).
 - Microscopy for acid-fast bacilli on centrifuged urine (Ziehl–Neelsen stain) and culture on Löwenstein–Jensen media (takes 2–6 weeks).

- EMUs for AFBs have a sensitivity of only 65% (although specificity is ~100%).
- More rapid results (<1 week) with a radiometric culture system (BACTEC).
- PCR for mycobacterial DNA can be helpful when available. It is a rapid test with high sensitivity and specificity.
- U&E (\downarrow Na^+ 2° to SIADH), SCr, LFTs, CRP, FBC, ESR.
- ► Consider HIV testing.
- Tuberculin skin testing is usually undertaken; however, beware false positives in those patient vaccinated with BCG and false negatives in those on immune suppression.
- Plain KUB may show calcification.
- IVU or CT-IVU: abnormal (70–90%), with calyceal tip erosions ('moth-eaten' calyx), pelvic distortion (e.g. the 'hiked-up' appearance), strictures, filling defects, and calcification.
- Renal tract USS if obstruction suspected.

Renal tuberculosis: TB-TIN and TB in patients with ESRD

Tuberculous interstitial nephritis (TB-TIN)

Pathogenesis

A presumed immune-mediated process. TB causes a parenchymal reaction characterized by giant cells, tubulointerstitial inflammation, and caseating granuloma formation. TB-TIN is a more insidious and less well-recognized form of renal involvement but is thought to be an underestimated worldwide cause of renal failure (e.g. in Asian patients presenting with advanced CKD and small kidneys on imaging).

Symptoms and signs

Usually presents as CKD in at-risk populations (esp. South Asians). Urinalysis is bland. USS shows normal or decreased renal sizes, usually with a smooth contour. EMU for AFBs are usually negative. CXR may demonstrate prior or active pulmonary TB. Skin tuberculin testing is often positive. Diagnosis made on renal biopsy, although this may not be undertaken if kidneys are small at presentation. *Mycobacterium tuberculosis* can be identified on tissue stain or paraffin-embedded samples, although detection rates are often low. Luciferase and fluorescence technique improve sensitivity and can detect low numbers of mycobacteria.

Management

Anti-TB treatment is associated with improved renal function, and recovery from even advanced CKD has been reported. Cure requires combination therapy for 6 months. Compliance may be problematic and should be reinforced through good patient education. The sensitivities of cultured *M. tuberculosis* should be confirmed, but this should not delay initiation of treatment once the diagnosis has been secured.

- ▶ Check local protocols for drug selection and dosing.
- ▶ A dose adjustment is required for most agents if ↓ GFR.

Initial phase (2 months)


Once-daily rifampicin, isoniazid, pyrazinamide (available in combination preparations, e.g. Rifater[®]). Add-on ethambutol or streptomycin if immunocompromised or previously treated for TB (Δ isoniazid resistance).

Continuation phase (further 4 months)

Rifampicin and isoniazid.

Notes

- Add pyridoxine 10–20mg daily (prevents the peripheral neuropathy associated with isoniazid).
- Check LFT before and 3-weekly during initial phase.
- Check visual acuity if using ethambutol (risk of irreversible optic neuropathy).
- If HIV-positive, prolonged multidrug treatment may be necessary.

-  Corticosteroids, e.g. prednisolone 0.5mg/kg for 2 months and weaned thereafter. This is poorly evidence-based. Theory: granulomatous inflammation heals by fibrosis so reduce inflammation to prevent secondary scarring. Generally reserved for those with severe ± rapidly progressive CKD.

TB in patients with ESRD

- Dialysis patients have a significantly increased (6–25-fold) risk of TB.
- ESRD is considered a state of relative immune compromise, mainly 2° to disruption of cell-mediated immune (CMI) responses. CMI response is primarily mediated by T cells, whose functions include the identification and killing of intracellular pathogens, such as *M. tuberculosis*.
- Nosocomial transmission of TB in dialysis units has also been reported.
- Risk factors include: older age, Asian race, smoking, malnutrition, and anaemia.
- The diagnosis in this population is difficult because disease is often non-pulmonary and symptoms may be non-specific.

Diagnosis

- Tuberculin skin test consists of intradermal injection of tuberculin. In positive cases, a T cell-mediated delayed type hypersensitivity reaction causes a variable degree of induration within 48–72 hours. However, a high prevalence of anergy in dialysis patients means that response rates are poor, so false positives are common.
- Interferon gamma release assays (IGRAs) appear more sensitive and specific in this population.
 - T cells from patients exposed to TB become sensitized to two proteins termed ESAT-6 and CFP-10. When these T cells are exposed to these antigens in the assay, they produce IFN- γ , and the strength of this response can be quantified.
 - Note: IGRAs do not distinguish between latent and active disease.
 - Examples include the T-SPOT TB test[®] and the QuantiFERON-TB Gold In-Tube[®] test (QFT-GIT).
- IGRAs have now been included in the guidelines for the detection of latent TB infection in many countries, including the USA and UK.

Schistosomiasis

Introduction

Schistosomal infestation (a water-borne trematode) affects as many as 200 million people worldwide and may lead to urinary tract disease or glomerulonephritis. *S. haematobium* is endemic in most of Africa and the Middle East. It preferentially migrates to the venous plexus surrounding the bladder, causing lower urinary tract disease. *S. mansoni* (additionally found in Latin America) and *S. japonicum* (found in Asia alone) migrate to the mesenteric vessels or portal tree, causing hepatosplenic disease

Pathogenesis

Acute infestation tends to occur in childhood in residents of endemic areas but can affect travellers of any age. It is characterized by dermal invasion ('swimmer's itch') and a subsequent systemic serum sickness-like syndrome ('Katayama fever') with eventual maturation of a trematode in blood vessels. Eggs released from mature worms cause delayed type hypersensitivity and granulomatous inflammation in local tissues.

Urinary schistosomiasis

Caused by *S. haematobium* infestation. Presents with terminal haematuria (frank blood at the end of micturition), dysuria, and frequency as a result of an inflammatory cystitis. A quiescent, asymptomatic period follows that can last for decades. Late schistosomiasis occurs in 10–40% and may lead to progressive bladder fibrosis and detrusor failure. Ureteric stricture formation with obstruction is common (~10%). Complications: recurrent bacterial infection, bladder calculi, CKD (and ESRD) 2° to obstructive nephropathy, and an increased risk of bladder cancer.

Investigations

- Typical live ova on urine microscopy (centrifuge sample to improve yield).
- FBC (eosinophilia), U&E, SCr, eGFR, LFTS.
- Serology: anti-schistosomal antibodies may be positive 4–8 weeks after exposure. They will not differentiate between past and active disease. However, a positive test in an individual who does not live in an endemic area can be helpful.
- PCR for schistosome DNA is highly sensitive and specific on stool and urine samples, if available.
- Plain KUB may demonstrate calcification.
- USS to exclude obstruction—treatment will often improve anatomical abnormalities in schistosomiasis, unlike GUTB (📖 p. 696).
- Cystoscopy may show a nodular or polypoid lesions ± ulcerating haemorrhagic cystitis.

Schistosomal glomerulonephritis

Complicates hepatosplenic disease in ~10% patients with *S. mansoni* (less common with other species). Although the worms have developed strategies to evade immune recognition, if these are incomplete, an antibody response may result in circulating immune complex formation. These

become trapped in glomeruli (esp. if liver fibrosis has caused poor immune complex clearance), causing inflammation and glomerulonephritis.

Presents as proteinuria (often nephrotic range), haematuria, and impaired renal function. Several histological variants are recognized on kidney biopsy, including mesangioproliferative, MCGN-like, and FSGS. Co-infection with *Salmonella* may lead to a diffuse proliferative lesion (presents as the acute nephritic syndrome). Cryoglobulinaemia (usually concomitant hep C) and secondary AA amyloidosis are also possibilities.

Treatment

African Association of Nephrology (AFRAN) classification (classes I–V):

- Classes I and II respond to anti-helminthic therapy.
- Classes III–V progress to ESRD in spite of therapy (75% progress to advanced CKD or RRT over 4–6 years).
- Praziquantel 40mg/kg PO stat (80–90% cure rate).
- If *S. japonicum*, ↑ dose to 60mg/kg in two divided doses.
- There may be some resolution of urinary tract lesions in urinary schistosomiasis (esp. if little fibrosis). However, strictures may require urological intervention.
- Schistosomal glomerulonephritis responds poorly.

Malaria

Introduction

Malaria is caused by *Plasmodium* parasites transmitted via *Anopheles* mosquitoes. It is endemic in many parts of the world, affecting 300–500 million people annually and causing 1–3 million deaths/year. Previously only *P. falciparum* and *P. malariae* were associated with renal disease, but AKI and glomerulopathy are now recognized with *P. vivax*.

AKI due to malaria can occur as part of multi-organ failure or as an isolated complication. The causes of AKI in malaria are complex and multiple. Histological findings include ATN (most frequent), interstitial nephritis, and a proliferative glomerulonephritis.

Glomerulopathy 2° to malaria is most common in childhood and adolescence, with glomerular lesions found post-mortem in ~20% of patients with falciparum malaria.

AKI 2° to malaria

AKI complicates *P. falciparum* malaria in 1–4% cases but is more common in non-immune travellers (~25%). If severe, >50% will require renal support, and mortality is ~10% (partly due to non-availability of RRT). Although *P. vivax* is usually considered a benign parasite with a low mortality rate, it can rarely cause severe disease with AKI.

Pathogenesis

Proposed mechanisms include immune-mediated glomerular injury, hyperbilirubinaemia (→ ATN), alterations in the renal and systemic haemodynamics, cytoadherence of infected RBCs (→ capillary obstruction), mononuclear cell infiltration (→ inflammatory cytokine release), and increased release of both reactive oxygen species and nitric oxide.

In addition, dehydration, haemolysis (→ haemoglobinuria), DIC, and rhabdomyolysis may all contribute.

Signs and symptoms

Nausea, vomiting, diarrhoea, malaise, headache, confusion, fevers, myalgia, jaundice (~75%), and haemoglobinuria (blackwater fever). ↓ BP, peripheral vasodilatation, anaemia, and hepatosplenomegaly.

Investigations

Urinalysis and uPCR (proteinuria usually <1g/24h). FBC (haemolytic anaemia), ↓ Plt (70%). Thick and thin blood film for parasitaemia (usually >5%). Haptoglobins. DIC (APTT, INR, D-dimers). U&E (↓ Na⁺ in >50%), SCr, CK, LFTs (hepatitis in ~20%), and serum lactate (acidosis common).

Management

- Manage patients with AKI in high dependency environment.
- RRT may need early initiation, as patients are highly catabolic. In addition, ↑ K⁺ can be severe (2° to haemolysis, rhabdomyolysis, and acidosis).
- Supportive blood products, as required.
- Culture blood, and consider empirical broad-spectrum antibiotics (bacterial superinfection is not uncommon).

- IV quinine loading dose as 20mg/kg (max 1.4g) over 4h, then 10mg/kg (max 700mg) IV over 4h qds for 7 days, with cardiac monitoring.
- Artemisinin derivatives clear parasitaemia more rapidly, act against more stages of the parasitic life cycle, and reduce mortality, in comparison to quinine, but are not widely available. Artesunate 2.4mg/kg IV first dose, followed by 2.4mg/kg at 12 and 24h, followed by 2.4mg/kg once daily for 3 days, then oral therapy, as necessary.
- Doxycycline may be added.
- If the patient has G6PD deficiency, seek expert help.
- ☞ The role of exchange transfusion is controversial and reserved for high-burden parasitaemia. Potential benefits are quicker reduction of parasitaemia and a decreased risk of severe intravascular haemolysis. The Centers for Disease Control (CDC) suggests it should be considered if parasite density is >10%, with evidence of end-organ complications.

Glomerular involvement in malaria

Transient nephrotic and nephritic illnesses may be seen during infection with *P. falciparum* and *P. vivax*. These glomerulopathies are reversible—usually resolving within 2–6 weeks of treatment. The histological lesion is typically mesangial hypercellularity with mesangial and subendothelial deposition of IgG, IgM, and C3. Serum complement components may be reduced 2° to immune complex formation.

Chronic malarial nephropathy (or quartan malarial nephropathy) is a different entity. It is the most common form of secondary glomerular disease in the tropics, causing nephrotic syndrome, mainly in children and adolescents. It is usually associated with *P. malariae*, occasionally *P. vivax*. The histological lesion is an MCGN-type pattern of injury, with subendothelial immune complex deposits containing IgG, C3, and (rarely) malarial antigens. Pathogenesis, particularly the role of the malarial parasite, is still a matter of significant debate.

The renal prognosis is poor. The nephrotic syndrome is steroid-resistant and generally does not improve with successful eradication of the malarial infection. Progression to ESRD occurs within 5 years.

Essential urology

- Urinary tract infection: introduction 706
- Urinary tract infection: investigations and treatment 708
- Urinary tract infection: miscellaneous 710
- Reflux nephropathy 712
- Congenital abnormalities of the kidney and urinary tract 714
- Nephrolithiasis 716
- Stone disease: evaluation 720
- Stone disease: management 722
- Acute renal colic 724
- Obstruction: overview 726
- Obstruction: pathophysiology 728
- How to approach obstruction 730
- Obstruction: imaging 732
- Obstruction: treatment 734
- Pelvi-ureteric (PUJ) obstruction 736
- Retroperitoneal fibrosis: overview 738
- Retroperitoneal fibrosis: management 740
- Investigation of a renal mass 742
- Renal cell carcinoma: general 744
- Renal cell carcinoma: diagnosis 746
- Renal carcinoma: management and follow-up 748
- Tumours of the bladder: overview 750
- Tumours of the bladder: pathology and management 752
- Tumours of the renal pelvis and ureter 756
- Benign prostatic enlargement: general 758
- Benign prostatic enlargement: investigation and management 760
- Prostate cancer: general 766
- Prostate cancer: investigation 768
- Prostate cancer: screening 772
- Prostate cancer: management 774

Urinary tract infection: introduction

Introduction

The incidence of UTI (including infections of the bladder and kidneys) is ~50,000 pmp, making it, by far, the most common disorder of the renal tract. 50% of ♀ will experience UTI in their lifetime, predominantly cystitis (usually occurring in a normal urinary tract). ~10% of post-menopausal ♀ and ~0.5% of younger sexually active ♀ will have a UTI each year.

A second infection is common in women who have had one UTI, but only 3–5% will develop recurrent UTIs (📖 p. 710). In men and children, UTI is rare and almost always associated with urinary tract abnormalities that require further investigation (📖 p. 708). Although serious morbidity from UTI is usually low, renal scarring can result from sporadic or recurrent infections. Bacteraemia from a UTI can be a life-threatening medical emergency. UTI in pregnancy is discussed on 📖 p. 842.

Definitions

Asymptomatic bacteriuria is the isolation of a significant bacterial count in an asymptomatic patient (📖 p. 710). *Uncomplicated UTI* is a symptomatic bladder infection (cystitis) in a ♀ with a normal urinary tract. *Complicated UTI* is a symptomatic infection of any part of the urinary tract in a ♀ with a functional or structural urinary abnormality. *Re-infection* is a recurrent UTI with the same or different organism, following clearance of the original UTI. *Relapse* refers to a recurrent UTI with the same organism that has not been adequately cleared.

Pathogenesis

In ♀, the pathogens responsible for UTI are found in the colonic flora. Subsequent UTI is usually ascending, i.e. after perivaginal, perineal, and transurethral colonization, often triggered by intercourse. Lactobacilli, found as commensals in the vagina, prevent urinary pathogens from colonizing the perineum—changes in the vaginal pH, use of spermicides, or antibiotic treatment may lead to failure of this defense mechanism.

Host factors predisposing to UTI

- Female sex.
- Sexual intercourse.
- Use of spermicides.
- Urinary stasis or incomplete bladder emptying.
- Comorbidities, esp. diabetes mellitus.
- Institutionalized patient.
- ↑ Age (→↓ oestrogen + vaginal pH).
- Eradication of vaginal commensal organisms (see 'Pathogenesis').
- Urinary tract stones.
- Urinary catheter.
- Highly concentrated urine (>800mOsmol/kg) or failed urinary acidification (pH >5).
- Non-secretion of certain blood group antigens (allows bacteria with specific adhesins to recognize urothelial cells).

Some women express an inherited and unique receptor on the urothelium that aids the binding of *E. coli*. Also, *E. coli* that expresses type P fimbriae (pili), an adhesin that promotes bacterial attachment to the urothelium, is particularly likely to cause pyelonephritis. There are many other factors that have been suggested to contribute to bacterial virulence.

Bacteriology

Uncomplicated UTI

- *Escherichia coli* (70–90%).
- Coagulase-negative staphylococci (*S. saprophyticus*) (5–20%).
- *Klebsiella* spp. (1–2%).
- Enterococci (1–2%).
- *Proteus mirabilis* (1–2%).
- *Citrobacter* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, group B streptococci (all <1% each).

Complicated UTI

- *E. coli* remains the most common, but *Proteus*, *Klebsiella*, *Citrobacter* spp., enterococci, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and group B streptococci account for a higher proportion.

Symptoms and signs

Cystitis or lower UTI

Dysuria, frequency, urgency, nocturia, suprapubic pain, or tenderness. Offensive urine or frank haematuria. Ask about previous episodes of UTI, recent antibiotic use, pre-existing LUTS (📖 p.78), and, sensitively, about new sexual partners and spermicidal use. Vaginal irritation ± discharge makes UTI less likely (vaginitis more so). ► In the elderly, UTI may present as confusion ± incontinence.

Pyelonephritis or upper UTI

Fever, chills, night sweats, rigors. Nausea, vomiting. Loin pain, costovertebral (renal) angle tenderness. May be systemically unwell, with progression to SIRS and shock a possibility.



► In immunocompromised (and children), all of the listed symptoms/signs may be absent—so maintain a high index of suspicion, esp. if unexplained fever.

Diagnosis



- A pure growth of a urinary pathogen:
 - $\geq 10^5$ cfu/mL urine remains the standard.
- However, at this cut-off, 30–50% of UTI will escape diagnosis. So, in addition, consider:
 - $\geq 10^{2-5}$ cfu/mL: in young women with suspected uncomplicated cystitis, children, ♂, or if pyelonephritis possible.
 - Bacteriuria $\geq 10^2$ cfu/mL associated with significant pyuria (± symptoms) is usually significant.
- Bacteriuria in the absence of pyuria almost always represents contamination.

Urinary tract infection: investigations and treatment

Investigations

- Dipstick urine: positive leucocyte esterase \pm nitrite reductase. Positive predictive value of $\sim 66\%$ and a negative predictive value of $\sim 90\%$. May be modest haematuria or proteinuria. *In low-risk cases, no further investigation is needed if positive dipstick with characteristic symptoms.*
- Clean-catch MSU for microscopy at $\times 40$ magnification (i.e. high-powered field), pyuria ($>10^4$ WCC per mL urine) \pm organisms (see  p. 707). WCC casts strongly suggest pyelonephritis.
- Culture: sample should be cultured within 2h of sampling. If not possible, store at 4° (for <48 h). Repeat urine culture to confirm eradication post-treatment is not recommended.
- A pregnancy test should be undertaken if appropriate.
- If suspected pyelonephritis: \uparrow WCC, \uparrow CRP, SCr, U&E.
- Imaging is only required in *complicated* cases, e.g. fever persists >48 h despite therapy, clinical deterioration, poorly controlled diabetes, immune compromised, systemic sepsis, recurrent episodes, stone former.
 - CT with contrast has become the investigation of choice and has superseded IVU. Stones should be excluded on the non-contrast images. CT will identify changes on renal parenchymal perfusion, obstruction, perinephric collections or fluid, and abscesses.
 - USS is also useful and preferred by many clinicians as an initial investigation, as it does not involve radiation or contrast, and it will exclude obstruction with hydronephrosis. However, a negative USS does not exclude pyelonephritis, and ureteric abnormalities will be missed. Pre- and post-micturition images of the bladder to exclude incomplete bladder emptying should be performed.
 - ^{99m}Tc -DMSA findings are non-specific, but it has a role in children.
- In ♂ , assess the prostate size and bladder emptying with *urodynamic flow studies* ( p. 760).
- Cystoscopy may be indicated in those at risk for bladder or prostate cancer, as well as those with evidence of impaired bladder emptying who may benefit from urethral dilatation.

Who needs closer attention?

- Symptoms >14 days.
- Recurrent UTI.
- ♂ .
- Children.
- Pregnant ♀ ( p. 842).
- Diabetic patients.
- The immune compromised (for renal transplant patients, see  p. 438).
- Proteus UTI—? associated stones.
- Known abnormal urinary tract.
- Stones.
- Indwelling catheter or ureteric stent.

Treatment

Antibiotic selection and duration of therapy varies widely. Prescribing choice should always be informed by local antimicrobial resistance patterns. In general, broad-spectrum agents, such as co-amoxiclav, quinolones, and cephalosporins, should be avoided, as they increase the risk of antibiotic resistance (as well as *Clostridium difficile*).

Uncomplicated lower UTI (cystitis)

For empirical therapy:

- *Either*: short-course (3 days) therapy:
 - Trimethoprim 200mg bd (or co-trimoxazole 960mg bd).
- *Or*: longer-course (7–10 days) therapy:
 - Nitrofurantoin 100mg bd (not in renal impairment).
- If second-line treatment is necessary, e.g. hypersensitivity reaction, side effects, failure of first-line treatment, then urine culture with sensitivity testing is recommended.
- Options:
 - Fluoroquinolones, such as ciprofloxacin 500mg bd or levofloxacin 250mg od.
 - Oral cephalosporins often offer a useful alternative.
 - Fosfomycin 3g single dose.
- Ampicillin/amoxicillin are less effective at eradicating vaginal and peri-urethral colonization.
- Encourage high fluid intake, e.g. >2L/day.

Complicated lower UTI

- ► At-risk patients: ♂, recent urinary tract instrumentation, recent antibiotics, diabetes mellitus, immunosuppressed, obstruction, structural abnormalities, functional abnormality (e.g. neurogenic bladder, reflux), foreign body, renal failure.
 - Empirical therapy should be started immediately (e.g. fluoroquinolones for 7–10 days), but antibiotic therapy should *always* be tailored against urine culture and sensitivity results.
 - Pregnant ♀ (📖 p. 842).
 - In the immunocompromised, consider additional single-dose aminoglycoside (e.g. gentamicin 3–5mg/kg IVI or IMI). For UTI in renal transplant recipients, see 📖 p. 438.

► Acute pyelonephritis

- Initial assessment will need to determine if treatment can be outpatient-based or whether admission is necessary (→ nausea and vomiting, systemically unwell).
- Suggestions (tailor against culture results):
 - Fluoroquinolones (e.g. ciprofloxacin 250–500mg bd PO) or levofloxacin 250mg od for 14 days.
 - Alternatives include co-amoxiclav IVI, then PO, or a third-generation cephalosporin IVI, then PO for 14 days.
 - Consider additional single-dose gentamicin 3–5mg/kg IVI.
- Rehydration with 0.9% NaCl.
- Appropriate analgesia and antiemetics.

Urinary tract infection: miscellaneous

Asymptomatic bacteriuria

- Common (1% in young ♀ vs ~20% in ♀ aged >80. Rare in ♂).
- Definition (♀): isolation of the same organism ($\geq 10^5$ cfu/mL) in two consecutive urine samples.
- Patient has no symptoms attributable to the urinary tract (by definition!).
- Associated with: sexual activity, diabetes, institutionalization, impaired urinary voiding, indwelling device (e.g. catheter or stent).
- ► Important in:
 - Pregnancy (📖 p. 842).
 - Those about to undergo urinary tract instrumentation (→ mucosal bleeding, overt UTI, and bacteraemia).
- These are the only two groups where screening is appropriate, and treatment is not advocated outside these circumstances.

Recurrent UTIs

Defined as >4 culture-proven UTIs in a year. A *recurrence* is not the same as a *relapse* (defined as return of symptoms with a culture of the same organism, following an initial UTI). Relapse can be treated with a prolonged (e.g. 2–4 weeks') course of antibiotics.

- Establish whether related to intercourse.
- Advise to increase fluid intake >2L/day, with frequent voiding.
- Double voiding *may* help bladder emptying.
- Spermicides or spermicide-coated condoms should be discouraged.
- Consider topical oestrogen creams (per vagina) in post-menopausal ♀.
- Cranberry juice: *in vitro* data confirm cranberry juice inhibits adherence of uropathogens to urothelial cells. Conflicting results in clinical studies (may be dependent on 'dose' and mode of administration (tablet vs drink)).
- 🍷 Probiotics: alter vaginal flora to inhibit colonization by uropathogens. Results from clinical trials to date have been disappointing.
- Consider investigations for an abnormal urinary tract: imaging (including bladder emptying), cystoscopy.
- For prophylaxis, see Box 9.1.

The following *do not* predispose to UTI: wiping patterns, voiding after intercourse, personal hygiene, showering, hot baths or saunas, tights or synthetic fabrics.

Catheter-related UTI

- Bacteriuria occurs in 3–10% of patients with an indwelling catheter/per day catheterized. There is no role for screening asymptomatic patients.
- Treatment is generally only required if significant local symptoms or systemic upset. If required, continue antimicrobials for a minimum of 7 days, and remove the catheter, if possible, as a surface biofilm will otherwise act as a reservoir of infection.
- Diagnosis: cultures positive for $>10^5$ cfu/mL *and* heavy pyuria (although pyuria is not always a reliable marker of infection in this context).
- Prevention is best: avoid catheterization or remove as soon as possible.

Box 9.1 Prophylaxis

Prophylactic antibiotics are an option if no remediable underlying cause is identified and can reduce recurrence rates by 95%. Ensure any current infection is successfully eradicated first. The optimum antibiotic regimen has not been established.

- If UTI related to sexual activity: trimethoprim 200mg, co-trimoxazole 480mg, or nitrofurantoin 50mg after intercourse.
- For others, offer nightly low-dose prophylaxis in a monthly rotation as: trimethoprim 100mg, then nitrofurantoin 50mg, then cefalexin 250mg. Alternatives include co-trimoxazole 480mg or amoxicillin 250mg.
- These may be adapted, according to previous culture results.
- Give prophylaxis for 1 year initially.
- Warn against the potential development of oral or vaginal candida and how this may be treated if it occurs.

Related disorders

► *Emphysematous pyelonephritis*

Caused by gas-forming *Enterobacteriaceae* and occurs predominantly in diabetic patients (90%). Presents as severe pyelonephritis. Gas usually visible on KUB or CT. Mortality is high (20–60%), but broad-spectrum antibiotics and urgent nephrectomy significantly improve outcomes.

Xanthogranulomatous pyelonephritis

A chronic unilateral pyelonephritis associated with renal calculi or obstruction and causing widespread parenchymal destruction. More common in diabetes mellitus. Presents as fever, nausea, anorexia, weight loss, flank pain, and systemic upset. The affected kidney is often palpable. Urinalysis and MSU for M,C+S confirm UTI (usually *Proteus* spp. or other Gram-negative organism). CT confirms diagnosis. Treat initially as for pyelonephritis. Relapse is common. A nephrectomy is often required. May be confused for renal cell carcinoma.

Acute bacterial prostatitis

Probably caused by reflux of infected urine into the prostatic ducts. Presents with symptoms of lower tract infection, associated with fever and, occasionally, with urethral obstruction. The prostate is swollen and tender on DRE. Urine culture will often demonstrate pyuria and bacteriuria. Treatment: fluoroquinolones (prolonged ≥ 4 weeks).

Interstitial cystitis

A sterile inflammatory cystitis, presenting in ♀ aged >40 (often with a prior history of recurrent UTI). Symptoms include frequency, dysuria, and (often disabling) suprapubic or pelvic pain. May be associated with sterile pyuria. Sensitivity to intravesical potassium solutions may help to confirm the diagnosis. Cystoscopy and bladder biopsy may show characteristic inflammation and ulceration. Treatment can be difficult. Tricyclic antidepressants can help with neuropathic pain. Oral (or intravesical) pentosan polysulfate sodium is efficacious in some cases.

Reflux nephropathy

Reflux nephropathy (RN) is a progressive lesion caused by repeated infections in the kidneys and almost always develops in childhood in the context of an abnormal urinary tract. The long-term renal scarring and CKD resulting from this early injury is called RN or *chronic pyelonephritis*. 5–12% of the ESRD population in the developed world is generally considered to have RN (although the diagnosis is often presumed in a patient presenting with scarred kidneys).

The main anatomical abnormality of the urinary tract is usually vesicoureteric reflux (VUR), but RN can also occur with incomplete bladder emptying or outflow obstruction.

The ureter inserts obliquely through the bladder wall, forming a compressible tunnel that acts as a one-way valve to prevent reflux of urine. A short or incompetent tunnel may allow reflux of urine into the ureters, as the bladder contracts during micturition. Superinfection is the norm. By late childhood, the bladder base thickens; the ureteric tunnel elongates, and free reflux generally no longer occurs.

Vesicoureteric reflux

- Genetically heterogeneous but:
 - Affects 0.1–1% of newborns.
 - Underlies 12–50% of children with a proven UTI.
- Is almost always present in children with proven renal scarring.
- It may be associated with renal dysplasia and hypoplasia (and ∴ childhood ↑ BP, CKD, and ESRD).
- Unilateral or bilateral (unilateral will not cause significant CKD).
- Ceases around puberty when anatomical changes mean that free reflux is no longer possible.
- Essentially a radiological diagnosis, classified grades I–V by severity (see Table 9.1).
- Surgical correction of incompetent valves offers no benefit over simple antibiotic prophylaxis and prompt treatment of UTIs in terms of long-term outcome.

Table 9.1 Classification of VUR

Grade I	Reflux into ureter, with no dilatation
Grade II	Reflux into ureter, pelvis, and calyces, with no dilatation
Grade III	Mild or moderate dilatation of the pelvis No, or only slight, blunting of the fornices
Grade IV	Moderate dilatation and/or tortuosity of the ureter and moderate dilatation of the pelvis and calyces. Complete obliteration of the sharp angles of the fornices but maintenance of the papillary impressions of most calyces
Grade V	Gross dilatation and tortuosity of the ureter, pelvis, and calyces Papillary impressions are no longer seen in the majority of calyces

RN: a new paradigm

More recently, however, the belief that reflux alone directly leads to renal scarring has been questioned. It is thought that VUR may simply be a marker of abnormal renal development, including renal dysplasia and hypoplasia. It is proposed that it is this abnormal renal development that predisposes to CKD. Evidence: renal lesions may be present antenatally in the absence of infection, and treatment of childhood VUR-associated UTIs often does not alter long-term renal outcomes.

RN may \therefore be better thought of as the sequelae of a developmental abnormality (renal hypoplasia or dysplasia), with associated VUR.

Clinical presentation

- In children, all UTIs should be subsequently evaluated for RN.
- In adulthood, the presentation is usually with unexplained CKD. \uparrow BP (~50% of adults). Proteinuria is low grade (<1g/day) unless progressive CKD (2° FSGS).
- Adults with UTI and a NORMAL renal tract will not develop RN.
- Pregnant women with RN may develop UTIs, functional deterioration, or \uparrow BP \pm pre-eclampsia and should be referred for specialist care.

Investigations

- ^{99m}Tc -DMSA scintigraphy (DMSA is taken up in functioning renal tubules) will demonstrate renal scars as areas of reduced uptake.
- IVU: classically renal scarring (as parenchymal loss) and 'clubbed calyces'. Localized papillary scars do not take up contrast well, blunting the normal appearance of the renal calyx.
- In children, the gold standard for diagnosis of VUR is a micturating cystogram, although isotope cystography (which avoids a urinary catheter) is often preferred, particularly in older children (📖 p.54–6).

Pathology

Kidney biopsies are rarely undertaken, as kidneys are often small at presentation. Characteristic appearances are chronic tubulointerstitial scars, with dilated, atrophied tubules and often an inflammatory cell infiltrate. Secondary hyperfiltration injury develops over time, with compensatory hypertrophy of unaffected segments, vessel changes, and glomerular collapse and sclerosis.

Management (in adults)

Given that reflux has ceased and that there is no new scar formation in adulthood, treatment is aimed at preventing CKD progression.

- Treat \uparrow BP and proteinuria, with ACE-I or ARB as first line (target BP <130/80mmHg).
- Treat any new urine infections vigorously.

Congenital abnormalities of the kidney and urinary tract

Introduction

A group of well-recognized developmental anomalies that are now collectively referred to as congenital abnormalities of the kidney and urinary tract (CAKUT) (see Table 9.2). Variations of these disorders are identifiable in 1 in 500 antenatal USS, and they are responsible for ~30% of all fetal abnormalities. Prior to routine antenatal scanning, these conditions were diagnosed when symptoms developed in childhood and, occasionally, adult life. They account for the majority of CKD (and ESRD) in infants.

Various gene mutations have been described, including *SALL1*, *SIX1*, *HNF-1B*, and *PAX2*. The conditions appear polygenic, with variable penetrance.

Clinical evaluation

Thorough post-natal assessment, as for any congenital abnormality. This should include maternal drug use (prescribed or recreational), family history, and a comprehensive physical examination (targeted at important dysmorphic features, such as ear malformations, hearing loss, optic nerve colobomas, digital anomalies, and abnormal external genitalia).

Investigation

Suspected urinary tract abnormalities typically require a post-natal USS and micturating cystography. MAG3 renography or DMSA scanning will determine split function. Cystoscopy may be necessary. It is important to appreciate that several abnormalities may be present together (e.g. VUR in an ectopic kidney). Genetic testing may be possible for several CAKUT-associated syndromes, e.g. CHARGE (**C**olobomas, **H**ear defects, **A**tresia choanae, **R**etardation of growth and development, **G**enital abnormalities and hypogonadism, **E**ar abnormalities ± deafness).

Table 9.2 Important CAKUT disorders

Abnormality	Features
Renal agenesis	The ureteric bud fails to communicate with the metanephric blastema in 1st trimester. Often associated with other malformations, including VUR, and with genetic syndromes (e.g. Potter's syndrome → bilateral renal agenesis). Outcomes depend on these associations.
Renal ectopia	Failure of renal ascent during embryogenesis. The kidneys are usually abnormally shaped and often functionally impaired. ~60% are pelvic kidneys. Often associated with ureteric abnormalities.
Renal fusion	>90% are <i>horseshoe kidneys</i> where there is fusion of the lower poles by a narrow isthmus (usually comprises functioning renal tissue). The kidneys are sited more caudally than normal. Often missed on USS. Commoner in ♂ (although associated with Turner's syndrome in ♀).

Table 9.2 (Continued)

Abnormality	Features
	Usually asymptomatic but may be associated with haematuria, abdominal pain, abdominal mass, UTI, ↑ BP. Concomitant ureteric abnormalities often present (esp. PUJ and VUJ obstruction). Associated with nephrolithiasis and malignancy (TCC in adults, Wilm's tumour in children).
	<i>Crossed fusion ectopia</i> occurs when one kidney crosses the midline and lies in an abnormally rotated position. Associated with ureteric and cloacal abnormalities.
Duplication	The development of an accessory ureteric bud causes a duplex kidney and collecting system. May be complete or partial. If complete, there are two renal moieties with separate collecting systems and ureters. These may drain aberrantly, e.g. into the vagina or posterior urethra (→ reflux and obstruction). If incomplete, the ureters usually join along their length. Common ~1% normal population. Familial. Associated with chromosomal abnormalities, e.g. Turner's syndrome. Usually asymptomatic.
Multicystic dysplastic kidneys	Failure of the ureteric bud and renal mesenchyme to unite, resulting in a multiloculated mass, comprising thin-walled cysts with atresia of the proximal ureter. 2 ♂ > 1 ♀. The renal tissue is non-functioning. Renal dysplasia is the term used when there is some functioning tissue within an abnormal kidney, with the two conditions part of a spectrum of developmental abnormality. ► 90% are unilateral but may be associated with contralateral abnormalities, such as VUR in 25%. Usually involute during childhood (and ∴ labelled as a 'solitary kidney' in later life). No intervention is required unless recurrent UTIs, bleeding or suspected malignancy. Weak association with ↑ BP.
Polycystic kidneys	See ☐ p. 592.
Obstruction	Antenatal renal tract dilatation is present in 1 in 200 antenatal scans but will resolve spontaneously in 50%. See also posterior urethral valves, PUJ and VUJ obstruction (☐ p. 736).
Megaureter	Either primary (majority) or secondary to distal obstruction. ♂ > ♀. Left > right. 25% bilateral. ⚠ Urinary sepsis.
Ureterocele	Cystic dilatation of the terminal ureter. Intra- or extravesical (latter often more problematic, e.g. obstruction).
Prune belly syndrome (Eagle-Barrett or triad syndrome)	Triad: deficient or absent anterior abdominal wall musculature, bilateral cryptorchidism (empty scrotum), plus urinary tract abnormalities (esp. megacystis and megaureter). Abnormalities in other organ systems in 75%. 95% are ♂. Genetic basis has not been established. Causes 1–3% of ESRD. Also associated with renal dysplasia, VUR, PUJ/VUJ obstruction, abnormally thickened bladder, GI abnormalities (e.g. malrotation), congenital heart disease, and hip dysplasia.
Cloacal abnormality	Failure of development of the urorectal septum in ♀ leads to a single opening of urethra, vagina, and colon. Associated with obstruction which requires surgical correction.

Nephrolithiasis

Introduction

Urinary tract stones affect 8–15% of people (2 ♂: 1 ♀, typical age 20–60 years). The incidence is increasing in developed countries. After a single stone, the likelihood of a second within 7 years is ~50% (>75% after a second). However, preventative measures are highly effective in most cases.

Nephrolithiasis refers to stone formation within the renal tubules or collecting system, although calculi are also commonly found in the ureters and/or bladder. Diffuse parenchymal calcification with the kidney is termed nephrocalcinosis (📖 p.45). In the absence of nephrolithiasis, most patients with nephrocalcinosis are asymptomatic (and renal function correlates poorly with the degree of calcification visible on imaging).

Stone formation

Stone formation around a crystal nidus is encouraged when the solubility of a urinary salt is exceeded in certain situations (termed 'supersaturation'). These include high solute delivery, concentrated urine (low volume), areas of stasis (anatomically abnormal urinary tract), and an excess of stone promoters over inhibitors. Supersaturation is dependent on free ion state, rather than absolute concentration, so will be significantly influenced by the other constituents and characteristics of urine, such as pH. Aggregation of crystals into stones involves a process of epithelial cell anchoring within the renal tubules.

Stone composition

An important part of management is to identify stone constituents and any metabolic predisposition to formation. Stone composition varies, according to geography. In the Mediterranean, >70% are uric acid, whilst, in the UK and USA, the majority are calcium oxalate or calcium phosphate. Both environmental and genetic factors influence this distribution.

Stone composition and incidence (UK)

- Calcium oxalate/phosphate: 60–80% (often mixed stones—pure calcium phosphate stones are uncommon).
- Struvite (magnesium ammonium phosphate) 10–20%
- Uric acid 5–10%

Stone types

Calcium-based stones

- Most are *calcium oxalate*, either alone or in combination with *calcium phosphate* or *urate*.
- An associated metabolic abnormality (or other predisposing factor) can be identified in many patients with recurrent stones, although some are truly idiopathic.

- Risk factors (see Table 9.3):
 - Excessive excretion of calcium (hypercalciuria), oxalate (hyperoxaluria), or uric acid (hyperuricosuria). Uric acid crystals often form the nidus that progresses to a calcium-based stone.
 - Factors that cause insolubility, e.g. insufficient citrate excretion (hypocitraturia). Citrate forms a *soluble* complex with calcium.
 - Low-volume, or concentrated, urine.
 - Abnormal urinary tract, e.g. medullary sponge kidney.
 - Renal tubular acidosis (📖 p. 824).

Table 9.3 Important metabolic risk factors for stone formation

Hypercalciuria	Hyperoxaluria
Common. Secondary to either ↑ GI absorption or reduced renal reabsorption	Secondary to either ↑ dietary oxalate or enhanced oxalate uptake
With normal serum Ca ²⁺ :	High vitamin C intake
<i>Idiopathic hypercalciuria (this is a polygenic disorder, ♂ > ♀)</i>	Malabsorption disorders (fat malabsorption → ↑ colonic fatty acid delivery → ↑ oxalate absorption):
With ↑ serum Ca ²⁺ :	<i>Crohn's disease</i>
<i>Hyperparathyroidism</i>	<i>Coeliac disease</i>
<i>Granulomatous disease, e.g. sarcoid</i>	<i>Chronic pancreatitis</i>
<i>Immobilization</i>	<i>Jejuno-ileal bypass</i>
<i>Malignancy</i>	Primary hyperoxaluria*
<i>Hyperthyroidism</i>	
Hypocitraturia	Hyperuricosuria
Metabolic acidosis (↑ citrate absorption)	High dietary purine or protein intake
Hypokalaemia	Cellular breakdown:
Hypomagnesaemia	<i>Tumour lysis, haemolysis</i>
Diarrhoea	<i>Myeloproliferative disorders</i>
UTI	Gout
Exercise	Uricosuric drugs, e.g. loop diuretics
Ketosis-promoting diets	Inherited metabolic conditions (e.g. Lesch–Nyhan syndrome)

* An inherited enzyme defect associated with systemic calcium oxalate deposition from childhood (→ cardiomyopathy, bone marrow failure, CKD). Two distinct liver enzyme defects are described (types I and II). Type II (enzyme: glyoxylate reductase/hydroxypruvate reductase) tends to be a milder disorder than type I (enzyme: alanine-glyoxylate aminotransferase).

Uric acid stones

Hyperuricosuria is most commonly associated with the formation of calcium oxalate stones! Pure uric acid stones are less common and are radio-lucent on KUB X-rays. Three key factors influence their formation: low urine volume, elevated serum uric acid concentration, and low urine pH (<5.5). Low urine pH results from high animal protein intake and impaired

ammoniogenesis (\rightarrow excess secretion of unbuffered H^+). An increase in uric acid stone formation has been seen in parallel with obesity and insulin resistance (perhaps 2° to \downarrow urine pH).

Struvite stones ('triple phosphate' or 'infection' stones)

Struvite (magnesium ammonium phosphate) stones are typically large stones associated with urease-producing (\therefore urea-splitting) bacteria and an alkaline urine. Urea breakdown produces excess ammonium and hydroxyl ions, a rise in urinary pH, and a decrease in phosphate solubility—thus encouraging the precipitation of insoluble magnesium ammonium phosphate. These stones can act as a reservoir for further infection and can rapidly expand to fill much of the collecting system (termed 'staghorn calculi' because of their characteristic appearance on imaging).

Many common bacteria are urease producers, particularly *Proteus* (others: *Haemophilus*, *Pseudomonas*, *Klebsiella*, *Yersinia*, *Staphylococcus epidermidis*, *Citrobacter*, *Serratia*, and *Ureaplasma urealyticum*). Note: *E. coli* does not produce urease.

Risk factors: ♀ > ♂ (2° to \uparrow incidence of UTI), long-term catheterization, urinary stasis (e.g. neurogenic bladder).

Antibiotic therapy (often long-term) and urological intervention, such as nephrolithotomy or open surgery, are usually required (although surgery may not always be possible, as patients are often complex with multiple comorbidities). Eradication of infection can be extremely difficult. Any available stone material should be cultured for antibiotic sensitivities.

Distal renal tubular acidosis (📖 p. 824)

- Characterized by impaired distal tubular excretion of H^+ , a non-anion gap metabolic acidosis, and an alkaline urine.
- Acidosis causes:
 - Skeletal release of calcium and phosphate ($\rightarrow \uparrow$ urinary excretion of both).
 - \uparrow citrate reabsorption in the proximal tubule.
- High urinary pH + hypocitraturia + \uparrow urinary excretion of Ca^{2+} and $PO_4 \rightarrow$ a 'perfect storm' for calcium phosphate precipitation.
- Nephrocalcinosis is not uncommon, in addition to nephrolithiasis.

Stone prevention: sodium bicarbonate and potassium citrate (correct metabolic acidosis and increase urinary citrate excretion). Avoid urine pH >6.5, as this encourages calcium phosphate precipitation. Large doses are often required.

Bladder stones

Usually arise in abnormal bladders. Predisposing factors include post-surgical reconstruction, UTI, bladder diverticulae, neurogenic bladder \pm bladder outflow obstruction.

Cystine

- Cystinuria is an autosomal recessive disorder, causing a tubular defect in the uptake of dibasic amino acid (cystine, ornithine, arginine, and lysine).
- There are two sources of cystine: (i) dietary and (ii) synthesized from methionine.
- Most cystine is reabsorbed in the renal tubules, with only ~20mg per day excreted in the urine under normal circumstances.
- In cystinuria, failure of uptake leads to excretion of >250mg/day.
- Cystine is poorly soluble, so this larger amount inevitably leads to insoluble crystal formation and stone development.
- Autosomal inheritance was first described in the 1950s. Initially, three types were proposed (types I–III). However, this terminology is now less popular, as types II and III have proved difficult to differentiate. The type II/III form has a more complex mode of inheritance (described as ‘incompletely recessive’). Clinically, even carriers of type II/III cystinuria may be stone formers.
- The genes (so far) associated with type I and types II/III are *SLC3A1* and *SLC7A9*, respectively, with multiple mutations identified. Although available, genetic testing is not in routine clinical use.
- Note: avoid cysteine/cystine confusion. Methionine is an essential amino acid. It can be converted to cysteine in the body. Two cysteine molecules then combine together (via a strong disulphide bond) to form one cystine molecule (hence cystine = ‘dimeric’ or ‘dibasic’).
- When cystine stones are broken with a laser, they give off a characteristic sulphuric rotten egg odour (the disulphide bond is broken, and sulphur is released).
- Cystinuria should be suspected in all childhood stone formers.
- The disorder usually presents during a patient’s teens or 20s, often with multiple and bilateral stones.
- Management:
 - Maintain high urine volumes (📖 p. 722).
 - Lower urinary pH (with potassium citrate) (📖 p. 723).
 - Restrict sodium intake (reduces calciuria) (📖 p. 722).
 - The precursor of cystine (methionine) is an essential amino acid, so complete dietary exclusion is not possible, but restriction, combined with reduced animal protein intake, is desirable (an excellent recipe book is available free at 🌐 <http://www.cystinuriauk.co.uk>).
- Drug therapy is required in only a minority of patients.
 - Mechanism: combine with cystine (at the disulphide bond) and increase solubility.
 - Tiopronin (alpha mercaptopropionylglycine) is the most commonly used, as it has fewer side effects than older alternatives. A typical regimen is 1,000mg/day in three divided doses (depending on urinary cystine levels and tolerability). Unlicensed in the UK but often used under specialist supervision.
 - Penicillamine; generally less well tolerated. Typical regimen: 1–3g/day in divided doses.
 - 🌐 Captopril: if others unsuitable. Efficacy uncertain.

Stone disease: evaluation

Clinical presentation

The clinical presentation of stone disease will vary, according to stone type, location, and size—ranging from small, asymptomatic, stones through to large infected and obstructing staghorn calculi.

Pain (📖 p. 724), haematuria (macroscopic and microscopic), infection (may be relapsing), and obstruction ($\Delta \rightarrow$ AKI if single functioning kidney) are the key clinical considerations. Progressive CKD is also possible from recurrent obstruction, infection, and renal interstitial damage (2° to the fibrosis incited by microcrystals).

Who to evaluate?

In patients presenting with a first urinary stone, *detailed* metabolic investigation is not usually justified or cost-effective. However, that is not to say that *no* evaluation should be undertaken. A basic assessment (history, physical examination, limited dietary assessment, limited blood testing, urinalysis, urine culture, and appropriate imaging) should be undertaken in all cases, with a more thorough metabolic evaluation (e.g. detailed 24h urine testing and comprehensive dietetic review) reserved for all recurrent stone formers and those known to have non-calcium-based stones. Where stone material is available, it should always be sent for analysis.

- History:
 - Age at first onset (younger age makes a metabolic abnormality, such as cystinuria or primary hyperoxaluria, more likely).
 - Number and frequency of stones to date (and previous interventions, such as lithotripsy, undertaken).
 - Site (recurrence at same site suggests a urinary tract abnormality).
 - Family history.
 - Stone type (if known). Non-calcium stones mandate closer scrutiny.
 - Associated urinary tract infection.
 - Relevant systemic disease (e.g. Crohn's disease, hypercalcaemic disorder, obesity, and insulin resistance (uric acid stones)).
- Drug history:
 - *Calcium stones*: loop diuretics, calcium supplements, antacids, vitamin D preparations, corticosteroids, theophylline, acetazolamide.
 - *Uric acid stones*: salicylates, probenecid.
 - *Crystalluria*: indinavir, nelfinavir (both antiretrovirals), and triamterene can cause crystalluria as a precursor to stone formation.
- Diet (📖 p. 723).
- Lifestyle: those who restrict their fluid intake to avoid inconvenient bathroom breaks, e.g. taxi drivers, surgeons. Exercise intensity.
- Obvious systemic predisposition, e.g. gouty tophi, spinal injury with bladder dysfunction.
- Urinalysis:
 - Microscopic haematuria. Proteinuria. Leucocytes and nitrites.
- Urinary pH:
 - Usually high if struvite or calcium phosphate stones.
 - Usually low if uric acid or calcium oxalate stones.

- Urine specific gravity: a high reading on a random sample suggests inadequate fluid intake.
- Urine microscopy for crystals (📖 p.28).
- MSU for M,C+S (? concomitant infection).
- Blood tests: U&E, bicarbonate, SCr, calcium (and PTH if calcium elevated), phosphate, serum urate.
- Stone analysis if possible. This is highly desirable—patients should be encouraged to retrieve stones.
- Urinary stone screen (📖 see below).
- Imaging (📖 see below).

Urinary values for 24-hour ‘stone screen’

Ensure that the collection is adequate. Urine creatinine of $>88\mu\text{mol/kg}$ (10mg/kg) in ♀ and $132\mu\text{mol/kg}$ (15mg/kg) in ♂ implies a complete sample.

Collect stone screen in acidified container for all investigations listed, except urinary uric acid which requires a plain container. Two 24h collections may be required to alleviate inpatient variability. The collection should be undertaken on a typical day with a typical diet.

Optimal ranges:

- Volume 2–2.5L.
- Calcium $<0.1\text{mmol/kg/day}$ (4mg/kg/day).
- Oxalate $<0.36\text{mmol/day}$ (40mg/day).
- Uric acid $<4.4\text{mmol/day}$ (750mg/day).
- Citrate $>1.67\text{mmol/day}$ (320mg/day).
- Phosphate $<35\text{mmol/day}$ ($1,100\text{mg/day}$).
- Sodium $<3,000\text{mg}$ (130mmol/day).
- Cystine negligible (can \therefore be measured on a spot sample).

Some specialist laboratories may also be able to provide supersaturation analysis (the ratio between ion activity product and its solubility product).

Imaging in nephrolithiasis

► Calcium-containing or struvite stones are radio-opaque, while uric acid and cystine stones are radiolucent, i.e. not visible on a plain X-ray. However, they will be visible as an acoustic shadow on USS and as a filling defect on contrast CT or IVU.

- CT-KUB offers the single best test. It can be rapidly performed, is more sensitive and specific than an IVU, and avoids the administration of contrast (although radiation dose is higher). A subsequent CT contrast study may help to identify an underlying urinary tract abnormality.
- Plain KUB allows monitoring of radio-opaque stones.
- IVU offers an alternative if CT unavailable.
- USS may be helpful if obstruction suspected and is also sensitive for stones in the renal pelvis but often misses ureteric stones.
- For considerations when stones occur in pregnancy, see 📖 p. 860.

Stone disease: management

Prevention of recurrent nephrolithiasis

General measures:

- Consider a specialist referral. Attendance at a stone clinic has been shown to reduce stone recurrence, independent of other factors!
- Increase fluid intake for daily UO >2.5L/day. Urine should appear clear, not dark and concentrated. Advise to:
 - Drink a large glass of water at specific times during the day, e.g. upon waking, arriving at work, etc.
 - Drink a glass of fruit juice with breakfast.
 - Keep a large bottle of water at their workplace and sip from it regularly throughout the day.
 - Drink a glass of water each hour, on the hour.
 - Add slices of lemon, lime, or orange to water. It improves flavour and helps to alkalize the urine.
 - Drink two full glasses of water at each meal (one before, one after).
 - Carry a refillable water bottle everywhere—walking, shopping, driving, watching television, etc.
 - Eat fruits and vegetables (contain a high amount of water).
 - Include more liquid and ‘wet’ foods in the diet, e.g. soups, stew, jellies, etc.
 - Drink before bedtime. Aim to provoke nocturia at least once per night.
- Reduce animal protein intake:
 - Protein ingestion → ↑ acid formation → reduced urinary citrate excretion → less citrate available to form a *soluble* complex with calcium.
 - It also generates sulphate ions that decrease calcium solubility.
 - Acidosis also decreases tubular calcium absorption.
 - Protein metabolism increases uric acid production and encourages uric acid stone formation in low pH urine.
 - Aim 0.8–1.0g/kg/day animal protein (meat, poultry, fish, eggs, cheese, yogurt), and advise regarding non-animal protein substitutes (lentils, chickpeas, kidney beans, butter beans, baked beans, quorn).
- Reduce Na⁺ intake <3g/day (<6g/day NaCl).
 - Na⁺ enhances calciuria (partly explaining the increased incidence of hypercalciuria in hypertensive patients).
 - Educate patients to understand salt content labelling on foods.
- Recommend a *normal* calcium intake of ~700–1,000mg/day.
 - ⚠ Many patients are erroneously told to reduce calcium ingestion. This risks osteoporosis (esp. ♀) and may actually promote stone formation (low Ca²⁺ intake → ↑ oxalate absorption and excretion).
 - Calcium supplementations should be avoided, however.
- Reduce dietary oxalate (see Table 9.4).
- If uric acid stones, reduce dietary purine intake (see Table 9.4).
- Increase intake of citrus fruits (a source of potassium citrate).
- Avoid excessive vitamin C supplementation (increases urine oxalate).
- Monitor urinary stone screen for efficacy of therapy.

Table 9.4 Dietary sources of oxalate and purine

High oxalate	High purine (uric acid)
Greens (e.g. spinach and kale), green beans, rhubarb, figs, beetroot, celery, spring onions, leeks, okra, cocoa and chocolate, berries (including strawberries, blackberries, etc.), plums, kiwi fruit, tangerines, lemons, tofu, soy milk, nuts, seeds, tea, coffee	Meat (particularly viscera, e.g. liver, kidney, heart), meat extracts (e.g. stock, broth, or gravy), anchovies, crab, oily fish, such as sardines and mackerel, shrimp, certain vegetables (including asparagus, cauliflower, peas, spinach, mushrooms), lentils, kidney beans, beer

Specific measures

Calcium oxalate/phosphate stones


- If $u\text{-Ca}^{2+}$ normal:
 - Potassium citrate 15–30mmol PO tds.
 - Potassium citrate increases urinary citrate and urinary pH. Aim for a pH of 6.5. Higher might encourage calcium phosphate stones.
 - Liquid preparations can be unpalatable, but tablet formulations (e.g. Urocit[®]-K wax tablet) are available (although more expensive).
 - The potassium salt is favoured over the sodium salt, as the latter promotes calciuria.
- If $u\text{-Ca}^{2+}$ raised:
 - Potassium citrate as for normal + either indapamide 2.5–5mg PO daily or hydrochlorothiazide 25–50mg PO daily (monitor K^+ with both).
 - Thiazide diuretics increase tubular Ca^{2+} reabsorption (note: avoid triamterene, as it causes crystalluria itself).
 - If $\downarrow K^+$ develops, add amiloride (for potassium).
- Recheck urinary citrate and calcium excretion after several weeks, and adjust appropriately.

Hyperoxaluria

- In malabsorption disorders, ensure adequate hydration. Hypocitraturia and hypokalaemia can occur and should be corrected. Colestyramine binds fatty acids and prevents their delivery to the colon (where they would otherwise increase oxalate absorption).
- Pyridoxine (vitamin B6) can be helpful, although large doses may be required.
- Calcium carbonate 500–1,500mg tds before meals may reduce oxalate absorption.
- Primary hyperoxaluria can only be cured by liver transplantation.

Struvite stones

Require vigorous eradication of infection; antibiotic therapy is often prolonged, e.g. 3–6 months, directed by cultures and sensitivities.

Cystine stones (see  p. 719).

Hyperuricosuria

Complete dissolution of uric acid stones can often be achieved, using a combination of high fluid intake, urinary alkalinization (pH >6.5), reduced dietary purine intake, and, if necessary, allopurinol 100–300mg PO daily.

Acute renal colic

Presentation

The syndrome caused by stone(s) passage down the urinary tract. Typically ♂ aged 20–40. Colicky abdominal pain (▶ often very severe), radiating from loin to groin (especially as the stone moves toward the vesicoureteric junction). Often abrupt onset, with progressive increase in intensity. Nausea and vomiting common. Renal angle tenderness, haematuria (often macroscopic), dysuria, strangury, frequency ± symptoms of UTI. ▶ Patients may be systemically unwell at presentation, with dehydration and ↓ BP. Predisposing factors include dehydration and exercise. Renal colic may also be caused by ureteric clots and papillary necrosis (📖 p. 585).

Investigations

- Dipstick urine for haematuria (microscopic haematuria is almost universal) as well as leucocytes and nitrites.
- Urine microscopy for crystals. MSU for M,C+S.
- SCr, U&E, CRP, FBC (▶ blood cultures if signs of infection).
- CT-KUB to confirm diagnosis, locate the stone, exclude obstruction, and predict response to lithotripsy. IVU if CT unavailable. Plain AXR may reveal radio-opaque stones (~80%). ⚠ A stone may be an incidental finding. Have you considered other causes of pain?

Management

- ▶▶ Infection ± obstruction are indications for urgent intervention.
- Analgesia: NSAIDs (e.g. diclofenac 75mg IM or via suppository) are often very effective (use with caution, i.e. correct dehydration; monitor renal function with prolonged use). Opiates may also be necessary, e.g. diamorphine 2.5–10mg SC/IM) (with antiemetic, e.g. metoclopramide 10mg IM/IVI or cyclizine 50mg IM).
- Desmopressin can reduce pain in many patients (antidiuretic effect ameliorates proximal ureteric distension). It acts quickly and has minimal adverse effects. Usually 1× 40 micrograms dose administered nasally.
- Oral rehydration. If vomiting, IVI 0.9% NaCl for UO >2L/day. No role for 'forced hydration' to assist stone passage.
- If stone ≤5mm, ~70–80% will pass spontaneously. 50% if 5–10mm. Majority of larger stones will not. Location is important: more distal stones pass ~75% of the time, proximal ~25%. Most pass in 1–3 weeks.
- α adrenoceptor blockade, e.g. tamsulosin 400 micrograms od for 4 weeks, has been shown to increase rate of passage (by ~30%), particularly for distal ureteric stones. Termed 'medical expulsive therapy' (MET).
- Proximal ureteric stones <20mm are best treated with ESWL (📖 p. 725). ESWL access to stones in the middle and distal ureter may be restricted by the pelvic bones, and ureteroscopy provides a very effective alternative. Percutaneous (and rarely open) nephrolithotomy have excellent results for calculi >20mm or complicated stones.

- ► If associated infection, co-amoxiclav IVI, then PO, or third-generation cephalosporin IVI, then PO, or fluoroquinolone (e.g. ciprofloxacin 250–500mg bd PO). Consider additional single-dose gentamicin 3–5mg/kg IVI. Discuss with microbiology.

- ►► An obstructed, infected system caused by stones (pyonephrosis) is an emergency. Septicaemia ± shock can supervene rapidly.
- Commence IVI antibiotics and fluid resuscitation immediately. Discuss with urology, and arrange an urgent referral for percutaneous nephrostomy and drainage (📖 p. 734).

Surgical management of stone disease: a primer

Surgical management of renal stone disease has changed significantly with the growth of minimally invasive techniques. In general, open surgical techniques have been relegated to second, even third, line.

- Extracorporeal shock wave lithotripsy (ESWL):
 - Acoustic shock wave energy is delivered under fluoroscopic or USS guidance. 1,500–2,500 shock waves are delivered during each session (typically ~30min).
 - It is an ambulatory procedure but requires analgesia and (often) IV sedation. It can be repeated at 10–14 day intervals.
 - Fragmentation is followed by clearance of fragments. Multiple large fragments can block the ureter—termed Steinstrasse or ‘Stone Street’. For stones >20mm, a ureteric stent is placed first.
 - Achieves very good rates of stone clearance for stones ≤20mm.
 - ESWL is now first-line in most cases, except larger (>10mm), more distal ureteric stones where ureteroscopy is preferred.
 - Success depends on the operator, equipment, stone characteristics (size, location, type—cystine and calcium oxalate stones are more difficult to shatter), and patient obesity.
 - Contraindications: AAA, pregnancy, bleeding tendency, UTI.
 - Side effects: haemorrhage, haematoma, adjacent organ damage.
- Ureteroscopy:
 - Increasingly small, flexible ureteroscopes are allowing access to the entire urinary tract. Stones are shattered, using a holmium laser, and the fragments can be retrieved.
 - More rigid scopes and basket techniques are no longer favoured.
- Percutaneous nephrolithotomy (PCNL):
 - Suitable for larger or proximal ureteric stones.
 - A sheath is passed into the pelvicalyceal system percutaneously (usually the dorsal calyx of the lower pole, although higher punctures allow antegrade ureteroscopy).
 - Laser or USS is used to fragment the stone or it is removed under direct vision.
 - Also allows chemolysis—the infusion of an alkaline solution to dissolve stones (usually uric acid). Less commonly used.
- Open surgery is now rarely necessary. Laparoscopic techniques are increasingly popular.

Obstruction: overview

- ▶ Urinary tract obstruction is a common, and potentially reversible, cause of both acute kidney injury and chronic kidney disease.
- Obstruction leads to delayed urinary transit, an increase in intratract pressures, and renal dysfunction.
- It will eventually cause dilatation of the renal pelvis and calyces. This is referred to as hydronephrosis.
- Obstruction causes renal failure when bilateral or when it involves a single functioning kidney.
- Obstruction accounts for ~5% of ESRD in those aged >65.

Definitions

- Obstructive uropathy*: the structural or functional changes in the urinary tract that impede the normal flow of urine. Classified according to site, degree, and duration. May be complete or partial.
- Obstructive nephropathy*: the kidney disease resulting from impaired urinary flow and consequent renal parenchymal damage.
- Hydronephrosis*: upper tract dilatation. Obstruction is not the only cause but is the commonest and must always be excluded. ▶ May not always be present in obstruction, particularly in early stage.

Epidemiology

Aetiology and frequency varies with age and sex (see Table 9.5).

Table 9.5 Epidemiology of obstruction

Age	Sex	Aetiology
<10	♂ > ♀	Congenital abnormalities; urethral valves, PUJ obstruction
>20	♀	Pregnancy and gynaecological malignancy
	♂ > ♀	Renal calculi
>60	♂	Prostatic disease

Classification

- Cause (see Table 9.6):
 - Congenital, e.g. urethral valves.
 - Acquired, e.g. prostatic disease.
- Level:
 - Upper tract: ureter or above.
 - Lower tract: bladder or below.
- Unilateral or bilateral:
 - Both kidneys are usually involved in lower tract obstruction.
 - An individual kidney can be affected by upper tract obstruction.
- Complete or partial:
 - Complete: ▶ commonest cause of anuria.
 - Partial: can be difficult to diagnose, as urine output may vary.
- Intrinsic or extrinsic:
 - Intrinsic: arising within the urinary tract, e.g. stone disease.
 - Extrinsic: arising externally, e.g. retroperitoneal fibrosis.

Table 9.6 Causes of urinary tract obstruction

Level of obstruction	Obstruction within the lumen	Obstruction within the wall	Extrinsic compression
Kidney	*Calculi Sloughed papillae (diabetes mellitus, sickle cell trait/disease, analgesic nephropathy, acute pyelonephritis)	Anatomical abnormalities, e.g. PUJ obstruction	Lower polar renal vessels crossing at PUJ Tumours Cysts
Ureter	*Calculi	Uroepithelial malignancy Stricture (malignant, post-surgery/radiotherapy, TB, schistosomiasis) VUJ obstruction	Prostatic malignancy Retroperitoneal malignancy (metastases, lymphoma) Retroperitoneal fibrosis (1° or 2°) Vascular, e.g. aneurysmal aorta or iliacs, congenital retrocaval right ureter Inadvertent surgical ligation Pregnancy
Bladder neck	*Calculi **Blood clot retention Blocked catheter	Uroepithelial malignancy Functional obstruction from neurological damage (e.g. DM, MS, spinal trauma) or drugs (e.g. anticholinergic)	Pelvic malignancy (e.g. cervical cancer) Uterine and ovarian masses Pelvic inflammation Prostatic enlargement
Urethra	*Calculi **Blood clots	Stricture (congenital meatal stricture, or acquired—usually post-infective, or post-surgical) Urethral valves Tumours	

* Calculi can be found anywhere along the urinary tract but most commonly at the ureteropelvic or vesicoureteric junctions.

** Blood clots may be caused by bleeding renal tumours, surgery, AV malformations, renal trauma (including renal biopsy), adult polycystic kidney disease, and traumatic catheterization.

Obstruction: pathophysiology

Normal physiology

Urine production is continuous, and it reaches the bladder as a result of several processes:

- Glomerular filtration pressure.
- Renal tract peristalsis. Pacemaker cells in the renal calyces initiate contraction of the renal pelvis. Subsequent coordinated ureteric smooth muscle contraction directs urine toward the bladder. Pressures reach 20–80cmH₂O (resting pressure is 0–5cmH₂O).
- Gravity.
- The vesicoureteric junction (VUJ) prevents retrograde ureteric urine flow during bladder contraction.

Pathophysiology

- There is a relationship between ureteric pressure and renal blood flow. Following an initial increase in both (minutes), further increases in ureteric pressure result in a reduction in renal blood flow (hours).
- This mismatch progressively widens, with consequent ischaemic injury.
- Impaired glomerular and tubular function result.

Glomerular

- Proximal tubular pressure rises early.
- This causes a net ↓ in hydraulic pressure gradient across glomerular capillaries and a significant reduction in GFR.
- Afferent arteriolar vasoconstriction (mediated by ↑ angiotensin II and ↑ thromboxane A₂ + ↓ NO and ↓ vasodilator prostaglandins) reduces both renal plasma flow and glomerular capillary pressure.
- Blood is redirecting away from non-filtering nephrons.
- Ischaemic nephrons release mediators of inflammation, leading to macrophage infiltration, interstitial fibrosis, and irreversible injury.

Tubular

- Tubular dysfunction often manifests after the resolution of obstruction.
- Includes reduced urinary concentrating ability (↓ expression of both Na⁺ transporters + aquaporins), abnormal electrolyte handling (mild Na⁺ wasting and ↑ K⁺ excretion), and acidosis (2° to abnormal intercalated cell H⁺ ATPase activity).
- In lower tract obstruction, the normally protective VUJ is rendered incompetent, allowing retrograde transmission of pressure.
- Hypertrophy of the ureteric musculature attempts to compensate for the increased resistance.
- The ureter becomes stretched and tortuous, resulting in ureteric distension and hydronephrosis. Fibrous bands develop along the length of the ureter, adding a further element of obstruction that may persist after the resolution of the original cause.

Histopathology

- Initial changes are of renal enlargement with oedema and pelvicalyceal dilatation.

- This advances to encompass distal tubular dilatation, proximal tubular cell atrophy, and, eventually, enlargement of Bowman's space, with periglomerular fibrosis.
- Continuing damage is essentially a form of ischaemic injury, with macrophage-derived TGF- β fuelling progressive, irreversible tubulointerstitial fibrosis.
- Unresolved obstruction eventually causes macroscopic change, characterized by dilatation of the renal pelvis, flattening of the papillae, and gradual thinning of the cortex and medulla.

Recovery of renal function

- The prognosis post-relief of obstruction is contingent on antecedent duration and severity.
- Available clinical and experimental evidence suggests that full recovery of renal function is possible after complete obstruction ≤ 7 days' duration.
- There may be some functional recovery after 4 weeks, but significant permanent renal damage is usually present beyond 6 weeks.
- Dialysis support is likely to be needed during this time.

▶▶ This underlines the need for prompt diagnosis and treatment of acute obstruction if permanent renal damage is to be avoided.

- The SCr and eGFR may underestimate the extent of parenchymal damage, with the hyperfiltration and hypertrophy of remaining nephrons masking nephron scarring and dropout. This is particularly relevant to unilateral obstruction where the contralateral kidney compensates to maintain function.
- In more chronic, or partial, forms of obstruction, renal parenchymal changes are likely to be well established, so return of renal function is unpredictable, at best. The renal cortical thickness on ultrasound (or other imaging) may give some indication of the potential to salvage GFR, but a degree of CKD is often inevitable.
- However, subsequent progression of CKD is often relatively slow, providing BP is well controlled.
- Evidence of tubular dysfunction often persists after the relief of chronic obstruction and can be clinically relevant, e.g. polyuria, mild salt wasting, and acidosis.

How to approach obstruction

►► It is vital that obstruction is considered and actively excluded in all presentations of AKI and many of CKD.

An accurate history may provide clues as to whether the obstruction is acute/chronic, unilateral/bilateral, congenital/acquired.

Clinical presentation

Symptoms

Depend on the cause and level of obstruction. ⚠ Unilateral obstruction and chronic partial obstruction can be clinically completely silent.

- Loin pain:
 - Flank pain suggests upper tract obstruction. Acute ureteric colic can be severe. It is usually unilateral and may radiate to the ipsilateral groin (📖 p. 724).
 - ► Flank pain, fever, and signs of pyelonephritis suggest obstruction with infection (→ requires emergency decompression of the affected system).
 - Pain radiating to the flank during micturition is suggestive of vesicoureteric reflux (📖 p. 712).
 - Pain after high-volume fluid intake (e.g. beer!) occurs in pelvi-ureteric junction (PUJ) obstruction (📖 p. 736).
 - Retroperitoneal fibrosis may cause backache (📖 p. 738).
- Haematuria:
 - Macroscopic haematuria occurs with calculi and uroepithelial tumours.
- Changes in urine volume:
 - ► Complete anuria should always suggest obstruction.
 - Polyuria can be a feature of partial obstruction.
- Lower urinary tract symptoms (LUTS) suggest bladder dysfunction or outflow obstruction.
 - Obstructive (voiding) symptoms: reduced urinary stream, hesitancy, interrupted flow, incomplete emptying, acute retention.
 - Storage (filling) symptoms: nocturia, daytime frequency, urgency, incontinence, dysuria.
 - Any patient presenting with CKD 3 or above with significant LUTS warrants a urinary tract ultrasound (including pre-/post-voiding).
- UTI:
 - Obstruction → urinary stasis → infection.
 - Obstructed urine is difficult to sterilize with antimicrobials.
 - A single UTI in a child or an adult ♂ is suspicious and should be further investigated. Recurrent infections in a ♀ should prompt the same.

Signs

- Palpable bladder (⚠ you will miss it if you do not look for it!).
- Loin tenderness.
- Flank mass (palpable hydronephrosis in a thin or young patient).

- Blood pressure:
 - ↑ BP (→ mediated via renin or salt and water retention in CKD).
 - ↓ BP (→ polyuria with salt and water wasting).
- Rectal and pelvic examinations may (often) be necessary.

Investigations

- Urinalysis:
 - Haematuria, leucocytes, nitrites.
 - Proteinuria, when present, is usually low-grade.
 - Bland urine, free of blood or protein, can point toward obstruction during the investigation of renal impairment, as it makes an intrinsic renal lesion less likely.
- MSU for M,C+S.
- Electrolytes:
 - Mild acidosis, with associated hyperkalaemia.
- Creatinine, eGFR:
 - Remember—these can be falsely reassuring in unilateral obstruction.
- CRP, WCC, blood cultures for infection.
- Consider a PSA in ♂ with marked LUTS (📖 p. 772).
- Imaging (📖 p. 732).

Obstruction: imaging

Imaging is fundamental to the accurate diagnosis of the site and cause of obstruction. Ultrasound is usually first-line, but other modalities may be necessary to further progress management.

► No single investigation can be considered to have completely excluded obstruction when clinical suspicion remains high.

Ultrasound (USS)

See Fig. 9.1.

- Portable, rapid, and non-invasive.
- Can measure pelvicalyceal diameter.
- May demonstrate dilated upper ureters.
- No contrast or radiation, so the imaging of choice in patients who have renal impairment or are pregnant.
- However, USS is operator-dependent, and obstruction (particularly early) can occur without a dilated system (<35% of patients with proven obstruction). Moreover, a dilated system demonstrates hydronephrosis, which is not the same as proving obstruction (see Box 9.2).

Box 9.2 Ultrasound and obstruction: the pitfalls

Obstruction without a dilated system (false negative)

- Hydronephrosis may not be apparent in early (first 2–3 days) obstruction.
- Dilatation may not occur if retroperitoneal tumour or fibrous tissue encases the kidney.
- ATN may coexist.
- ATN → oligo-anuria → no hydronephrosis develops.
- Partial obstruction may not cause a demonstrable hydronephrosis (although GFR is still reduced).

Dilated system without obstruction (false positive)

- Anatomical variants: extrarenal pelvis, megaureter (often secondary to vesicoureteral reflux) (📖 p. 712).
- Pregnancy: progesterone effects on smooth muscle can cause dilated ureters and pelvis.
- Post obstruction: an abnormal 'baggy' system may persist after the resolution of chronic obstruction. Comparison with previous imaging will be helpful in this situation.
- Further imaging (CT or isotope renography) may be necessary.

CT

- Highly sensitive for calculi. A non-contrast CT-KUB is now the investigation of choice for acute flank pain (📖 p. 724).
- Superior anatomical definition to USS. More likely to demonstrate site and nature of obstruction. If clinical findings and USS equivocal, CT KUB is most likely to provide the most information on the site and cause of the obstruction.

- Particularly helpful for the diagnosis of extrinsic compression and retroperitoneal fibrosis, as well as the staging of tumours.
- IV contrast improves diagnostic utility, ⚠ but take care to reduce the risk of contrast nephropathy in the presence of renal impairment (📖 p. 148).



Fig. 9.1 Renal ultrasound appearances of acute obstruction with pelvicalyceal dilatation. Reproduced with permission from Warrell D, Cox T, Firth J, and Benz EJ (eds) (2004) *Oxford Textbook of Medicine*, 4th edn, p.451. Oxford University Press, Oxford.

Intravenous urography (IVU)

Increasingly redundant. Previously used to determine the level of obstruction through delayed films (e.g. 20min, 1h, 2h, 4h, 8h). However, this is rarely necessary, and, if desirable, a CT-IVU would generally be preferred.

MRI

- MR urography provides detailed anatomical information.
- Also offers helpful functional information, including renal transit times.
- ⚠ No ionizing radiation, but the potential for gadolinium to cause nephrogenic systemic fibrosis (NSF) restricts its routine use in higher stages of CKD (📖 p.51).
- Useful if known contrast allergy.

Isotope renography (with diuretic)

- A DTPA or MAG-3 renogram (📖 p.54) may show delayed isotope excretion in the presence of obstruction.
- The addition of a loop diuretic can differentiate between simple dilatation and true obstruction. Normally, the diuretic, administered 30min after the isotope, would cause prompt washout from the kidney. Persistence suggests obstruction. Excretion of both kidneys can be compared.
- Also estimates split function and may contribute to the assessment of whether attempts to salvage a kidney are likely to be worthwhile.
- ⚠ Sensitivity decreases if renal function is significantly impaired.

Obstruction: treatment

Overview

► Effective interdisciplinary communication between nephrology, urology, and radiology is essential.

Management is directed by: (i) the site, duration, and cause of obstruction; (ii) the presence of infection; and (iii) the degree of metabolic disturbance.

Treatment goals

- Treat any emergent metabolic or fluid and electrolyte disturbances, e.g. $\uparrow K^+$, pulmonary oedema. This may require dialysis or CRRT; ► Seek expert help.
- ► If there is evidence of sepsis (fever, abnormal urinalysis or urine microscopy, \uparrow WCC, \uparrow CRP, shock), then take appropriate cultures, and treat urgently.
- Prompt relief of obstruction to prevent further metabolic disturbance and protect the kidney(s) from irreversible renal damage.
 - If the duration of obstruction is unclear, assume it is acute.
 - If a single kidney is obstructed, do not be reassured by preserved GFR—the obstructed kidney may still need urgent intervention.
- Manage the underlying pathology, e.g. recurrent stones, tumour.

Relief of obstruction—general principles

- Bladder outflow obstruction can often be relieved with a urinary catheter. If this cannot be passed per urethra, a suprapubic catheter may be necessary.
- In an emergency situation or if infection above the obstruction is suspected, upper tract obstruction should be relieved through the placement of a percutaneous nephrostomy under LA.
- Subsequent antegrade stenting of the obstruction through the nephrostomy may be possible.
- In non-emergency situations and when the patient is fit for GA, cystoscopic placement of retrograde ureteric stents is an appropriate approach.
- Urinary catheters and ureteric stents require follow-up and elective replacement. ⚠ Be vigilant for infection or blockage.

Percutaneous nephrostomy

Is it necessary?

- *Pros:*
 - Decompresses an obstructed system and rapidly improves renal function.
 - Decompression of one kidney should be sufficient initially (preferentially decompress the kidney with the most parenchyma visible on imaging first).
 - Will decompress an infected system with minimal instrumentation.
 - No GA required.
 - Allows time for a more definitive management plan to be developed.

- **Cons:**

- Invasive. Potential complications: bleeding and infection.
- Not always available 24 hours a day (although it should be).
- Temporary although can occasionally be left long-term in those unfit for further intervention or on a palliative treatment pathway.

How urgent is it?

- Obstructed infected urinary system → ► emergency nephrostomy required.
- If severe renal failure, $K^+ > 6.0 \text{ mmol/L}$, or pulmonary oedema, then dialysis prior to a nephrostomy may be desirable. ► Seek expert help.
- Once a patient is safe, a delay of hours to ensure an expert operator may be justified.

How should I prepare the patient?

U&E, FBC, clotting screen, G&S. Liaise closely with the interventional radiology team. They should gain informed consent.

Post-procedure care

- Regular post-nephrostomy observations and clinical review are mandatory, particularly in the presence of sepsis.
- Careful fluid balance: there is likely to be a brisk post-obstructive diuresis. See Post-obstructive diuresis below.
- Make sure the nephrostomy is well secured!
- As well as being therapeutic, a nephrostomy also has diagnostic potential. A nephrostogram involves injection of contrast via the nephrostomy to examine antegrade ureteric flow and identify the level and source of obstruction.

Post-obstructive diuresis

- A large-volume diuresis (0.5–1L/h) post-relief of obstruction.
- Most common after the treatment of bilateral obstruction or obstruction of a single functioning kidney.
- Results from either:
 - Appropriate excretion of retained salt and water in renal failure, or
 - Inappropriate losses due to tubular dysfunction.
- Consequences: salt loss, volume depletion, electrolyte disturbances, ATN with delayed recovery of renal function.
- Management:
 - Regular assessment of fluid balance, including BP, hourly UO, clinical assessment, daily weights.
 - Regular U&E (12-hourly if diuresis large). Also monitor K^+ , bicarbonate, calcium, phosphate, and magnesium daily.
- Fluid replacement:
 - *Once euvolaemic*, administer IVI 0.9% NaCl as UO + 50mL/h.
- Replace electrolytes, as necessary.
- ⚠ Remember the diuresis may initially result from the appropriate excretion of the salt and water retained during obstruction. The aim is not to perpetuate fluid overload, but to prevent volume depletion.

Pelvi-ureteric (PUJ) obstruction

Definition

- Proximal obstruction at the ureteric junction of the renal pelvis, resulting in reduced or absent urinary flow and a high-pressure renal pelvis.
- May coexist with vesicoureteric reflux (📖 p. 712) or VUJ obstruction.

Aetiology

May present antenatally, in childhood, or in adults.

- Congenital:
 - Intrinsic: ♂ > ♀, proximal ureteric developmental defect.
 - Extrinsic (rare): external compression (e.g. aberrant renal vessel).
- Acquired:
 - Intrinsic: stricture (infection, trauma), uroepithelial malignancy.
 - Extrinsic: malignancy, retroperitoneal fibrosis.

Symptoms and signs

- Increasingly diagnosed with maternal USS screening. It is the most common cause of antenatal hydronephrosis (~1 in 1,500 live births). L > R but may be bilateral.
- Children may present with failure to thrive, flank pain, urinary tract infections, a palpable mass, haematuria, hypertension, or renal impairment (if bilateral).
- 20% diagnosed as adults (with a large number presumably never diagnosed at all). Classically causes flank pain after alcohol, coffee, or diuretics (Diettel's crisis).

Investigation

- USS (preferred) or CT will show dilatation of the renal pelvis with a normal distal ureter.
- Diuretic isotope renography demonstrates obstruction with delayed 'washout'.
- Serial scans are performed to determine optimal management.
- Micturating cystoureterogram (MCUG) may demonstrate concomitant VUJ obstruction or posterior urethral valves.

Management

- No randomized trials:
 - Generally conservative unless: impaired renal function (often manifesting as a change in split renal function), recurrent UTIs, calculi, persistent pain, increasing hydronephrosis.
 - Prophylactic antibiotics of little benefit.
- Surgery:
 - Pyeloplasty involves resecting the abnormal ureteric segment and reattaching normal ureter to the renal pelvis. Various techniques are available, including open, laparoscopic, and endoscopic. All are very successful.

If the obstruction is due to aberrant vasculature, the PUJ is repositioned above the vessel.

Vesicoureteric junction obstruction

- VUJ (like PUJ) obstruction can be congenital or acquired.
- It may present with a similar constellation of symptoms to PUJ obstruction but often later in childhood or as an adult.
- It is very important to look for associated VUR (📖 p. 712) and PUJ obstruction.
- If surgery is necessary, it involves re-implantation of the ureter.

Posterior urethral valves (PUV)

- A developmental abnormality in males, leaving obstructing membranous folds in the lumen of the posterior urethra.
- The most common cause of urinary obstruction in infants (~1 in 8,000).
- The most common cause of CKD due to obstruction in children (~15% progress to ESRD).
- PUV cause dilatation of the proximal urethra, with hypertrophy of the bladder wall, bilateral megaureters, and hydronephrosis.
- Most are identified by antenatal USS (bilateral hydronephrosis, dilated bladder, and dilated posterior urethra: 'keyhole sign').
- Associated with other abnormalities, including urinary tract (VUR, renal dysplasia) and non-urinary tract (e.g. lung hypoplasia).
- Children present with failure to thrive, abdominal distension, UTIs, incontinence (daytime and nocturnal enuresis), and other urinary symptoms, including frequency, straining, poor stream, and large voids.
- MCUG is used to confirm diagnosis.
- Management includes urinary drainage in the newborn, usually by catheterization. Cystoscopic resection of the PUV should be undertaken as early as possible.
- Fetal intervention is now being undertaken in some specialist centres for severe cases.
- If PUV ablation is not possible, then a vesicostomy or other form of urinary drainage procedure should be considered.
- Bladder dysfunction is common and often persistent, requiring ongoing management, such as clean intermittent catheterization.

Retroperitoneal fibrosis: overview

Overview

- Retroperitoneal fibrosis (RPF) describes a group of disorders characterized by the development of fibroinflammatory tissue that surrounds and encases the abdominal aorta and other retroperitoneal structures, including the ureters.
- Encasement impairs ureteric contractility and causes an obstructive uropathy and then nephropathy.
- There are idiopathic (70%) and secondary forms. Both are uncommon (~1 per 200,000–500,000 population).
- The idiopathic form usually occurs age 40–60, with a 3:1 ♂:♀ ratio.

Aetiology

- 1° and 2° RPF are usually very similar pathologically.
- A tough, plaque-like material encases the major vessels and ureters.
- Microscopically, there is a macrophage- and plasma cell-rich inflammatory infiltrate, with progressive fibrotic change.
- This fibrous tissue consists of fibroblasts (including activated myofibroblasts) and type I collagen.
- The causes of this process remain poorly understood. Suggestions:
 - They are an inflammatory reaction to aortic atherosclerosis. Evidence: leakage of proinflammatory lipid-derived material, such as ceroid (an oxidized LDL) across the wall of atheromatous aortas.
 - It is an autoimmune phenomenon. Evidence: coexisting autoimmune conditions, autoantibodies (60% ANA +ve in one series), HLA associations (HLA-B27 or HLA-DRB1 03).

Causes

- Idiopathic.
- Inflammatory periaortitis (severe atherosclerosis), e.g. aortic aneurysm.
- Drug-induced: classically methysergide, but also bromocriptine, methyl dopa, and possibly beta-blockers.
- Chronic retroperitoneal infection (particularly TB).
- Other inflammatory conditions (e.g. sarcoidosis).
- After retroperitoneal trauma.
- Erdheim–Chester disease: a rare histiocyte disorder, characterized by osteosclerotic bone lesions. Extraskelatal effects may include retroperitoneal infiltration.
- Malignant:
 - Lymphoma, lymphoproliferative disorders, carcinoid.
 - Metastatic or locally invasive malignancies (e.g. colon).
 - Post-radiotherapy.

Clinical features


- Symptoms may be insidious and present >6 months prior to diagnosis (which is often considered only when ↑ SCr becomes apparent).
- Usually non-specific, e.g. malaise, anorexia, fever, and weight loss.
- Flank and low back pain are relatively common.

- Vascular encasement may produce oedema or claudication.
- Associations: inflammatory bowel disease, sclerosing cholangitis, ankylosing spondylitis, SLE, scleroderma, vasculitides, Raynaud's.
- An association is also emerging with the relatively new clinicopathological entity of IgG4-related sclerosing disease. This has been described in various tissues, particularly pancreatic ('autoimmune pancreatitis'), and is characterized by ↑ circulating IgG4 as well as IgG4 plasma cell-rich inflammatory infiltrates.

Investigations

- FBC (normocytic normochromic anaemia).
- U&E, SCr, eGFR (impaired renal function).
- ESR (a consistent marker of inflammation, useful for monitoring).
- CRP.
- ANA and other autoantibodies (variably +ve).
- Immunoglobulins (polyclonal hypergammaglobulinaemia).
- High serum IgG4 concentration.
- Urinalysis is typically bland.

Imaging

- USS will demonstrate uni- or bilateral hydronephrosis.
- CT shows fibrotic plaque enveloping the aorta and IVC and extending laterally to encompass the ureters (see Fig. 9.2,  p. 741). May also show associated atherosclerosis and aneurysmal change.
- Metastatic deposits, haemorrhage, and other disorders can have similar appearances. Look for other signs of malignancy: local bone destruction, lymphadenopathy, and anterior aortic displacement.
- Variable degree of enhancement with contrast, particularly in early inflammatory phase.
- MRI is an alternative, showing high signal density in early stages and lower density with fibrosis or treatment.
- PET scanning shows high levels of uptake in active areas.

Biopsy

- A tissue biopsy is desirable to exclude alternative diagnoses.
 - A CT-guided TruCut needle biopsy can be performed but can miss active areas (PET may help to identify these).
 - Open or laparoscopic may be preferred.

Retroperitoneal fibrosis: management

Management

The aims of management of RPF include:

- Preservation of renal function; obstruction requires urgent treatment, as per 📖 p. 734.
- Resolution of inflammatory processes (and ∴ both local and systemic symptoms).
- Prevention of progressive fibrosis.
- Exclusion of secondary causes, particularly malignancy.

Patients are best managed with an integrated medical and surgical approach, although there are no controlled trials to guide therapy.

Medical management

- May be appropriate without surgery if no renal impairment.
- Stop any possible contributory drugs.
- Corticosteroids ↓ inflammatory tissue encasing the ureter(s) and may restore ureteric contractility and patency. Response is unpredictable.
 - Start prednisolone 0.5–1mg/kg/day for ~4–8 weeks.
 - Slowly taper to 10mg, according to inflammatory markers (ESR, CRP) and serial imaging.
 - Reconsider diagnosis if unresponsive.
 - Aim to discontinue after 12–24 months.
 - Relapse is not uncommon, so long-term surveillance is mandatory.
- Combined corticosteroids and MMF show promise as initial therapy.
- Azathioprine and methotrexate have both been used successfully, both when steroid therapy has failed and as steroid-sparing agents.
- Tamoxifen (⚠ SE: thromboembolism) is a potential alternative when steroids are contraindicated. Protocols vary, and mechanisms are unclear (may increase fibroblastic release of antifibrotic TGF-β).
- Potential therapies include anti-CD20 therapy and TNF-α inhibitors.

Surgical management

- Preoperative medical therapy may have reduced inflammation.
- Open exploration with ureterolysis is the first step. The ureters (usually with JJ stents *in situ*) are identified, freed, and moved laterally.
- The ureters are then manipulated to prevent re-obstruction.
 - Wrapping with a protective layer of omental fat is the commonest approach.
 - Ureteric intraperitoneal transplantation is an alternative.

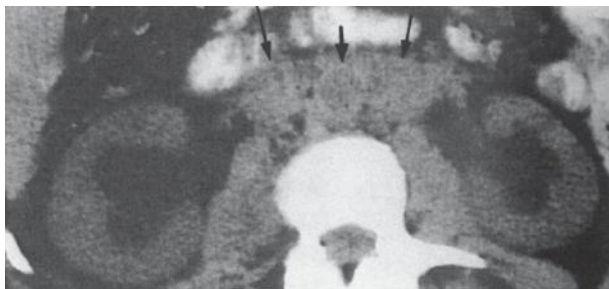


Fig. 9.2 Retroperitoneal fibrosis—CT appearances. Note the peri-aortic mass and aortic calcification. Reproduced with permission from Warrell D, Cox T, Firth, and Benz EJ (eds) (2004) *Oxford Textbook of Medicine*, 4th edn, p.454. Oxford University Press, Oxford.

Investigation of a renal mass

► The primary goal of investigation of a renal mass is to exclude malignancy.

Renal masses may be single or multiple, cystic or solid (see Table 9.7).

Table 9.7 Types of renal masses

	Solid	Cystic
Single	Renal cell carcinoma Angiomyolipoma Oncocytoma Xanthogranulomatous pyelonephritis Metanephric adenoma AV malformation	Simple cyst Complex cyst Cystic RCC
Multiple	Inherited, e.g. von Hippel–Lindau disease, tuberous sclerosis	Autosomal dominant (or recessive) polycystic kidney disease Acquired cystic disease

- They are often asymptomatic: ~50% of new cases of renal cancer are incidental findings on imaging.
- Simple renal cysts are commonly observed in normal kidneys. Their incidence increases with age.
- USS will not detect lesions <5mm.
- The differential diagnosis and investigation of renal cystic disease are discussed elsewhere (📖 p. 598).

See Table 9.8 for classification.

Simple cysts

- USS criteria:
 - Round.
 - Smooth-walled.
 - Anechoic.
 - Good ultrasound transmission through the cyst.
- If all these features are present, a cyst is very likely to be benign.
- ► If uncertainty persists, proceed to contrast-enhanced CT.
- CT criteria:
 - Smooth and thin-walled.
 - Similar density to water.
 - No contrast enhancement.
- The Bosniak classification is the standard for radiological assessment of renal cysts (see Table 9.8).
- Equivocal cases should be followed, with repeat scans every 6–12 months.

The solid renal mass

- The concern is malignancy (carcinoma), but solid lesions can also be benign (e.g. angiomyolipoma).

- CT, and particularly MRI, may detect small quantities of fat, highly suggestive of an angiomyolipoma.
- ⚠ However, imaging cannot exclude malignancy with absolute certainty.
- Lesions <1.5cm cannot be accurately characterized by imaging. Active surveillance of these is generally advocated.
- ► Features of concern:
 - Contrast enhancement.
 - Thickened or irregular wall.
 - Necrotic areas (implying rapid growth).
 - Diameter >3cm (more likely to metastasize).
- In these circumstances, removal is usually necessary.
- For smaller lesions in patients at high surgical risk, alternatives beyond surveillance are percutaneous radiofrequency ablation or cryotherapy.

Biopsy

- High false -ve rate is the principal problem with CT-guided biopsy.
- ⚠ If you find yourself discussing a biopsy—ask yourself, ‘Should I be considering removal?’.
- Haemorrhage is an important complication.
- ☠ The risk of tumour seeding along the needle track has probably been exaggerated in the past.
- Useful if mass in a single kidney.

Table 9.8 Bosniak classification of renal cysts


Bosniak class	Features	Malignant potential
I Simple cyst	Simple cyst, hairline thin wall, no septa, no calcifications, no solid components. No contrast enhancement.	0%
II Cystic lesion	A few hairline thin septations. Fine calcification in the wall or septa. Uniformly hyperdense lesions <3cm that are well marginated. No contrast enhancement.	
IIF Complex cyst	Increased number of septa, which may be minimally thickened. Nodular calcification. No contrast enhancement. Hyperdense intrarenal lesions ≥3cm also included here.	
III Indeterminate cyst	Cystic masses, with thick or multiple septation and irregular calcification. Contrast enhancement of wall or septa.	
IV Presumed malignant cyst	All of the above, with additional enhancing soft tissue components, independent of the wall or septum.	>85%

Reproduced from Bosniak MA *Radiology* 262(3) 781–5 (2012), with permission.

Renal cell carcinoma: general

Overview

- RCCs are adenocarcinomas arising from tubular epithelium.
- Account for >80% of primary malignant renal tumours and ~3% of cancers overall.
- Risk factors:
 - Smoking (1/3 of cases; often present with more advanced disease).
 - Long-standing hypertension (mechanism unknown).
 - Obesity.
 - Acquired cystic disease (including long standing ESRD patients and ADPKD).
 - Occupational exposures (cadmium, asbestos, and others).
 - Analgesic nephropathy.

Several important subtypes with specific pathological and molecular characteristics (see RCC: pathological and molecular subtypes,  p. 745).

Epidemiology

- Peak incidence age 60–70.
- 1.5:1 ♂:♀ ratio.
- More common in developed world.
- Incidence is increasing (partly because of small incidental tumours presenting earlier on imaging) and survival rates improving.

Genetics

- There is evidence for a strong genetic predisposition, including:
 - Risk of a second RCC is high in those with first at a young age.
 - Several hereditary syndromes are associated with RCC, including: von Hippel–Lindau (VHL) (most common), hereditary papillary renal carcinoma, familial oncocytoma, and Birt–Hogg–Dube syndrome.
- Factors suggesting a genetic influence in those without a defined hereditary syndrome include: onset age <40, multifocal disease, and close relatives with RCC.
- Several genetic mutations in both sporadic and hereditary RCC have been identified, particularly on the short arm of chromosome 3 (3p).
- Inactivating mutations of the *VHL* gene (chromosome 3p25) are particularly common.
- VHL protein functions as a tumour suppressor, targeting the products of hypoxia-inducible genes for proteasomal degradation. These include:
 - VEGF (→ angiogenesis).
 - TGF- α (→ cell growth).
- ↓ VHL protein → protein overexpression → epithelial proliferation + angiogenesis → neoplastic transformation.
- Genetic heterogeneity is suggested by the involvement of other genes.
 - Inactivating mutations of two genes (*SETD2* and *JARID1C*) involved in the histone integrity have recently been described.
 - Overexpression of p53 protein is present in ~50% tumours (and associated with a worse prognosis).

RCC: pathological and molecular subtypes

Clear cell (~75%)

Originate from proximal tubule. Cells have clear cytoplasm. Deletion of chromosome 3p typical.

Papillary (~15%)

Originate from proximal tubule but pathologically and genetically distinct. Frequently multifocal. Classified into two subtypes, with different genetic and prognostic inferences. Chromophilic.

Chromophobic (~5%)

Originate from intercalated cells. Lack the lipid content of clear cell tumours and appear darker macroscopically. Chromosome 3p intact.

Oncocytic (<5%)

Originate from cells of the collecting duct. Oncocytes are recognized as well-differentiated cells with eosinophilic, mitochondria-rich cytoplasm. Generally behave in a benign manner.

Collecting duct (<1%)

Younger age groups. Aggressive tumour, with some similarities to urothelial cancer. Often presents with haematuria.

Medullary carcinoma (<1%)

Variant of collecting duct carcinoma. Associated with sickle cell trait.

Translocation carcinomas (<1%)

Younger age groups, especially those receiving chemotherapy for other childhood cancers. Heterogeneous genetic abnormalities, often involving transcription factors. Incidence increasing.

von Hippel–Lindau (VHL) disease

- Autosomal dominant multisystem disorder, characterized by benign and malignant tumours in many organ systems.
- ~1 in 35,000 live births. ~90% penetrance by age 65.
- VHL gene inactivation → overproduction of vascular growth factors.
- Manifestations:
 - Renal involvement in 60%: cysts (70%), RCC (always clear cell, usually multiple) (50%), ESRD from the required surgical removal of renal tissue (25%).
 - Retinal and CNS haemangioblastomas.
 - Pheochromocytoma.
 - Pancreatic neuroendocrine tumours and pancreatic cysts.
 - Epididymal cystadenoma.
 - Endolymphatic sac tumours (arise in the temporal bone, causing hearing loss, tinnitus, vertigo, and facial nerve dysfunction).
- Families often subcategorized, according to their pheochromocytoma and RCC pedigree.
- Mean onset of clinically manifest disease is age mid-20s. A multidisciplinary approach, with surveillance from childhood, is mandatory.

Renal cell carcinoma: diagnosis

Clinical features

- <10% exhibit the classic triad of pain, haematuria, and a palpable mass.
- Up to 50% are asymptomatic (incidental radiological finding). This is increasing with the widespread use of abdominal imaging.
- Haematuria (→ invasion of the collecting system; occurs in ~40% of those presenting 'non-radiologically').
- Flank or back pain (→ capsular stretch), radiating to the groin, can occur with larger tumours.
- Palpable mass.
- Scrotal varicocele (left > right) due to testicular vein obstruction (finding one should always provoke suspicion. Arrange an USS).
- Lower limb oedema 2° to IVC invasion.
- ~25% present with metastases (nodes, skeletal, liver, lung, cerebral).

Paraneoplastic syndromes with RCC

- Paraneoplastic phenomena are relatively common with RCC.
- RCC has ∴ been called 'the internist's tumour' because it can present with non-specific symptoms to a general physician.
- These tend to occur late and suggest a poorer prognosis.
- Caused by tumour cytokine (e.g. IL-6) or hormone (e.g. EPO) production.
- Include:
 - Fever and night sweats.
 - Weight loss and cachexia.
 - Malaise.
 - Erythrocytosis (RCC produces EPO).
 - Disproportionate anaemia.
 - Hypercalcaemia (skeletal metastases or production of PTHrP).
 - Hepatic dysfunction without liver metastases (Stauffer syndrome).
 - 2° AA amyloid deposition.
 - Polymyalgia.
 - Dermatomyositis.
 - Neuropathy.
 - Hypertension (↑ renin).
 - Ectopic hormonal production (e.g. ACTH-like substance).
 - Elevated ESR.

Work-up

- Imaging (📖 p. 742):
 - USS: usually first-line.
 - CT: for diagnosis and initial staging. Chest CT for metastases.
 - MRI: more sensitive for collecting system and IVC involvement.
 - Bone scan: if skeletal pain, ↑ Ca^{2+} , or ↑ alkaline phosphatase.
 - PET: not used for routine staging. May detect occult metastases.
 - DMSA: to determine split renal function, i.e. what would the consequence of a nephrectomy be?

- Biopsy:
 - CT-guided. Increasingly used to guide treatment.
Risks: haemorrhage (tumour seeding has been overstated in the past).

Prognosis

Staging, histological grading, and tumour subtype are relevant, and models to integrate all three have been developed in some centres.

Staging

- The TNM (2010) classification is used (see Table 9.9).
 - T1N0: 5-year survival >90%; T4N2M1: 5-year survival <10%.

Table 9.9 The TNM stage classification for renal cell cancer

T	Primary tumour
T1a	Tumour <4cm; renal limited
T1b	Tumour >4cm, but ≤7cm; renal-limited
T2a	Tumour ≥7cm, but ≤10cm; renal-limited
T2b	Tumour ≥10cm; renal-limited
T3a	Invades renal vein or branches, or perirenal fat, but not beyond Gerota's fascia
T3b	Extends into vena cava below the diaphragm
T3c	Extends into vena cava wall or vena cava above the diaphragm
T4	Invades beyond Gerota's fascia, including extension into adrenal gland
N	Regional nodes
N0	No regional node involvement
N1	Single regional node
N2	More than one regional node
M	Distant metastases
M0	No distant metastases
M1	Distant metastases

Fuhrman's nuclear grade

- Grading, according to histological criteria, also predicts survival.
Fuhrman's grading (1–4) is the most widely used.

Tumour subtype

- Tumour subtype may also influence the prognosis of localized disease, e.g. chromophobe survival > papillary > clear cell.

Other

- Poor patient performance status and paraneoplastic symptoms are adverse prognostic indicators.
- Molecular and cytogenetic markers are likely to play a progressively more important role in the future.

Renal carcinoma: management and follow-up

Management

Management is directed by the possibility of cure—based principally on tumour staging. For localized disease, surgical resection alone may be curative. Unfortunately, tumours are often already locally advanced or metastatic at presentation. Recurrence after resection is not uncommon.

Surgery

- Radical nephrectomy is the conventional approach and preferred when evidence of local invasion (e.g. renal vein, perinephric fat, or adrenal).
- Partial nephrectomy (open or laparoscopic) may be favoured for smaller, non-invasive tumours. Outcomes are good and local recurrence rates low. Such ‘nephron-sparing’ surgery is particularly useful in several situations:
 - Single functioning kidney.
 - Contralateral kidney has significant functional impairment.
 - Bilateral tumours or hereditary multicentric disease.
- Surgery to remove isolated metastases (e.g. lung) is recommended in carefully selected cases.
- A debulking nephrectomy prior to systemic therapy has shown a survival benefit. Removal of RCCs rarely induces spontaneous remission of metastases through immunological mechanisms.
- 📌 The role of adjuvant systemic therapy, in addition to surgery, for localized disease is unproven. Trials are ongoing.

Energy ablation therapy

- Cryotherapy or radiofrequency ablation can be used to obliterate tumour tissue *in situ*.
- Option for smaller (<4cm) tumours in patients unsuitable for surgery.
- Follow-up data now emerging. Local recurrence not uncommon.

‘Conventional’ chemotherapy

- Limited role, as RCC, particularly clear cell tumours, often exhibit P-glycoprotein-mediated multidrug resistance.

Cytokines

- Systemic treatment of RCC is one of the most rapidly evolving areas in medical oncology. Enrolment into approved clinical trials should be encouraged.
- Cytokine therapy (IFN- α ± IL-2) was the standard first-line systemic therapy until relatively recently.
- Mechanism of action is unknown but probably involves induction of anti-tumour immunity.
- However, response rates were low and relatively short-lived. Remission in ~10%.
- High-dose IL-2 causes significant toxicity (→ proinflammatory cytokine cascades). ► Side effects common and often severe (↓ BP, arrhythmias, dyspnoea, fever, nausea, ↑ SCr, CNS toxicity, skin rashes). IFN- α SE: flu-like symptoms (fever, malaise, myalgia, etc.).

Molecularly targeted therapy

- Improved understanding of the molecular pathogenesis of RCC has identified VEGF and mTOR as targets for therapeutic intervention.
- Systemic therapy targeting VEGF is now the standard of care for first-line treatment of metastatic RCC.
- There are two approaches to VEGF inhibition:
 - Blockade of intracellular VEGF signalling through tyrosine kinase inhibition, e.g. sunitinib, sorafenib, and pazopanib. Sunitinib and pazopanib are NICE-approved and have become first-line treatment. SE: ↑ BP, renal and hepatic toxicity, thromboembolism, cardiac toxicity, thyroid dysfunction, GI toxicity, skin rashes.
 - Monoclonal Abs to circulating VEGF (e.g. bevacizumab). Rare in the UK.
- Temozolomide and everolimus inhibit mTOR and provide an option if disease progresses despite VEGF inhibition (SE: nausea, anorexia, anaemia, pneumonitis).

Follow-up

Surveillance for local and contralateral recurrence as well as metastatic disease is mandatory. The frequency of follow-up appointments and repeat imaging is based on risk stratification for each given clinical scenario. Several algorithms have been developed to assist this process.

Wilms' tumour (nephroblastoma)

- Embryonal neoplasm arising in the kidney. It is the commonest renal malignancy in children and represents ~8% of all childhood cancer.
- Peak age 3–4 years (rare age >10). ♂ = ♀.
- More common in a number of congenital syndromes, but these still represent only a small proportion of the total.
- *WT1* was the initial Wilms' associated gene identified. However, the situation is much more complex, with several others now known.
- Clinical features:
 - ~3/4 present with an abdominal mass (often noticed by a parent).
 - ~1/2 report abdominal pain.
 - ↑ BP (→ tumour renin production), haematuria, fever.
- Staging delineates local spread and presence of metastases (particularly pulmonary).
- ⚠️ Diagnostic biopsy not always undertaken (although desirable if preoperative chemotherapy is under consideration).
- Classic 'triphasic' histology: epithelial, stromal, and blastemal elements all coexist. Anaplastic features carry a worse prognosis.
- Treatment:
 - The majority of patients will be cured.
 - Surgery, followed by adjuvant chemotherapy (e.g. vincristine ± dactinomycin), as determined by staging. Preoperative chemotherapy is favoured in many centres. The use of radiotherapy is diminishing (→ subsequent growth restriction).
- Follow-up: pulmonary relapse is more common than renal. In addition, prospective assessment of the long-term side effects of anthracycline-based chemotherapy (e.g. cardiac function) is mandatory.

Tumours of the bladder: overview

- Bladder cancer is the second commonest malignancy of the urinary tract and one of the top five cancers in the UK and USA.
- Median age: 70; 2.5 ♂:1 ♀.
- Caucasians > black people (although prognosis worse in the latter).
- 90% are transitional cell cancers (TCCs), derived from urothelium.
- Although the bladder is the most common site, TCCs can arise anywhere from the renal pelvis to the urethra (□ p. 756).
- Squamous cell cancers (SCCs), often 2° to chronic schistosomal infection, are much more common in developing countries (~75% cases). SCCs can also be secondary to stone disease and other causes of chronic inflammation.
- Prognosis is varied, depending on histology and staging. Low-grade, 'superficial' tumours have a very different outcome from high-grade 'invasive' ones.
- TCCs have one of the highest recurrence rates of any malignancy.

Risk factors

Transitional cell (TCC)

- ▶~80% of TCCs are associated with an environmental exposure.
- Cigarette smoking is the most important (by far) and associated with a 4-fold risk (relevant carcinogens include β-naphthylamine and 4-aminobiphenyl).
- Aromatic amines, aniline dyes, and hydrocarbons. Occupations at ↑ risk include: petroleum industry and lorry drivers (diesel fumes), plumbers, metal workers, dry cleaners, painters, hairdressers, rubber, textile and leather industry workers.
- Urban > rural areas.
- Previous haemorrhagic cystitis from cyclophosphamide therapy (→ acrolein; a carcinogenic urinary metabolite. Mesna inactivates urinary acrolein and may be used as chemoprophylaxis).
- Previous pelvic radiotherapy.
- Prolonged immunosuppression (e.g. transplant recipient).
- Late risk after bladder augmentation procedure (e.g. ileocystoplasty).
- Phenacetin (an analgesic), prior to its withdrawal.
- ☞ High fluid intake may dilute carcinogens, reducing urothelial exposure and ∴ risk.

Squamous cell (SCC)

- Squamous metaplasia → ↑ risk of SCC.
- Causes: chronic cystitis, bladder stones, long-term urinary catheters.
- *Schistosoma haematobium* infection is responsible for the majority worldwide, particularly the Middle East.

Genetics

- Several genetic mutations have been identified.
 - Altered tumour suppressor expression, e.g. p53 (chromosome 17).
 - Deletion of 9p21 (site of tumour suppressor p16).
 - Aneuploidy of chromosomes 3, 7, and 17.
 - Altered c-myc and c-jun oncogene expression.

Clinical features

- Haematuria:
 - Painless visible haematuria in ~80% patients.
 - ~15% patients presenting with macroscopic haematuria will have bladder cancer.
 - <5% patients presenting with microscopic haematuria will have bladder cancer.
- Irritative symptoms (📖 p.78), e.g. frequency, urgency, nocturia, dysuria.
- More advanced disease: pain, pelvic mass, systemic symptoms (weight loss, fatigue, anorexia, etc.).

Investigations

- Urine cytology:
 - 100mL freshly voided urine. Avoid first morning sample.
 - Sensitivity is quite low and centre-dependent.
 - Sensitivity increases for higher-grade tumours (→ pleomorphism and increased nuclear:cytoplasmic ratio).
- Urinary biomarkers:
 - Novel protein and genetic markers are gradually expanding their diagnostic utility. They include tumour cell-associated antigens (via immunohistochemistry) and genetic abnormalities (via fluorescence *in situ* hybridization—FISH).
 - Many identified but few routinely available. Further proof of clinical utility is required.
 - Commercially available tests include: (i) a FISH assay with probes for chromosomes 3, 7, 17, and 9p21 and (ii) a quantitative immunoassay for nuclear matrix protein (NMP-22), a housekeeping protein active during cell division.
- Cystoscopy:
 - Size, number, position, morphology of tumours. Rigid cystoscopy allows biopsy.
 - Photodynamic cystoscopy: a photoactive substance that accumulates in neoplastic cells (e.g. 5-aminolevulinic acid) is instilled and fluoresces under light of the appropriate wavelength. Aids the identification of carcinoma *in situ* (CIS).
- Biopsy/cystoscopic resection:
 - Biopsy areas displaying abnormal urothelium.
 - Random biopsies may be necessary to detect CIS, including of prostatic urethra.
 - Inclusion of muscularis propria necessary to ensure accurate staging.
- Imaging:
 - USS to exclude hydronephrosis (even if SCr normal—as unilateral obstruction may occur). Not useful for staging.
 - CT: for staging. In addition, upper tracts must be assessed for synchronous tumours by contrast-enhanced CT.
 - MRI as good as CT for staging and may better delineate extravesical invasion.
 - Bone scan if skeletal pain, ↑ ALP, or ↑ Ca²⁺.
 - CXR for lung metastases if muscle-invasive (and if CT chest not undertaken during staging).
 - PET: limited role in local disease, as 18F-FDG undergoes urinary excretion. May have a role in detection/monitoring of metastases.

Tumours of the bladder: pathology and management

Pathology

- TCC (90%) > SCC (5%) > adenocarcinoma (2%) > sarcomas (rare) > small cell (rare).
- TCC has a range of phenotypic expressions: papillary (~70%), sessile (~10–20%), nodular (~10%), or carcinoma *in situ* (CIS).
- The usual growth pattern is papillary, projecting out into the bladder lumen. This may gradually invade deeper, breaching basement membrane, lamina propria, and, eventually, muscle, prior to distant spread.
- Often multifocal. ~30% tumours are synchronous at presentation (2° to the 'field change' effect of environmental exposures).
- WHO classifies tumours pathologically as low-grade (formerly grades 1–2) or high-grade (grade 3). Low-grade tumours rarely progress to more aggressive, muscle-invasive forms (see Table 9.10).
- The term 'superficial' tumour is misleading and best avoided. Low- and high-grade tumours follow different biological pathways, have different outcomes, and require different treatments, regardless of 'superficiality'.
- ► CIS does not imply early disease or a good outcome—it is often characterized by high-grade dysplasia and a poor prognosis. Many patients with CIS have coexisting papillary tumours ('pure' CIS in <10%).

Staging and prognosis

- The most significant prognostic factors are: (i) depth of invasion (stage); (ii) histological grade; (iii) presence of CIS; (iv) previous recurrences.
- Progression risk relates to grade. Low-grade <10% progression (rarely invade muscle). High-grade >30% progression.
- The majority of tumours (>70%) are non-muscle-invasive at diagnosis.
- Non-muscle-invasive tumours have a relatively good prognosis, with 5-year survival rates of >80%. Tumours are much more likely to recur than progress. 5-year survival deteriorates to <25% by stage T4.
- Prognosis therefore depends on both stage and grade. As a rough guide, for superficial tumours:
 - Ta low grade: prognosis very good.
 - Ta high grade: prognosis less good.
 - T1 low grade: prognosis good.
 - T1 high grade: prognosis poor.
- Diffuse CIS → higher recurrence rates and poorer prognosis.
- ~50% with muscle-invasive disease have occult metastases at diagnosis.
- Prognosis for those with distant disease is poor (<10% alive at 2 years).

Table 9.10 TNM staging of bladder cancer

T Primary tumour	
CIS	Carcinoma <i>in situ</i> , high-grade dysplasia, confined to the urothelium
Ta	Papillary tumour confined to the urothelium
T1	Invasion into the lamina propria
T2	Invasion into the muscularis propria
T3	Invasion into the perivesical fat
T4	Involvement of adjacent organs (e.g. prostate, rectum)
N Regional nodes	
N+	Lymph node involvement
M Distant metastases	
M+	Distant metastases

Management

- The depth of bladder wall invasion determines treatment (non-muscle-invasive: Ta, T1, and CIS. Muscle-invasive: T2–T4).

Non-muscle-invasive

- Transurethral resection (TURBT):
 - Smaller TCCs may be resected as one piece with underlying muscle. Larger tumours require more extensive resection.
 - Should be followed with a single dose of intravesical chemotherapy (e.g. mitomycin) to ↓ recurrence risk (administered within 6h of resection).
 - Repeat TURBT at ~6 weeks if: (i) residual tumour; (ii) no muscle in initial specimen (→ risk of understaging); (iii) high-grade disease.
- Subsequent treatment depends on the risk of recurrence and progression. Broadly:
 - Low-risk (Ta staging, <3 lesions, <3cm, low-grade dysplasia, papillary): follow with active surveillance.
 - High-risk (T1 staging or above, CIS, >3 lesions, >3cm, high-grade dysplasia, non-papillary): further intravesical treatment. Usually immunotherapy with bacille Calmette–Guérin (BCG). Usually induction treatment weekly for 6 weeks (+/– intermittent maintenance therapy for 1–3 years). Reduces progression risk by ~25% (SE: cystitis, haematuria, fever, arthralgia, hepatitis, and pneumonitis).

Muscle-invasive disease (or failure of conservative treatment)*Radical cystectomy with urinary diversion*

- Bladder removed with local lymph node dissection. The prostate and seminal vesicles are also removed in ♂ (SE: impotence), and cervix, uterus, ovaries, and anterior vagina in ♀.
- Commonly performed as open surgery, but laparoscopic and robotic techniques are becoming well established.
- Operative mortality of 2–5%, but overall perioperative morbidity (cardiovascular, atelectasis, sepsis, bowel and urine leaks, bleeding, wound infections) highly significant (~30–60%).
- There is evidence that neoadjuvant chemotherapy has a role prior to surgery, and it should be considered in all suitable patients.
- Urinary diversion:
 - Ileal conduit: a segment of ileum is used to create a stoma.
 - Orthotopic neobladder: pouch formed from bowel and connected to the urethra (prostatic urethral disease precludes this option).
 - Continent cutaneous pouch: similar to neobladder, but externalization using bowel (often appendix) allows drainage via a catheter.
- Metastatic disease is treated with cisplatin-based chemotherapy.
- In patients who are not considered to be candidates for cystectomy, bladder preservation with a radical TURBT +/- chemotherapy may be an option.

Radical external beam radiotherapy

- Generally reserved for those unfit for surgery, in a poor prognostic group, or needing palliation of local symptoms (e.g. haematuria).

Follow-up

See  p. 757.

Bladder adenocarcinoma

- Uncommon; ~2% malignant bladder tumours.
- Varied histologic patterns, but most often a glandular (enteric) morphology.
- Need to be differentiated from metastatic adenocarcinoma; e.g. prostate, colon.
- May arise from urachal remnant.
- Tend to be aggressive with extra-vesical extension at presentation.
- Treatment is surgical, with or without adjuvant chemotherapy and radiotherapy.



Tumours of the renal pelvis and ureter

Overview

- Tumours can arise anywhere from renal calyces to the vesicoureteric junction.
- 70% occur in the distal ureter, 25% mid, and 5% upper.
- Multicentric disease common, but bilateral tumours rare.
- ~5% of patients with bladder cancer will develop an upper tract lesion (higher for CIS).
- ~30–40% of patients with an upper tract lesion will develop a bladder tumour (→2° to field transformation effect and downstream seeding).
- Risk factors and genetics reflect those for bladder cancer (📖 p. 750)
- There are additional associations with Balkan endemic nephropathy (📖 p. 582), aristocholic, or Chinese herb, nephropathy (📖 p. 583) and Lynch syndrome.

Clinical features

- Frank haematuria (>60%).
- Flank pain 2° obstruction (30%).
- Lower urinary tract symptoms are uncommon. Many patients are asymptomatic.

Investigations

- Urine cytology is less sensitive than for bladder lesions.
- Contrast CT (or retrograde ureterography) to demonstrate a filling defect.
- The contralateral ureter must be evaluated.
- Cystoscopy to assess synchronous bladder tumour(s).
- Ureteroscopy ± biopsy. Biopsy will determine histological grade but may understage.
- Additional investigations, as for bladder tumours (📖 p. 751).

Pathology

- Benign tumours (e.g. fibroepithelial polyps) are rare.
- >90% are TCCs. Others: SCCs (→ risks include calculi, particularly staghorn calculi, and chronic infection), adenocarcinomas, small cell tumours, and metastases.
- Histologically identical to bladder tumours.
- ▶~40% are invasive at presentation—a far higher proportion than for bladder tumours.

Staging

Described by the TNM system, comparable to bladder tumours.

Management

- Endoscopic/percutaneous procedures:
 - 'Kidney-sparing' techniques.
 - Require careful patient selection (e.g. solitary kidney, bilateral lesions, unfit for more aggressive surgery).
 - Prospective surveillance for residual or recurrent tumour is essential.

- Nephroureterectomy:
 - Remains the benchmark.
 - Laparoscopic outcomes now as good as open surgery.
 - The entire ureter is removed, including a cuff of normal bladder (retained ureteric stumps → tumour recurrence in ~25%).
 - Segmental ureteric surgery with re-implantation may be possible for isolated, distal, low-grade tumours.
- Adjuvant chemotherapy is often given for T3/4 or node +ve disease.
- The role of topical chemotherapy or BCG immunotherapy is less well defined than for bladder tumours. However, single dose intravesical mitomycin C post nephroureterectomy appears to decrease the risk of recurrent disease.

Prognosis

- Determined by stage, histological grade, and the patient's age.
- Molecular and cytogenetic markers may play a greater prognostic role in the future.
- 5-year survival 60–90% for non-invasive disease. This falls to <5% for T4 tumours.

Follow-up of transitional cell tumours

- TCCs have one of the highest recurrence rates of any malignancy.
- Follow-up is determined by tumour grade, tumour stage, and the nature of initial treatment undertaken.
- Although based on repeat cystoscopy and imaging, clinical assessment and urine cytology (low sensitivity, higher specificity) also form part of surveillance.
- Urinary biomarkers are likely to play a more prominent future role.

Bladder tumours

- The majority of patients have an intact bladder and require long-term surveillance (i.e. large numbers, time-consuming, and costly).

Non-muscle-invasive (example regimens)

- Low-risk tumours: repeat cystoscopy at 3 months. 6–12-monthly thereafter.
- High-risk tumours: 3-monthly for the first year, 4-monthly for second, then 6-monthly for 5 years (or recurrence or progression occurs).

Muscle-invasive

- After radical cystectomy, patients remain at risk of distant metastases as well as recurrence in the upper tracts and urethra.
- CT imaging of the chest, abdomen, and pelvis 6–12-monthly is generally advocated (● whether early detection of metastases confers a survival advantage remains unproven).

Upper tract tumours

- Post-nephroureterectomy, both cystoscopic surveillance (3-monthly for the first year, then 6–12-monthly) and imaging (contrast CT or retrograde ureterography) of the contralateral ureter is necessary.
- Renal-sparing treatment strategies mandate particularly stringent surveillance, as recurrence risk is higher.

Benign prostatic enlargement: general

Background

- The prostate is a walnut-sized gland, surrounding the proximal urethra at the bladder apex. It comprises several zones, enclosed in an outer capsule, and functions to secrete an alkaline seminal fluid.
- Benign prostatic hyperplasia (BPH), or hypertrophy, results from cellular proliferation in the peri-urethral transition zone and is a histological diagnosis.
- Benign prostatic enlargement (BPE) is the clinical term referring to increased gland size.
- Gland enlargement → bladder outlet obstruction (BOO) → lower urinary tract symptoms (LUTS).
- BPH is an unwelcome consequence of ♂ ageing. ~50% develop it by age 60 and ~90% by age 85.

Pathophysiology

- Remains incompletely understood.
- Heightened sensitivity to multiple growth factors and cytokines appear important.
- Androgen dependency is particularly well described.
 - 5 α -reductase converts testosterone → dihydrotestosterone (DHT) within the prostate.
 - Prostatic DHT levels are not increased, but androgen receptor expression is demonstrably more abundant in hyperplastic glands.
 - BPH is rare in ♂ with hypogonadism.
- Proliferation (stromal > epithelial) occurs primarily in the peri-urethral transitional zone.
- Impaired apoptosis may also contribute to cell accumulation.
- Twin studies suggest a partial genetic susceptibility.
- LUTS result from:
 - Bladder outlet obstruction.
 - Bladder dysfunction: ↑ filling pressures → bladder wall hypertrophy, trabeculation, poor compliance (↓ smooth muscle, ↑ collagen), detrusor overactivity (sensitivity to small urine volumes), and, eventually, incomplete voiding.
 - α_1 -adrenergic receptor stimulation in prostatic smooth muscle and the bladder neck → ↑ smooth muscle tone.

Clinical features

- ► BPE adversely affects the quality of life of many ♂ over age 50.
- LUTS refresher: frequency, urgency, nocturia, poor or intermittent stream, dribbling, incomplete bladder emptying (see [p. 78](#)).
- Not all men with LUTS have BPE (and not all men with BPE have LUTS).
- Prostatic volume and symptoms tend to increase over time.
- More severe symptoms are commoner in black men.
- Severity and response to treatment can be assessed with the international prostate symptom score (IPSS) (see Box 9.3). The final question relates to quality of life and is a strong determinant of the need for intervention.
- Erectile dysfunction is commonly associated with LUTS.

- Ask about medications (diuretics, anticholinergics, tricyclics, opiates) and lifestyle factors (caffeine, alcohol, excess liquid intake).
- A self-completed voiding diary undertaken over a few days can further assess symptoms, liquid intake, and bladder capacity. Diaries can also serve as a platform for subsequent self-management.

Complications

- Bladder dysfunction, post-void residual urine volumes, acute urinary retention, recurrent UTIs, obstructive nephropathy, bladder stones, haematuria.

Differential diagnosis

- Prostate: prostate cancer, prostatitis, prostatodynia.
- Bladder: overactive bladder (see [□](#) p. 765), bladder dysfunction (e.g. neurological disorder), tumour, stone, foreign body (e.g. stent).
- Urethra: stricture (previous trauma, STD).

Box 9.3 International prostate symptom score (IPSS)

Scoring system

- Seven questions about LUTS. Answers are on a scale of 0–5.
- For questions 1–6, the choice of answers is: not at all (score 0); less than one time in five (1); less than half the time (2); about half the time (3); more than half the time (4); almost always (5).

Questions

1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?
2. Over the past month, how often have you had the urge to urinate again less than 2 hours after you finished urinating?
3. Over the past month, how often have you found you stopped and started again several times when you urinated?
4. Over the past month, how often have you found it difficult to postpone urination?
5. Over the past month, how often have you had a weak urinary stream? (Compare with your stream size at age 30.)
6. Over the past month, how often have you had to push or strain to begin urination?

For question 7, the choices are: never (0); once (1); twice (2); three times (3); four times (4); five or more times (5).

7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

Add the scores to give the category of symptom severity (mild <8; moderate 8–19; severe 20–35).

A further question addresses quality of life.

- If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about it?
 - Delighted (0), pleased (1), mostly satisfied (2), mixed feelings (3), mostly dissatisfied (4), unhappy (5), terrible (6).

Benign prostatic enlargement: investigation and management

Physical examination

- Palpable bladder.
- Digital rectal examination (DRE).
 - Size, consistency, contour, surface texture. Pain. Sphincter tone (↓ if underlying neurological disorder). Normal prostate volume is ~20g (~2 index fingers across).
- Neurological examination may be necessary.
- BP: may be elevated if chronic retention and obstructive uropathy. BP will also help plan management with selective vs. non-selective α blockade (📖 p. 761).

Investigations

- Urinalysis and MSU for M,C+S.
- PSA:
 - BPH does not cause prostate cancer, but ♂ at risk for BPH are also at risk for prostate cancer.
 - PSA levels correlate with prostate volume, so PSA is less specific for cancer in an individual with BPH.
 - May help predict response to treatment.
 - Measurement is recommended in many guidelines. Discuss with patient, and interpret in conjunction with DRE.
 - May be helpful if treatment with an 5α -reductase inhibitor is being considered, as these would be expected to reduce the PSA by ~50% after 6 months.
- eGFR:
 - Renal insufficiency is uncommon so not universally indicated at initial presentation (exception: high residual volume).
- USS:
 - Prostate and bladder volumes may predict response to treatment.
 - Exclude hydronephrosis if retention or ↓ eGFR.
- Transrectal ultrasound (TRUS):
 - For detailed volumetric assessment. Desirable prior to surgery and 5α -reductase inhibitors (see 📖 p. 761).
 - Consider if ↑ PSA.
- Upper tract imaging:
 - If haematuria, stones, ↓ eGFR, large residual volume, upper tract infection.
- Maximal flow rate (Q_{max}) and flow pattern:
 - Useful for initial assessment and to gauge response to treatment.
 - $>15\text{mL/s}$ is normal.
 - The shape of the flow pattern curve *may* help differentiate BOO from impaired bladder function.
- Urodynamics (pressure flow studies):
 - Invasive (urethral catheter and transrectal probe).
 - Differentiates BOO from detrusor dysfunction (BOO: ↑ voiding pressures ($>60\text{cmH}_2\text{O}$) and ↓ Q_{max} ($<15\text{mL/s}$)).

- Consider if complications, such as incontinence, or accurate prediction of surgical outcome is desirable (e.g. high-risk candidate).
- Flexible cystoscopy:
 - If atypical features (e.g. haematuria), prior to invasive treatment, or if an alternative diagnosis (e.g. stricture) is being considered.

Management

Overview

- Patients with minor symptoms (IPSS score <7), no complications, and an acceptable quality of life are managed with adaptive lifestyle measures and watchful waiting. Reassess at least annually.
 - Lifestyle measures: ↓ liquid intake (particularly night-time); modify diuretic therapy; ↓ caffeine and alcohol; void prior to bedtime, travel, or meetings. Improve glycaemic control in diabetic patients.
- Failed lifestyle measures, or moderate to severe symptoms (IPSS score ≥8) can be treated with drug therapy. A 3–6 point reduction in IPSS score can be expected (~60% men report an improvement).
- Indications for surgery: acute urinary retention, recurrent macroscopic haematuria, recurrent UTIs, obstructive nephropathy, failure of medical therapy.

Drug therapy

α_1 receptor blockade

- α_1 -adrenergic receptor-mediated smooth muscle tone in both prostate and bladder neck contribute to LUTS. There are several receptor subtypes, with the α_{1a} receptor most relevant in prostatic tissue.
- Selective α_{1a} antagonists require less dose titration and may have fewer vascular side effects.
 - Tamsulosin 0.4mg PO od or alfuzosin 10mg PO od.
- Non- α_{1a} selective agents are still effective (and less expensive) but require more careful dose titration.
 - Doxazosin 1mg PO od (bedtime), titrate to maintenance 2–4mg.
 - Terazosin 1mg PO od (bedtime), titrate to maintenance 5–10mg.
- SE: postural ↓ BP, dizziness, ejaculatory disorder, nasal congestion.
- Rapidly improve symptoms (within days) but do not demonstrably ↓ the overall risk of acute retention or requirement for surgery.
- Intraoperative floppy iris syndrome (miosis, iris billowing, and prolapse) is more common during cataract surgery in those receiving α_1 -blockers (particularly tamsulosin) and causes technical issues for the surgeon.

5 α -reductase inhibitors

- Inhibit 5 α -reductase ∴ block prostatic conversion of testosterone → DHT and impede gland growth.
- Improve LUTS through a reduction in prostate volume.
- Greatest benefit in those with higher initial prostate volume (>40g on DRE or USS) or progression of symptoms despite on an α -blocker.
- Peak effect is delayed for 3–6 months. Continue long term.
- ↓ incidence of acute retention and the requirement for surgery.
- Examples: finasteride 5mg PO od, dutasteride 0.5mg PO od.

- Side effects: ↓ libido, erectile dysfunction, ejaculatory disorder, gynaecomastia, but often better tolerated than α -blockers.
- May ↓ PSA by 50% ∴ caution when interpreting measurements.
- ⚠ 5 α -reductase inhibitors have been associated with a higher risk of high-grade prostate cancer in clinical trials, albeit with a lower incidence of prostate cancer overall (this may be a consequence of sampling a smaller prostate).

Combination therapy

- Since α -blockers provide rapid symptomatic relief and 5 α -reductase inhibitors gradually influence underlying pathology, concomitant use makes good sense, particularly where initial prostate volumes are high.
- Combination → ↓ progression, improved symptoms (and IPSS score), ↓ risk of retention, and ↓ requirement for surgery.
- Withdrawal of the α -blocker may be possible after 6 months.

Anticholinergic agents

- May be beneficial where storage LUTS (urgency, frequency, nocturia, small urine volumes, urge incontinence) dominate symptoms without significant obstruction or a residual volume.
- This clinical scenario is often described as an 'overactive bladder'.
- Examples: oxybutynin, tolterodine, solifenacin, and darifenacin.
- Generally effective and well-tolerated, although dry mouth common.
- Also consider bladder training and biofeedback techniques.
- ⚠ May worsen obstructive (voiding) symptoms, increase residual volumes, and precipitate urinary retention.

Phytotherapy

- Plant extracts are widely used for both self- and prescribed treatment.
- Suggested active components include polysaccharides, fatty acids, phytosterols, lectins, and flavonoids. Anti-androgenic, anti-inflammatory, and other effects have been postulated.
- Extracts of saw palmetto (American dwarf palm) and *Pygeum africanum* (African plum tree) are the most common.
- ⚠ Evidence base is limited. Some studies demonstrate modest symptomatic improvement, whilst others show no benefit over placebo.
- Minimal adverse effects.

Phosphodiesterase-5 enzyme inhibitors

- Sildenafil or tadalafil may improve mild to moderate LUTS (nitric oxide may mediate relaxation of the prostatic urethra).
- Role needs further clarification but may prove useful where coexisting BPE and erectile dysfunction.
- ⚠ There is a potential interaction between α blockers and PDE-5 inhibitors causing postural hypotension.

Invasive procedures

See Table 9.11.

Transurethral resection of prostate (TURP)

- The historical gold standard, although the number performed is falling, as alternatives, including medical therapies, are introduced and refined.
- Involves the passage of a diathermy loop through a urethral sheath. Prostatic tissue is shaved away under direct vision. Prostate 'chips' are available for histology (~5% incidental prostate cancer).
- Requires hospitalization. Regional or general anaesthesia.
- Morbidity (~20% → prolonged hospital stay) and mortality (~0.25%).
- Good symptomatic and urodynamic outcomes.
- Complications:
 - Bleeding (leave catheter in place until cleared).
 - Urinary infection (prophylaxis is generally given).
 - Urethral stricture.
 - Absorption of hypotonic irrigation fluid through exposed veins → ↓ Na⁺ (now rare with saline irrigation for bipolar cautery).
 - Damage to bladder sphincter mechanism.
 - Retrograde ejaculation into the bladder.
 - Urinary incontinence.
 - Erectile dysfunction (nerve damage).

Open prostatectomy

- Very large prostates (>100g). Inner core of the prostate shelled out via a lower abdominal incision. Laparoscopic technique is an alternative.

Bladder neck incision and transurethral incision of the prostate (TUIP)

- The main alternative to TURP for many years. Short GA. An incision is made to widen the prostatic urethra and bladder neck. Suitable for patients with smaller prostates if unfit for TURP. Fewer complications but retreatment often necessary.

Newer techniques

- See Table 9.11.
- Longer-term outcome data for newer therapies are still emerging.

Table 9.11 Prostate: surgical techniques**Non-TURP surgery**

Bladder neck incision and transurethral incision of prostate (TUIP)

See text.

Open prostatectomy

Very large prostates. See text.

TURP

Monopolar

Requires hypotonic glycine irrigation.

Bipolar

Normal saline irrigation.

Laser techniques—vaporization or ablation

Photoselective vaporisation of the prostate (PVP)

KTP (potassium titanyl phosphate) laser.
So called 'green light' laser surgery.
Ambulatory setting with minimal anaesthesia.
Good outcomes. Gaining in popularity.

Holmium laser ablation of the prostate (HoLAP)

Similar to PVP, but with an alternative laser.

Laser techniques—enucleation

Holmium laser enucleation of the prostate (HoLEP)

Laser used to cut and/or enucleate the prostate.
Similar technique to TURP.
Good symptomatic and urodynamic outcomes.
Pros: ↓ bleeding, fluid absorption, impotence and retrograde ejaculation. ↓ length of stay.
Cons: irritative LUTS persists for a few weeks.

Other

Transurethral microwave therapy (TUMT)

Delivers energy via a catheter.
Ambulatory setting with minimal anaesthesia.
Associated with significant prostatic swelling (catheter required until this subsides).
Repeat treatment or surgery may be necessary.

Transurethral needle ablation (TUNA)

High frequency radio waves → thermal injury.
Ambulatory setting. Good outcomes.

Mechanical methods

Prostatic stents are very rarely used (principally in a palliative setting).
Encrustation, pain, incontinence, and overgrowth of tissue (making removal difficult) are common.

The overactive bladder

Introduction

- An important syndrome defined by symptoms: urinary urgency (\pm incontinence) dominates, usually with frequency ($\geq 8x$ in a 24h period) and sometimes with nocturia ($\geq 3x$ at night).
- Urgency is a sudden, overwhelming, desire to pass urine. It is an unpleasant symptom that has a debilitating impact on quality of life.
- Pathophysiology appears multifactorial, but involves detrusor overactivity. Possible mechanisms: increased muscarinic sensitivity, overactive afferent sensory pathways and subtle urothelial dysfunction.

Investigation

- ► Infection should always be excluded: urinalysis, MSU for M, C+S.
- Bladder diary, symptom questionnaires (many available),
- Other: assessment of post-void residual volume (usually USS—further assessment may be necessary if $>150\text{mL}$), urodynamics (characteristic phasic increases in detrusor activity) \pm cystoscopy in atypical or refractory cases.

Management

- Lifestyle modifications
 - Modify amount and timing of fluid intake, absorbent pads if incontinence, double void techniques (if residual volume).
 - Bladder training. This is an organised regime of voiding that can be highly successful, but requires (persistent) patient motivation.
 - Pelvic floor muscle therapy improves urethral sphincter control and may be effective, esp. in younger patients. Use in conjunction with biofeedback electrodes (abdominal, anal, vaginal) is common.
- Anticholinergics.
 - Inhibit involuntary detrusor muscle contraction; examples: tolterodine, oxybutynin and solifenacin
 - SE: dry mouth, constipation, blurred vision, confusion (Δ elderly).
 - Contraindications: BOO and narrow angle glaucoma
- β_3 adrenergic agonists
 - Recently introduced after success in clinical trials; e.g. mirabegron.
- Botulinum toxin.
 - Inhibits acetylcholine release and therefore detrusor stimulation. Requires direct detrusor injection. Good symptomatic improvement in clinical trials (including incontinence).
- Sacral neuromodulation.
 - Surgical electrode insertion at S2-3 level. An external pulse generator confirms efficacy prior to permanent implantation.
 - Symptomatic improvement in $\sim 2/3$ rds (may persist 3–5 years).
 - SE: pain at implant site, lead migration, leg pain, urinary retention, altered bowel habit.
- Surgery (last resort).
 - Augmentation entero-cystoplasty (with a GI segment, usually ileum) to \uparrow functional bladder capacity and \downarrow intravesical pressure.
 - Ileal conduit formation in refractory cases.

Prostate cancer: general

Background

Although it is often stated that more men die *with* prostate cancer than *of* prostate cancer, this still means that many men succumb to the disease every year. In addition, this belief may only hold true for populations where PSA testing is high and not where men present with symptomatic disease. Prostate cancer is the second commonest cause of cancer death in men in the UK after lung cancer. However, the clinical phenotype ranges from microscopic, slow-growing, well-differentiated tumours to aggressive cancers with rapid local invasion and distant spread. This has meant that screening for prostate cancer has become a very controversial topic.

Epidemiology

- Incidence has risen steadily since the mid-1970s. Reasons: ageing population, improved cancer registries, improved diagnostic accuracy, incidental cancer histology of prostate 'chips' at TURP. But, most importantly, the widespread use of PSA testing (and TRUS biopsies) has led to the diagnosis of cancers that would not previously have come to clinical attention during a man's lifetime.
- Very rare age <40, uncommon age <50. Common age >80 (found at post-mortem in 80%).
- ~1 in 6 ♂ will develop the disease, and ~1 in 25 will die from it.
- Average age at diagnosis 70–74, average age at death 80–84.
- A variation in the prevalence of prostate cancer around the world (Europe, USA, and Australia > Asia and North Africa) suggests genetic factors.
- Black men > white men > Asian men (possibly 2° to hormonal differences).
- Familial predisposition also occurs (~5–10% cases). Such patients tend to present ~5–10 years earlier.
- 🦋 Other risk factors may have a limited role: obesity, diet (high in animal fat, low in vegetables), and hormones (there appear to be no differences in serum androgen concentrations, but the use of 5 α -reductase inhibitors for BPH reduces prostate cancer incidence overall, albeit with an increase in higher-grade tumours).

Genetics

- There is evidence for a genetic component, but the identification of specific genes has proved difficult.
- Risk is increased $\times 2$ in ♂ with ≥ 1 affected first-degree relatives. Risk increases with the number of affected family members, especially if relatives are diagnosed at a young age (<60).
- There is a high rate of disease concordance in identical twins.
- Several single nucleotide polymorphisms (e.g. in the 8q24 and 17q regions) are associated with an increased risk (the more SNPs present, the higher the risk).
- The presence of *BRCA1* and (particularly) *BRCA2* mutations appears to increase risk (and worsen prognosis).

- Recently, a novel G84E mutation in the transcription factor *HOXB13* in the 17q region has been associated with a significantly increased risk of hereditary prostate cancer.

Pathology

- High-grade prostatic intraepithelial neoplasia (PIN) is a precursor of malignancy. It is intermediate between normal prostate epithelium and cancer.
- 95% adenocarcinomas. 4% have transitional cell morphology (arising from prostatic urethral urothelium). Squamous cell and neuroendocrine tumours are very rare.
- 70% arise in the peripheral, 15–20% in the central, and 10–15% in the transitional zone. Many cancers are multifocal, involving multiple zones.
- Local invasion causes spread into the bladder neck (transition zone tumours) and ejaculatory ducts and seminal vesicles (peripheral zone tumours).
- Capsular penetration, with spread along the perineural or vascular spaces, occurs relatively late.
- Metastasizes to bone more commonly than any other site, causing sclerotic lesions.
- The natural history of the disease is extremely variable. Some low-grade tumours follow an indolent course, whilst others rapidly invade and metastasize.

Clinical features

Prostate cancers are often identified in asymptomatic patients, following an abnormal screening PSA level or DRE (or as an incidental pathologic finding at TURP).

Local disease

- LUTS (often late and more likely to be 2° to BPE), erectile dysfunction, haematospermia.
- Urinary retention, back or leg pain, and frank haematuria were more common in the pre-PSA era.

Advanced disease

- Weight loss and anorexia.
- Anaemia.
- Bone marrow suppression.
- Skeletal pain.
- Spinal cord compression.
- Leg swelling and pain 2° to venous and lymphatic obstruction.
- Uraemic symptoms from obstructive uropathy.

Physical examination

- DRE: nodules, changes in texture, asymmetry. Obliteration of the lateral sulcus or seminal vesical involvement indicates locally advanced disease. ⚠ Many cancers are found in glands that feel normal. Furthermore, an abnormal prostate on DRE should always be investigated, even if the PSA is normal (~20% patients).
- Distended bladder.
- Abnormal lower limbs or neurological findings.

Prostate cancer: investigation

Investigations

- Urine for M,C+S.
- PSA (📖 p. 772).
- U&E, eGFR, Ca^{2+} , alkaline phosphatase (skeletal involvement).
- Transrectal ultrasound (TRUS):
 - Used to evaluate abnormalities on DRE and to guide biopsy.
 - Tumours are often, but not universally, hypoechoic.
 - Also permits gland volume measurement.
 - Useful prior to focal therapy (e.g. cryotherapy) and for the detection of seminal vesicle invasion or extracapsular extension.
 - Biopsy is usually necessary, regardless of TRUS appearances, as TRUS alone is not sufficiently sensitive.
- TRUS-guided biopsy:
 - Indicated for tissue diagnosis in those with \uparrow PSA or abnormal DRE.
 - Performed as an ambulatory technique under LA.
 - Extended biopsy protocols, with more extensive sampling, is now the norm. These usually involve the removal of at least 10–12 cores.
 - Repeat biopsy may be necessary.
 - A transperineal (TP) approach is also commonly used and has the advantage of allowing additional samples to be taken (particularly when a TRUS biopsy has proved inconclusive).
 - Complications: haemospermia (common), haematuria, pain, Δ infection, voiding difficulties, PR bleeding.
- Imaging:
 - USS pre- and post-micturition (with flow rate) + upper tracts if significant BOO or residual bladder volume.
- Further imaging contributes to pre-treatment staging:
 - Both CT and MRI can detect local tumour invasion and lymphadenopathy. MRI generally provides more accurate T staging.
 - Endorectal MRI, via an endorectal probe, improves spatial resolution of MRI for zonal anatomy, extracapsular extension, and seminal vesicle involvement.
 - Pre-biopsy 3-Tesla multiparametric MRI is increasingly used to identify suspicious areas that can subsequently be targeted for TRUS or TP-biopsy. These scans can also generate a cancer risk score.
 - MR spectroscopy imaging (MRSI), a technique that utilizes metabolite ratios within prostate tissue to distinguish normal from malignant tissue, has an evolving role.
 - Bone scan: if T3 or T4 disease, PSA $>20\text{ng/mL}$, skeletal symptoms, $\uparrow \text{Ca}^{2+}$ or alkaline phosphatase. Correlate with plain X-rays.
 - Prostate-specific membrane antigen (PSMA) PET: a radiolabelled mAb to prostate-specific membrane antigen can localize soft tissue metastases.
 - FDG-PET has only limited utility: tracer uptake is variable, and accumulation in the bladder obscures the area of interest.

Staging

- Staging guides initial therapy and is undertaken using the TNM system.
- In addition, histological grade is determined from biopsy specimens, using the Gleason score.
- Gleason grade is based on the extent to which the epithelium has a normal glandular structure (1–5). Experience and skill on the part of the pathologist is essential.
- Based on growth pattern and degree of differentiation, tumours are graded from 1 to 5 where grade 1 is the most and grade 5 the least differentiated. Adding together the values for the two most prevalent patterns of differentiation derives a composite Gleason score, e.g. for a biopsy consisting of predominant grade 4 and secondary grade 3 disease, the composite score is 4 + 3, or 7.
- 2–4 = low-grade or well-differentiated; 5–7 = moderate grade or moderately differentiated; 8–10 = high-grade or poorly differentiated.
- In the TNM classification, anatomic staging is undertaken both clinically (cT) and pathologically (pT) (see Table 9.12).
 - cT (based on DRE, imaging, and TRUS biopsy) informs initial treatment decisions but may underestimate disease extent.
 - pT (restaging at prostatectomy) provides a more exact assessment.

Table 9.12 The 2010 TNM stage classification for prostate cancer

T Primary tumour		
cT1	Not palpable or visible on imaging (e.g. identified at TURP, or on TRUS biopsy performed to investigate elevated PSA)	Subdivided a–c, based upon the extent of gland involvement
cT2	Palpable, confined to prostate	
cT3	Extends through capsule.	
cT4	Fixed to, or invades, adjacent structures	
pT2	Confined to prostate	Subdivided a–c, based upon the extent of gland involvement
pT3	Extraprostatic extension	
pT4	Invasion (rectum, pelvic wall, or levator muscles)	
N Regional nodes		
Nx	Not assessed	
N0	Negative	
N1	Positive	
M Distant metastases		
M0	No metastases	
M1	Distant metastases—subclassified, according to location(s)	

- Disease-free survival for localized prostate cancer varies widely, as treatment outcomes depend on tumour aggressiveness.
- With this in mind, the 2010 TNM classification uses clinical stage, Gleason score, and PSA to inform five prognostic groups.
- Other models have previously been developed to predict higher risk disease. Examples: Memorial Sloan-Kettering Cancer Center risk groups (🔗 <http://www.mskcc.org/mskcc/html/10088.cfm>) and Partin tables (🔗 <http://urology.jhu.edu/prostate/partintables.php>).
- There is also growing interest in molecular prognostic markers, such as p53, E-cadherin, cathepsin-D, and angiogenesis (microvessel density).
- Overall, 5-year survival for low-volume, localized disease (often detected through screening) is 100% but ~30% in those with metastases.

Prostate cancer: screening

Introduction

Cancer screening

Successful screening requires accurate, acceptable, and cost-effective tests that identify clinically relevant cancers at a preclinical stage. Treatments should be available that can improve outcomes when administered early (and not cause harm).

Prostate cancer screening rationale

Early detection and management of asymptomatic prostate cancer through screening could reduce morbidity and mortality, compared to treatment instituted at the time of clinical presentation and diagnosis.

Prostate-specific antigen (PSA)

- PSA is an epithelial cell glycoprotein that liquefies semen.
- Malignant prostate tissue generates more PSA in the blood than normal or hyperplastic tissue (\uparrow cellularity + disruption of the prostate: blood barrier).
- Developed for cancer surveillance, but use as a screening tool grew rapidly: by 2001, 75% aged >50 in the USA had undergone testing.
- PSA has doubled the lifetime risk of a diagnosis of prostate cancer.
- $\sim 90\%$ of prostate cancers are now detected through PSA screening.
- It is difficult to define a normal range for PSA—it is a continuum that increases with age >40 (Δ a 'normal' PSA does not rule out cancer).
- Nonetheless, 0–4.0ng/mL is the generally accepted range (see Box 9.4). A PSA of >4.0 ng/mL gives:
 - $\sim 20\%$ sensitivity and $\sim 90\%$ specificity for prostate cancer.
 - Positive predictive value $\sim 30\%$ ($>50\%$ for PSA levels >10 ng/mL), i.e. $\sim 2/3$ of σ with an elevated PSA do not have cancer.
- If PSA >10 ng/mL, $<50\%$ tumours will be prostate-localized.
- Other causes of an \uparrow PSA: BPE, prostatitis, cystitis, ejaculation (in previous 48h), perineal trauma, vigorous exercise, urinary retention, DRE (minimal effect), prostate biopsy (in previous 6 weeks).
- Conversely, treatment with 5 α -reductase inhibitors \downarrow PSA by $\sim 50\%$.

Box 9.4 Measures to improve diagnostic utility of PSA

- *Lower PSA cut-off* (e.g. <3 ng/mL). Involves a trade-off between sensitivity (which improves) and specificity (which deteriorates), i.e. more false positives and more unnecessary biopsies.
- *PSA velocity*. PSA increases more rapidly in σ with cancer. A rise of >0.75 ng/mL/year suggests increased risk.
- *PSA density*. Prostate cancers produce more PSA per volume of tissue than benign conditions. Requires TRUS or endorectal MRI to determine prostate volume, so a specialist tool only.
- *Free PSA*. PSA exists in a free, as well as bound, form. The ratio of free to total PSA is reduced in men with cancer ($<25\%$).
- *Age- (or race-) specific reference ranges*, for example:
 - Age 50–59: 0–3.0ng/mL; age 60–69: 0–4.0ng/mL; age >70 : 0–5.0ng/mL.

Potential benefits

- May detect prostate cancer before symptoms manifest.
- May detect early cancer, enabling cure or life-extending treatment.

Why the ongoing controversy?

Screening is certainly associated with detection of more cancers, but:

- PSA testing was introduced without evidence from clinical trials. Although patchy observational data lend support to screening, the two largest randomized controlled studies have proved inconsistent.
 - The European Randomised Study of Screening for Prostate Cancer (ERSPC) demonstrated a 20% ↓ in mortality in men aged 55–69 after 9 years. It suggested saving one life would require diagnosis and treatment in 48 men.
 - The United States Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial has found no benefit after 13 years.
 - Neither study is flawless—both have been subjected to criticism.
- A significant number of tumours detected are clinically indolent, i.e. unlikely to cause clinical illness during a man's lifetime.
- The ideal screening investigation would identify asymptomatic men with aggressive localized tumours. PSA testing falls short of this aspiration, as it cannot differentiate slow-growing from aggressive cancers.
- PSA screening has inadequate sensitivity and specificity.
- Optimal screening intervals are unclear.
- PSA testing is not cancer-specific (also elevated in benign conditions) or diagnostic (it triggers further diagnostic investigation, i.e. biopsy).
- It is not clear if it should be combined with DRE for initial screening (variably recommended in international guidelines).
- The optimal treatment for early cancer is unknown—active surveillance might be as good as radical prostatectomy or radiotherapy.
 - However, the majority with an early-stage cancer (understandably) opt for aggressive treatment.
 - Such (over-) treatment can cause harm. Complications include urinary, sexual, and bowel dysfunction (as well as anxiety).

Guidelines

- Routine screening is not currently recommended in the UK. Rather, a programme of informed choice is suggested, i.e. men concerned about prostate cancer should receive clear and balanced information about the pros and cons of PSA testing.
- In the USA, both the American Cancer Society and American Urological Association advocate screening. However, the influential Preventative Services Task Force has recently recommended against it. This has refuelled an already long running debate in a country where prostate cancer screening costs an estimated \$3 billion annually.
- In general, screening, or at least a discussion about screening, is recommended for men aged ≥ 50 on an annual basis, unless life expectancy is < 10 years (through comorbidity or age > 75).
- Discussions should begin age 40–45 in black men or those with a family history.

Prostate cancer: management

Overview

The overall direction of treatment should be guided by:

- Life expectancy (as determined by age and comorbidity).
- Predictions of tumour aggressiveness.
- Informed patient choice (see Table 9.13 for risk stratification).

Localized (prostate-limited) disease

Overall 10-year survival is >90%. Treatments include radical prostatectomy, radiation (either brachytherapy or external beam radiotherapy), and active surveillance. If any offers an advantage is controversial. Ongoing clinical trials (e.g. PIVOT, ProtecT) hope to resolve this.

Table 9.13 Risk stratification for localized prostate cancer

	PSA (ng/mL)		Gleason score		Clinical stage
Low risk	<10	and	≤6	and	T1–T2a
Intermediate	10–20	or	7	or	T2b–T2c
High risk	>20	or	8–10	or	T3–T4

Table 9.14 Management options for localized prostate cancer

	Low risk	Intermediate	High risk
Watchful waiting	Option	Option	Option
Active surveillance	Preferred	Option	Not advocated
Prostatectomy	Option	Preferred	Preferred
Brachytherapy	Option	Option	Not advocated
Radiotherapy	Option	Preferred	Preferred

Regular follow-up, including PSA, is mandatory. PSA post-prostatectomy should be <0.2ng/mL and post-radiation <0.5ng/mL. PSA doubling time may also be used as an indicator of the need for 'salvage' treatment.

Locally advanced (non-prostate-limited) disease

Androgen ablation with radiotherapy is generally advocated. Prostatectomy may be appropriate in selected cases.

Metastatic disease

The goals are to control symptoms and slow further progression.

Treatment modalities

See Table 9.14 for management options.

Watchful waiting

Monitoring with hormonal manipulation and palliation when disease progression occurs. Usually reserved for elderly, comorbid patients.

Active surveillance

Definitive treatment (surgery/radiation) is deferred until evidence of progression, with the aim of avoiding unnecessary complications in those whose cancers may not progress. PSA is performed 3–6-monthly and DRE annually. Most protocols include repeat biopsy(s).

Radical prostatectomy

- The prostate and seminal vesicles are completely removed. Lymph node sampling and dissection is often undertaken.
- Retropubic approach: open or laparoscopic technique, the latter often with robotic assistance. Perineal approach: less pain, hidden scar, and shorter hospital stay, but less access to lymph nodes.
- Complications: impotence, stricture, urinary and faecal incontinence.
- ☛ Surgical margins and lymph node positivity will determine need for adjuvant radiotherapy or hormone manipulation. Trials ongoing.

External beam radiotherapy

SE: radiation proctitis, cystitis, and urethritis. Erectile dysfunction.

Brachytherapy

Transperineal implantation of radioactive seeds.

Hormone-based therapy (androgen deprivation)

- Aims to decrease androgenic tumour stimulation and ∴ delay progression.
- Bilateral surgical orchidectomy (castration): effective but unpopular.
- ‘Medical’ castration:
 - Gonadotropin-releasing hormone (GnRH) analogues →↓ luteinizing hormone (LH) production →↓ testicular androgen synthesis. Initially, ↑ androgen production, potentially causing disease ‘flare’. Examples: leuprolide, goserelin (depot formulations often used).
 - GnRH antagonists → block GnRH receptors without initial flare. Example: degarelix.
 - Oestrogens →↓ hypothalamic GnRH release →↓ pituitary LH release →↓ testicular androgens. Example: diethylstilbestrol.
 - Anti-androgens → competitive blockade of androgen receptors. Since androgen levels remain normal, side effects (esp. impotence) are fewer (although gynaecomastia can be problematic). Examples: bicalutamide, flutamide. Often used in together with a GnRH analogue, either initially (to ↓ androgen flare) or continuously (to block 10% contribution of adrenally synthesized androgens).
 - SE: ► common and require detailed discussion. Sexual dysfunction (majority), hot flushes (majority), fatigue, anaemia, muscle wasting, osteoporosis (and fractures), gynaecomastia, ↓ genitalia size, ↓ body hair, psychological changes.

- Intermittent treatment regimens (according to PSA) are often used, with increasing evidence to support this approach.
- Eventual PSA 'escape', despite castrate levels of testosterone heralding a deteriorating prognosis.
- Second-line hormonal treatments, including abiraterone and enzalutamide, significantly improve survival and show that the androgen receptor remains a relevant therapeutic target despite castrate levels of testosterone. Corticosteroids, e.g. dexamethasone (→ ACTH suppression → ↓ adrenal androgens) have a limited role.

Other

- Chemotherapy (docetaxel, cabazitaxel) reserved for 'castration-resistant' tumours.
- Several new agents have shown significant promise and are either in, or about to enter, clinical practice. These include radioisotopes (alpharadin) and bone-targeting agents, such as bisphosphonates (zoledronic acid, mAb directed against RANKL (denosumab), and immunotherapy.

Fluids and electrolytes

- Sodium: salt and water balance 778
- Hyponatraemia—approach 780
- Hyponatraemia—assessment 782
- Management of hyponatraemia 784
- Hyponatraemia with encephalopathy 786
- Hypernatraemia 788
- Treatment of hypernatraemia 790
- Oedema and its treatment 791
- Diuretics 792
- Potassium 794
- Hyperkalaemia 796
- Hypokalaemia 798
- Bartter's, Gitelman's and Liddle's syndromes 800
- Calcium, magnesium, and phosphorus 802
- Hypocalcaemia 804
- Hypercalcaemia 806
- Hypomagnesaemia 808
- Hypermagnesaemia 810
- Hyperphosphataemia 811
- Hypophosphataemia 812
- Acid–base 814
- Excretion: the kidney in acid–base 818
- Metabolic acidosis 820
- Renal tubular acidosis 824
- Lactic acidosis 828
- Alkalosis 830
- Mixed disturbances 834
- Tubular rarities 836

Sodium: salt and water balance

The human body is made up of 50–60% water by weight. More accurately, total body water (TBW) in litres can be estimated as weight (kg) \times a correction factor, as in Table 10.1.

Table 10.1 Estimation of TBW

	♂	♀
<65 years old	0.6	0.5
>65 years old	0.5	0.45

So, in a 70kg ♂ <65 years old, TBW = $0.6 \times 70 = 42\text{L}$. Water is contained in specific compartments:

- Intracellular space ($\sim 2/3$ TBW, or 28L in a 70kg ♂).
- Extracellular fluid is then $\sim 1/3$ TBW, or 14L in a 70kg ♂. This includes:
 - Interstitial fluid ($\sim 2/3$ ECF water, or 9.4L in a 70kg ♂).
 - Plasma ($\sim 1/3$ ECF water, or 4.6L in a 70kg ♂).

The hydrophobic cell membrane acts as a barrier between intra- and extracellular fluid, and the capillary wall separates plasma from the interstitium. Every compartment maintains osmotic pressure through an actively retained specific solute:

- Intracellular: K^+ (pumped inwards by Na^+/K^+ ATPase).
- ECF: Na^+ (see next paragraph).
- Plasma: proteins (esp. albumin, impermeable through the normal endothelial barrier).

Extracellular volume is controlled by Na^+ retention and excretion (water will passively follow salt). The body ignores the ECF as a whole and ‘samples’ a portion of it: the effective arterial blood volume (EABV).¹

- Amounts to $\sim 700\text{mL}$ (blood in the arterial tree at any one time).
- Is a function of cardiac output (CO) and systemic vascular resistance (SVR).

Changes in EABV (due to hypovolaemia, \downarrow CO, or \downarrow SVR) are sensed by:

- Systemic baroreceptors (carotid sinus, aortic arch).
- Intrarenal volume sensors (juxtaglomerular apparatus).

With \downarrow EABV, these volume sensors activate the sympathetic nervous system, with Na^+ then retained by the kidney (often to $\text{u-Na}^+ < 10\text{mmol/L}$). Conversely, with \uparrow EABV, salt wasting ($>100\text{mmol/L}$) takes place with appropriate changes in TBW. This requires intact renal salt handling (and kidney function) for such homeostasis.

Low-pressure volume receptors, sited in the atria and the great veins (NOT contributing to EABV sensing), are also important: \uparrow ECF leads to increased atrial natriuretic peptide (ANP) release and renal salt wasting, as well as suppressing sympathetic tone. These receptors may control non-osmotic ADH release if the ECF is underfilled.

Falling EABV increases sympathetic tone

- ↑ circulating catecholamines, leading to ↑ CO and ↑ SVR.
- Activated renin–angiotensin system, improving renal haemodynamics and salt retention through 2° hyperaldosteronism.
- ↑ non-osmotic ADH (vasopressin) release.

Rising EABV (including low-pressure whole ECF sensing)

- ↑ ANP (atrial natriuretic peptide, a potent natriuretic).
- Suppressed renin production and thus angiotensin and aldosterone.

Water handling

TBW is mainly regulated by cerebral (circumventricular) and peripheral osmoreceptors (*not* volume sensors) capable of sensing changes in ECF osmolality: ↑ osmolality triggers thirst and pituitary ADH (vasopressin) release. Relatively dilute urine arrives at the collecting duct, as Na⁺ reabsorption in the ascending limb of the loop of Henle occurs without water (this is the basis for the countercurrent mechanism, leading to a hypertonic medullary interstitium).

Without ADH, this fluid is passed, little modified, as urine (and polyuria of DI (📖 p. 789)). ADH binds V₂ (vasopressin) receptors on the basolateral aspect of the principal cells in the collecting duct, leading to translocation of aquaporins to the apical membrane where these water channels allow free water absorption along an osmolar gradient into the hypertonic interstitium.

With water loading, osmoreceptors sense a falling osmolality. Thirst and ADH release are suppressed → dilute urine is formed, rapidly (within 6h) restoring normal osmolality (~285mOsmol/kg).

With water depletion, osmoreceptors sense ↑ osmolality, trigger ADH release, retain water, with (highly) concentrated urine. Increased thirst eventually corrects the absolute water deficit.

So, for normal water homeostasis, an individual needs:

- An intact thirst centre.
- Access to water.
- The ability to secrete ADH (vasopressin).
- A responsive collecting duct.

Abnormalities in one or more of these components → abnormal water homeostasis.

Reference

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Hyponatraemia—approach

The NR for Na^+ is 135–145mmol/L. As with many electrolyte disorders, $\downarrow \text{Na}^+$ is relatively common in hospitalized patients—this is particularly true for elderly inpatients where up to 6% will have $\text{Na}^+ < 125$. However, even in an apparently healthy elderly (>65) population, 7% of people have $\text{Na}^+ < 137$. The effects of ageing on the kidney may impair free water excretion or, at least, slow the capacity to excrete a water load. This may be further exacerbated by prescribed drugs, such as diuretics or NSAIDs.

Most hyponatraemic patients are thought to be asymptomatic—but perception and gait disturbances increase as Na^+ falls (and improve with correction). Investigators have correlated $\downarrow \text{Na}^+$ with fracture risk and compared the effects of chronic (apparently) asymptomatic hyponatraemia with similar features of alcohol use.² In hospital, symptomatic hyponatraemia is associated with a mortality of 10–50%. As hyponatraemia usually occurs as a result of altered water balance, making the correct clinical assessment of body water is then the key to management.

Assessment starts with volume status

Is the patient clinically:

- Hypovolaemic?
- Euvolaemic?
- Hypervolaemic?

Pseudohyponatraemia

Pseudohyponatraemia results when Na^+ is corrected for a falsely large volume, rather than the actual aqueous phase: occurs with \uparrow lipids, \uparrow plasma proteins (\blacktriangleright myeloma), or hyperglycaemia (\blacktriangleright for every 5mmol/L above the normal range for glucose, correct \downarrow by 1.7mmol/L). Glycine- or sorbitol-containing bladder irrigants may also be absorbed, esp. after prostatectomy, falsely $\downarrow \text{Na}^+$.

Causes

Hypovolaemic hyponatraemia (depleted ECF where Na^+ loss $>$ water loss)

- Renal losses:
 - Diuretics (thiazides, in particular).
 - Osmotic diuresis (glucose, urea in recovering ATN).
 - Salt-wasting nephropathy (due to chronic tubular dysfunction).
 - Addison's disease.
- Non-renal losses:
 - Diarrhoea or vomiting.
 - Sweating.
 - 'Third space' losses (burns, bowel obstruction, pancreatitis).

\blacktriangleright Severe volume depletion causes a state of appropriate ADH secretion: although initially suppressed as $\text{Na}^+ \downarrow$, hypovolaemia overrides osmoreceptor-induced inhibition and is a potent stimulus for ADH release despite the Na^+ concentration.

Hypervolaemic hyponatraemia (excess ECF where water retention > Na⁺ retention)

- CCF.
- Nephrotic syndrome or CRF.
- Cirrhosis.

Euvolaemic hyponatraemia (with a normal ECF)

- Syndrome of inappropriate antidiuretic hormone secretion (SIADH):
 - Pneumonia, COPD, TB, other lung diseases (usually with ↓ pO₂).
 - Malignancy (usually small cell lung cancer, occasionally head and neck tumours).
 - Drugs (antipsychotics, NSAIDs, antidepressants).
 - Neurological disease (e.g. CVA, trauma, acute psychosis, tumours).
 - Pain, opiates, stress (Δ surgery).
- Hypothyroidism.

Reference

2. Renneboog B, Musch W, Vandemergel X, et al. (2006). Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *American Journal of Medicine*, **119**, 71e1–8.

Hyponatraemia—assessment

Symptoms and signs

Rare if chronic or $\text{Na}^+ > 125 \text{ mmol/L}$. Common if acute or $\text{Na}^+ < 110 \text{ mmol/L}$. Headache, apathy, confusion (esp. in elderly) \rightarrow seizures and coma. Symptoms due to cerebral swelling as osmolality falls: the encephalopathy is exacerbated by $\downarrow p\text{O}_2$ of any cause.

If \uparrow ECF (overloaded) or \downarrow ECF (dry), the diagnosis is usually apparent.

Investigations

► Everything depends on good clinical volume assessment.

Recheck an abnormal result (Δ 'drip arm' Na^+ in patients on 5% dextrose infusions).

- U&E, plasma osmolality (normal/ \uparrow if pseudohyponatraemia).
- $\downarrow \text{K}^+$ and $\downarrow \text{Mg}^{2+}$ potentiate ADH release (Δ diuretics).
- Urine osmolality (u-Osm *should* be $< 100 \text{ mOsmol/kg}$ and will be if ADH suppressed (e.g. psychogenic polydipsia)).
- Urine Na^+ (if $< 20 \text{ mmol/L}$ = non-renal salt losses; if $> 40 \text{ mmol/L}$ = SIADH (unless salt intake low))— Δ diuretics may confound interpretation of urinary electrolytes.
- Urine dipstick for SG and protein.
- TSH and 9 a.m. cortisol if indicated.
- Ca^{2+} , albumin, glucose, LFT. \downarrow s-urate is common with SIADH.


► Consider Addison's if $\downarrow \text{Na}^+$, $\uparrow \text{K}^+$, and volume depletion—check random cortisol and ACTH, and, if unwell, treat with vigorous 0.9% saline replacement and IMI hydrocortisone.

Diagnosing SIADH

- $\downarrow \text{Na}^+$ in patients not on diuretics.
- Euvolaemic (i.e. no oedema).
- Normal renal, adrenal, and thyroid function.
- Urine osmolality $> 100 \text{ mOsmol/kg}$, often $> 300 \text{ mOsmol/kg}$.
- Urine $\text{Na}^+ > 20 \text{ mmol/L}$ (unless salt-restricted).
- Serum urate may be \downarrow as well.

► ADH may be released inappropriately from the pituitary or from cells of neuroendocrine origin in the lungs.

Cerebral salt-wasting

Brain injury of any cause (SAH, trauma, tumour) → brain natriuretic peptide (BNP, ≈ ANP; see  p. 778) release, resulting in salt wasting and volume depletion. ↓ ECF → appropriate ADH release and ↓ Na⁺.

Is probably overdiagnosed. Confirm if:

- Volume-deplete.
- With volume resuscitation, u-Osm rapidly rises (with ADH suppression).

Management of hyponatraemia

In all cases

- Identify those at most risk for neurological complications, and manage those most at risk with repeated review:
 - Acute hyponatraemia (<48 hours).
 - Thiazide-induced \downarrow Na^+ .
 - Premenopausal ♀ (? oestrogen, \uparrow responsiveness to ADH).
 - Malnourished or alcoholic patients.
 - Even if well, \uparrow surveillance, as for symptomatic patients, with repeated Na^+ checks (see below).
- Assess the volume status correctly (📖 pp. 12 and 114): the key to correct diagnosis and management.
- Stop contributing drugs \pm fluids (Δ 5% dextrose).
- Correct \downarrow K^+ (📖 p. 798) and \downarrow Mg^{2+} (📖 p. 808), if present.

Is the patient symptomatic (encephalopathic) or is $\text{Na}^+ < 120\text{mmol/L}$?

- No: respond according to volume status (📖 see below). As a general rule, err on the side of cautious correction (if correction is needed at all).
- Yes: see 📖 p. 786. Requires action—urgent if symptomatic.

Managing asymptomatic hyponatraemia

Hypovolaemic hyponatraemia

- Resuscitate with 0.9% NaCl (154mmol/L NaCl) at 1–3mL/kg/hr. Always correct \downarrow K^+ in concert by adding 20–40mmol KCl to each 1L 0.9% NaCl.

Euvolaemic hyponatraemia

- Usually SIADH in hospitals and in the elderly (see 📖 p. 785).

Hypervolaemic hyponatraemia

- Manage conservatively *fluid restriction* <1L/day (\approx 5 cups/day), and consider 20–40mg furosemide od.

Managing asymptomatic SIADH

- Fluid restrict <800mL/day—but do not expect this alone to work.
- Salt and loop diuretic: PO NaCl as 600mg 4–8 tablets daily (contains 10mmol/tab Na⁺, e.g. Slow Sodium[®]), furosemide 20–40mg/daily (free water excretion in excess of urinary salt loss). ⚠ Monitor closely (reserve as an inpatient tool).
- Demeclocycline 150–300mg 6-hourly induces nephrogenic diabetes insipidus, reversing ADH effect. Use with caution in chronic hyponatraemia, as diuresis may be brisk. Gut side effects often limit longer-term use.
- Urea 30–90g/day (not readily available in the UK).

An alternative strategy would involve using *vaptans*:

- Tolvaptan (oral) and conivaptan (parenteral use for <4 days) are 'aquaretics'.
- Serious liver injury has limited use, and evolving data suggests a limited role for these agents.
- Oral competitive vasopressin (V₂) receptor antagonists, blocking the action of ADH on V₂ (and V₁) receptors, so preventing tubular water uptake.
- Cause increased excretion of free water (without electrolyte disturbance) by reducing AQP2 activity in the collecting duct, leaving cells insensitive to ADH and less permeable to water.
- Demonstrated in phase II and III trials to effectively reverse hyponatraemia in euvoaemic and hypervolaemic states.
- Expect ↑ Na⁺ 6–7mmol/L on tolvapatan 15mg od.
- ⚠ Do not fluid-restrict—allow patients access to free water, and monitor serum Na⁺ regularly.
- Predominantly studied in *chronic* hyponatraemia with Na⁺ >120mmol/L.
- Uncertain: indications for treatment (level of Na? Symptoms?), long-term survival advantage (may ↓ hospital stay), duration of treatment.

Hyponatraemia with encephalopathy

🧠 The brain and \downarrow Na^+

The skull limits the brain's capacity to increase in size: with \downarrow Na^+ , a falling osmolality \rightarrow \uparrow intracellular water and symptomatic brain swelling. The tight junctions between endothelial cells and astrocyte foot processes that constitute the blood–brain barrier permit aquaporin-mediated water movement along osmotic gradients. In response, the cerebral ECF is rapidly reduced (to allow more room) and intracellular organic solutes (including the amino acid taurine) exported (lessens the osmolar gradient that causes water influx) over 1–2 days.

If too rapid correction of chronic \downarrow Na^+ occurs, osmotic or *central pontine myelinosis* (CPM) may occur. As the brain cannot restore the solute contribution to intracellular tonicity quickly, when the ECF osmolality is rapidly normalized, water leaves cells, causing cerebral dehydration and demyelination (affecting the whole brain, not just the pons, as in the original description). Symptoms become apparent after around 24 hours.

- Manage in high dependency setting.
- Na^+ by as little as 3–7mmol/L will usually treat symptoms.
- Repeat Na^+ every 2 hours initially, and then 4-hourly.
 - IF acute, <48 hours' duration (often post-operative):
 - Aim for \uparrow Na^+ by 2mmol/L/h or until asymptomatic.
 - *Never correct by >10mmol/L/24 hours.*
 - IF chronic, >48 hours' duration:
 - *Always consider CPM.*
 - Aim for \uparrow Na^+ by 0.5mmol/L/h to \uparrow by 6mmol/L or until asymptomatic.
 - *Aim for +8mmol/L in 24 hours, and do not correct by >10mmol/L/24 hours.*
- Other measures:
 - Add in furosemide to prevent volume overload (as 20mg IV 8-hourly). The diuresis caused will be hypotonic (i.e. water in excess of salt), adding to sodium correction.
 - In volume-overloaded patients intolerant of salt loads, 20% mannitol may be useful to allow use of 3% saline.
 - *Do not correct by >10mmol/L/24 hours.*
- Calculate Na^+ deficit, and select appropriate mode of administration.
- Na^+ deficit = total body water \times [desired Na^+ – actual Na^+].
 - TBW = 60% body weight in ♂ and 50% body weight in ♀ .
 - If age >65, use 50% BW in ♂ and 45% BW in ♀ .
 - For example, aiming for a safe Na^+ of 125mmol/L in 53-year-old 70kg ♂ with Na^+ 115, deficit = $0.6 \times 70 \times 10 = 420\text{mmol Na}^+$.
- Generally, use 2.7% or 3% (hypertonic) saline, containing 462mmol and 513mmol NaCl , respectively, per 1L.
- Deliver via a central line.
- Estimate effect of infusion by calculating change in Na^+ :

$$\text{Change in Na}^+ = \frac{\text{Infusion fluid Na}^+ - \text{Na}^+}{\text{TBW} + 1} \quad \text{for 1,000 mL infusion}$$

For example, in the above patient, using 3% hypertonic saline
1L over 24 hours:

$$\text{Change in Na}^+ = \frac{513 - 115}{42 + 1} = 9.25 \text{ mmol/L}$$

If a rapid increase were required (e.g. if fitting) and a target of >120 mmol/L were desired over 3 hours (see next paragraph), aim to infuse $[5/9.25 \times 1\text{L}] = 540$ mL of 3% saline at 180 mL/h.

☛ An alternate strategy in fitting patients is to give a bolus of 100 mL 2.7% or 3% NaCl, and repeat after 10 minutes.

Sodium 'guesstimates': for every 1L infused, a crude estimate of the sodium change in plasma might be:

- 3% NaCl (Na^+ 513 mmol/L) \uparrow 13 mmol/L.
- 0.9% NaCl (Na^+ 154 mmol/L) \uparrow 1.4 mmol/L.
- 5% glucose (Na^+ 0) \downarrow 3.5 mmol/L.

Do not guess if you have time.

Hypernatraemia

Serum Na^+ $>146\text{mmol/L}$ is usually due to a water deficit and is associated with severe underlying disease and significant mortality ($\pm 50\%$). With $\uparrow \text{Na}^+$, ECF osmolality \uparrow , increasing osmotic drag on the intracellular compartment. This leads to cellular dehydration, most importantly in the brain: loss of volume creates vascular shear stress, resulting in bleeding and thrombosis. As in hyponatraemia (📖 p. 780), compensation begins with cellular retention of salts and organic solutes in the brain, increasing cellular tonicity and lessening water losses to the hyperosmolar ECF (occurs over days). Overzealous correction leads to too rapid intracranial expansion of the brain, with potential tentorial herniation. Causes include:

Excess hypertonic fluids

- IVI infusions (▶ antibiotics), TPN, or enteral feeds.
- Rarely, salt ingestion, or sea water near-drowning.

Excess water loss

- Renal:
 - Diabetes insipidus (see Box 10.1), with/out altered thirst.
 - Diuretics.
 - Osmotic diuresis (glucose in DKA, urea in recovering ATN).
- Gut:
 - Diarrhoea (and laxatives, such as lactulose).
 - Vomiting, NG losses, or fistulae.
- Skin:
 - Sweating, burns.

Decreased thirst

In the unwell and elderly, esp. if on psychotropic drugs.

Symptoms and signs

Reflect cerebral dehydration. Thirst, apathy, weakness, confusion \rightarrow \downarrow consciousness, seizures, and coma. Cause often apparent clinically, with sepsis, pneumonia, and uncontrolled diabetes common.

Investigations

U&E, plasma osmolality, glucose. Urine Na^+ , osmolality. With osmotic diuresis, u-Osm is always $>300\text{mOsmol/kg}$.

Box 10.1 Diabetes insipidus


► Polydipsia and polyuria (>6L/day) in adults without diabetes is usually due to DI or psychogenic polydipsia.

ADH (also called arginine vasopressin, AVP) binds the V_2 receptor on collecting duct cells, leading to surface expression of free water channels, or aquaporins, through which water is rapidly taken up.

DI can be cranial (i.e. impaired release of ADH):

- Trauma or post-operative.
- Tumours or infiltrative processes (sarcoid, TB).
- Infective (meningitis, encephalitis).
- Cerebral vasculitis (SLE, Wegener's).

More commonly, DI is nephrogenic (resistance to ADH). Causes include:

- Congenital.
- Drug-induced (*lithium*, amphotericin, foscarnet, demeclocycline).
- Hypokalaemia or hypercalcaemia.
- Tubulointerstitial disease (medullary cystic disease,  p. 599).

Lithium prevents translocation of aquaporins to the collecting duct apical membrane and is the most common cause of nephrogenic DI.

Diagnosis rests on finding \uparrow UO (>3L/day) with dilute urine (<300mOsmol/kg). Exclude osmotic diuretics, \downarrow K^+ , or \uparrow Ca^{2+} . A fluid deprivation test \pm DDAVP (synthetic analogue of ADH) is diagnostic (► seek expert advice).

Treatment depends on cause.

Cranial DI is treated with intranasal desmopressin 10–20 micrograms bd. Drug effect lasts for 6–12 hours.

Nephrogenic DI, if congenital or lithium-induced, is treated with thiazide diuretics (hypovolaemia \rightarrow \downarrow Na^+ absorption proximally, \therefore reduced water delivery to the collecting duct) and NSAIDs (such as indometacin which antagonizes the effect of ADH).

⚠ Simultaneous use of desmopressin and 5% glucose should be used with extreme caution (analogous to pouring water into a closed box).

Treatment of hypernatraemia

► Treat the underlying cause.

- Aim for Na^+ 145mmol/L.
- Calculate water deficit (and include ongoing losses in calculations):

$$\text{Change in Na}^+ = \frac{\text{Infusion fluid Na}^+ - \text{Na}^+}{\text{TBW} + 1} \quad \text{for 1,000 mL infusion}$$

- TBW = 60% body weight in ♂ and 50% body weight in ♀.
- If age >65, use 50% weight in ♂ and 45% weight in ♀.

For example, in a 53-year-old 70 kg ♂ with Na^+ 170mmol/L, TBW = 42L. Using 5% glucose (no Na^+), $[0 - 170]/43 = -3.95\text{mmol/L}$. So, 1L 5% dextrose will reduce Na^+ to 166mmol/L. Aiming to correct only 0.5mmol/L/h will require 1L/8h, or 125mL/h if no ongoing fluid losses. As a rule of thumb, allow for 1.5L insensible loss/day.

- Reassess patient repeatedly.
- If $\uparrow \text{Na}^+$ is acute (<24 hours), can be reversed quickly. Usually occurs with infusion of hypertonic solutions, but also with rapid loss of hypotonic fluid (sweating, burns).
 - Correct at 1mmol/L/h.
 - Measure Na^+ 2-hourly initially, then 4-hourly.
- If chronic (>24 hours), correct more slowly to prevent rehydration injury to the brain:
 - Document neurological status.
 - Correct at no greater than 0.5mmol/L/h or no less than 10mmol/L/day.
 - Correct 50% of the water deficit in first 12–24 hours.
 - Correct remaining water deficit over next 24–48 hours.
 - Measure Na^+ 2-hourly initially, then 4-hourly.

Choice of fluid

- Water PO, if orientated, or per NG if able.
- 5% glucose or 0.45% (half-normal) saline IVI if cannot use the gut. May require insulin to control hyperglycaemia if using 5% glucose.

Oedema and its treatment

Oedema occurs with interstitial expansion of the ECF, becoming clinically apparent if >2L fluid excess in this compartment. It is most obvious in the dependent areas (ankles), but it may affect the face and eyelids, especially in the morning. Anasarca refers to severe oedema, progressing from the peripheries to the trunk. Oedema may occur with other extravascular signs of salt and water retention (pleural effusions, ascites). Causes include:

- Congestive heart failure.
- Liver failure.
- Nephrotic syndrome (📖 p. 554).
- Acute or chronic renal failure (\downarrow GFR \rightarrow \downarrow salt excretion).
- Drug-induced (NSAIDs, calcium channel blockers).
- Premenstrual or pregnant ♀ (oestrogen effect).
- Venous insufficiency (localized oedema).

Development of oedema

For oedema to develop, salt and water retention must occur (to expand the ECF) and/or capillary permeability must increase (to allow fluid shifts into the interstitium).


The 'overflow' hypothesis suggests that Na^+ retention is the primary factor in the development of oedema: any state that leads to \downarrow EABV (📖 p. 778) \rightarrow 2° hyperaldosteronism, sympathetic overactivity, and non-osmotic ADH release. This then causes salt and water retention, an increase in ECF volume, and oedema.

The 'underfill' hypothesis explains oedema associated with \downarrow albumin as a fall in plasma oncotic pressure (provided largely by albumin) with unchanged hydrostatic pressure, resulting in fluid movement into the extravascular space. This then leads to 2° fluid retention.

Oedema and hypoalbuminaemia in the nephrotic syndrome

Experimental evidence suggests the 'underfill' hypothesis to be incorrect with \downarrow s-albumin: the transcapillary oncotic gradient is maintained with hypoalbuminaemia, as interstitial colloid osmotic pressure (COP) is reduced in tandem with falls in the plasma COP (the interstitial fluid not only maintains a COP countering plasma COP, but can be varied). Rather, inflammatory cytokines impair capillary permeability, a falling EABV \rightarrow salt retention, \uparrow urinary albumin modifies Na^+ handling directly in the nephron, and renal resistance to ANP develops. The net effect is one of salt retention, with equilibration of the expanded ECF into the interstitium.

Diuretics

All diuretics block the reuptake of Na^+ , and thus Cl^- and water. All circulate highly protein-bound and are thus not well filtered by the glomerulus. This complex is taken up from the peritubular fluid by proximal tubular cells and the diuretic released prior to excretion to act in the urinary space (except for spironolactone and other mineralocorticoid receptor antagonists). For use in hypertension, see  p. 498.

Commonly used diuretics include

Loop diuretics

- Site of action: blocks Na^+ uptake at the $\text{Na}^+\text{K}^+2\text{Cl}^-$ (NKCC) co-transporter in the thick ascending limb of the loop of Henle.
- Specific side effects: \uparrow u- Ca^{2+} , ototoxicity.
- Examples: furosemide, bumetanide, torasemide.

Thiazide diuretics

- Site of action: blocks Na^+ uptake at the Na^+Cl^- co-transporter in the distal tubule.
- Specific side effects: \uparrow u- Ca^{2+} (may cause hypercalcaemia).
- Examples: bendroflumethiazide, hydrochlorothiazide, metolazone, indapamide.


Amiloride/triamterene

Site of action: blocks Na^+ uptake at the apical Na^+ channel (ENaC) in the collecting duct.

Mineralocorticoid receptor antagonists

- Site of action: blocks Na^+ uptake by downregulating apical Na^+ channel (ENaC) expression in the collecting duct. Spironolactone enters cells from the circulation, rather than the urinary space, and binds the intracellular mineralocorticoid receptor (MR).
- Specific side effects: \uparrow K^+ , anti-androgenic effects (not eplerenone).
- Examples: spironolactone, eplerenone.
- General side effects include: \downarrow K^+ (not with spironolactone), \downarrow Na^+ , \downarrow Mg^{2+} , \uparrow uric acid, skin rashes, interstitial nephritis, dyslipidaemia (\bullet^{\ominus} insulin resistance, impotence).

Using diuretics in oedematous states

 Always institute appropriate salt restriction when using diuretics, and consider fluid restriction to $<1,000\text{mL/day}$.

- Assess volume status daily.
- Measure weight daily to assess response.
- Strict input/output charts may be helpful.
- Measure serum electrolytes regularly.
- Monitoring u- Na^+ excretion may be helpful in diuretic resistance.

⚠ *Do not forget bed rest as a useful tool in mobilizing oedema and encouraging diuresis.*

Nephrotic syndrome

Often requires high doses of loop diuretics (furosemide 160–240mg daily), as ↑ urinary albumin binds free diuretic. Consider add-on thiazide diuretics (e.g. metolazone 2.5–5mg/day PO), but beware rapid-onset ↓ Na⁺, and titrate dose against daily weight loss.

● Furosemide and albumin infusions are frequently used in an attempt to improve drug delivery—probably without real benefit. May be of use if s-Alb <20g/dL. Administer as 100mL 20% human albumin solution, with 40–160mg furosemide IVI, over 2–4 hours.

Renal failure

Loop diuretic if GFR <50mL/min. May require 240mg PO daily in 2–3 divided doses. Best response with IVI loop diuretic (furosemide 200mg) or as continuous infusion (furosemide 10–50mg/h to a maximum of 500mg/day to prevent ototoxicity). Bumetanide is better absorbed and should be considered in diuretic resistance (up to 8mg/day). If poor response, consider add-on thiazide, as described in ‘Nephrotic syndrome’.

Congestive cardiac failure

Loop diuretics better than thiazides, e.g. furosemide 40mg od. Evidence from RALES and EPHEsus trials has confirmed a role for mineralocorticoid receptor blockade, so this class often used as first line. Hyperkalaemia is a real concern, as such patients are often on ACE inhibitors or β-blockers (📖 p. 797).

Cirrhosis

Spironolactone (50–200mg od) prevents 2° hyperaldosteronism, with add-on thiazide (*not* loop—too marked a diuresis may precipitate ARF) if required. Resistant ascites is best treated with paracentesis under albumin cover. As it is difficult to resorb more than 1L of ascites over a day, a diuresis that sees daily weight loss of >0.5kg (where 1kg is a surrogate for 1L negative balance through diuresis, and not related to paracentesis) should cause concern over precipitating pre-renal failure.

Potassium

K^+ is the second most abundant cation in the body (~3.5mol). Dietary K^+ amounts to 80–150mmol/day. Only around 65mmol is present in the ECF, with the great majority (98%) found within cells in muscle (and, to a lesser extent, liver, red cells, and bone). Once absorbed, K^+ is rapidly buffered by removal from the ECF into the intracellular compartment: insulin and β -adrenergic catecholamines stimulate membrane Na^+/K^+ -ATPase to pump K^+ into cells (in a 3:2 ratio). This electrochemical gradient (the cell membrane potential) is critical to nerve conduction, muscle contraction, and normal cell function.

Total body K^+ balance is regulated by renal excretion: K^+ is freely filtered at the glomerulus (~700mmol/day) and is reabsorbed by the PCT (75%), the loop of Henle (15%), and the α -intercalated cells of the collecting duct. K^+ secretion is responsible for most urinary potassium loss and is tightly controlled by aldosterone in the DCT and the principal cells of the collecting duct. The collecting duct ROMK channel is the major channel through which K^+ is secreted, whereas maxi- K^+ tends to respond to increased flow in the distal nephron and secrete K^+ .

In health, around 1–1.5mmol/kg/day is excreted in urine, with a small fraction (~10mmol) in faeces.

► Obligate urinary K^+ loss (10–15mmol/day) will always occur, no matter how low the serum K^+

Aldosterone secretion is increased directly by hyperkalaemia (and hypovolaemia) and suppressed by hypokalaemia, controlling K^+ in the normal range (3.5–5.0mmol/L). Aldosterone \rightarrow Na^+ absorption through ENaC, the epithelial sodium channel. As luminal electronegativity increases with Na^+ absorption, Cl^- uptake is enhanced along paracellular pathways, with secretion of K^+ and H^+ back into the lumen. Other factors are important in urinary K^+ excretion:

- Flow in the distal tubule activates stretch-sensitive K^+ channels \rightarrow \uparrow urinary K^+ loss.
- \uparrow tubular sodium delivery \rightarrow \uparrow luminal sodium-activating ENaC directly.
- ADH or vasopressin may stimulate (some) sodium reabsorption, so \uparrow K^+ loss.
- Alkalosis.

WNK proteins (with no lysine (K)) are key modulators of K^+ excretion and potentially of fluid and sodium balance as well—their role in K^+ control continues to be clarified.

Hyperkalaemia

See  p. 130 for further discussion.


True hyperkalaemia is either due to increased release from cells or decreased excretion by the kidney. Since the release of important trials using spironolactone or eplerenone (in addition to ACE inhibitors) in the treatment of heart failure, dangerous hyperkalaemia has become more common in those with better renal function.

Pseudohypokalaemia

▶ ↑ K⁺ is often spurious: always recheck result. Traumatic venepuncture → cellular K⁺ leakage and false hyperkalaemia. This → 1–2mmol/L rise in the apparent K⁺. Fine-bore needles, tourniquets, and fist clenching can all induce mechanical release of K⁺ from cells, as can cold temperature.

More common with ↑ WCC (>100) or ↑ platelet count (>400 × 10⁹).

Common causes include

- CKD per se.
- K⁺-rich diets (bananas, other fruits) with CKD.
- Drug-induced (esp. combinations of the following):
 - ACE inhibitors/ARB.
 - K⁺-sparing diuretics (spironolactone, eplerenone, amiloride).
 - NSAIDs.
 - Heparin and LMW heparins (inhibit normal aldosterone release).
 - Ciclosporin.
 - High-dose trimethoprim.
 - Digoxin *toxicity* (but not therapeutic levels of digoxin).
 - β-blockers.
- Hypoaldosteronism (including type 4 RTA,  p. 825).
- Addison's.
- Increased release from cells:
 - Acidosis (lactic).
 - Insulin deficiency (DKA).
 - Rhabdomyolysis, strenuous exercise, or tumour lysis.
 - Massive haemolysis.
 - Succinylcholine use.

Hyperkalaemia with aldosterone antagonism

RALES and EPHEBUS, two major trials demonstrating a 15–30% reduction in mortality due to CCF in patients treated with agents that block the action of aldosterone (spironolactone, eplerenone), launched an era of aldosterone antagonism in heart failure and beyond. Widespread use (occasionally inappropriate) has followed—clinical trials have been designed to exclude those with significant renal disease (those most at risk of hyperkalaemia).

In 2004, Juurlink *et al.* described the effects of instituting these trials in less well-defined populations with heart failure in Ontario and demonstrated a 6-fold ↑ in hyperkalaemic deaths. Since ACE inhibitors/ARB are also indicated to treat CCF, serious hyperkalaemia may occur. If using such combination therapy:

- Calculate GFR (📖 pp. 30–37)—caution if abnormal.
- Stop NSAIDs.
- Advise about dietary K^+ restriction (📖 p. 259).
- If ↓ GFR <60mL/min, add in loop diuretic to waste K^+ .
- If acidotic ($s\text{-HCO}_3^- < 21\text{mmol/L}$), add NaHCO_3 500–600mg bd.
- Do not increase spironolactone above 25mg/day if + ACE inhibitor.
- Check K^+ regularly. If $K^+ > 5.5\text{mmol/L}$, discontinue either ACE-I/ARB or spironolactone/eplerenone.

⚠ Hyperkalaemia arises when dehydration, concurrent illness, or deteriorating renal or cardiac function supervenes in patients on combination therapy. Always check K^+ . Those with $K^+ > 5.0$ are at risk.

Rare causes of hyperkalaemia include

- *Hyperkalaemic periodic paralysis*: mutations in skeletal Na^+ channel SCN4A coded on 17q23 lead to episodic paralysis, ↑ K^+ , and ↓ Na^+ in response to varied triggers, as Na^+ and water are pumped into cells in exchange for K^+ .
- *Type 1 pseudohypoaldosteronism*: presents in infancy as salt wasting, ↓ Na^+ , and collapse. Either due to resistance to the actions of aldosterone (defect in type 1 mineralocorticoid receptor, with ↑ K^+) or defects in ENaC (📖 p. 931).
- *Gordon's syndrome* (type 2 pseudohypoaldosteronism or familial hyperkalaemic hypertension): the clinical inverse of Gitelman's syndrome (📖 p. 800). Presents as ↑ BP, ↓ renin and aldosterone, ↑ K^+ , and acidosis and normal renal function. Mutations in genes encoding WNK-1 and -4 (negative regulators of NCCT, 📖 p. 930) are responsible and lead to reduced functioning thiazide-sensitive Na-Cl co-transporter in the distal tubule.

Hypokalaemia

One of the most common electrolyte abnormalities seen, esp. in patients on diuretics. Although K^+ of 3–3.5mmol/L is generally well tolerated, hypokalaemia of <2.5mmol/L can be life-threatening (esp. in the presence of digitalis or if the drop is rapid).

Causes

- Inadequate intake <25mmol/day (either dietary or IV).
- Increased gut losses:
 - Vomiting or NG losses ($\uparrow Na^+$ loss in vomitus \rightarrow 2° hyperaldosteronism and $\uparrow NaHCO_3$ delivered to the distal nephron).
 - Diarrhoea or laxative abuse.
 - VIPoma, Zollinger–Ellison syndrome.
 - Ileostomy or enteric fistula, colonic villous adenoma.
- Redistribution into cells:
 - β -agonism (any cause of \uparrow sympathetic drive, e.g. delirium tremens).
 - β -agonist drugs (bronchodilators, decongestants, tocolytics).
 - Insulin, theophylline, or caffeine (activate Na^+/K^+ -ATPase pump).
 - Δ Refeeding in malnourished (and total body K^+ deplete) patients.
 - Alkalosis.
 - Vigorous exercise
- 1° hyperaldosteronism: adrenal adenoma (Conn's syndrome), bilateral adrenal hyperplasia—plasma aldosterone:renin ratio.
- Renin-secreting tumours (\uparrow BP in the young).
- Cushing's disease.
- 2° hyperaldosteronism (📖 p. 478):
 - Liver failure, heart failure, nephrotic syndrome.
- Renal losses:
 - Diuretics (esp. thiazides, loops), including abuse of diuretics.
 - Acquired renal tubular disease (📖 p. 76) or RTA (📖 p. 824).
 - Bartter's, Liddle's, and Gitelman's syndromes (📖 p. 800).
- Other drugs:
 - Amphotericin and aminoglycosides (tubular toxicity).
 - Glucocorticoids (esp. at high dose) or mineralocorticoids.
 - Carbenoxolone and liquorice (have a mineralocorticoid effect).
- Hypomagnesaemia.
- Familial hypokalaemic periodic paralysis.
- Thyrotoxic periodic paralysis.
- Correction of vitamin B12 deficiency.

Symptoms and signs

See previous list of causes for specific associations—usually picked up on U&E.

- ▶ Take a full drug history, particularly for diuretics. Exclude diarrhoea.
- Fatigue, constipation, proximal muscle weakness, and \downarrow tone (progressing to ascending paralysis as K^+ \downarrow).
- Cardiac arrhythmias, esp. if underlying heart disease. Chronically, \uparrow BP, glucose intolerance, and \downarrow urinary concentrating ability.

Investigations

- U&E, Mg^{2+} . Venous pH, and calculate the anion gap. Either perform 24-hour urinary K^+ or do spot u- K^+ and u-Cr. Calculate the urinary K/Cr ratio (KCR).
- Also, CK (may have spontaneous rhabdomyolysis). Digoxin level if on drug.
- If 24-hour u- K^+ <15mmol/L, losses are EXTRARENAL.
- Or, depending on the KCR, focus attention as shown in Table 10.2.

Table 10.2 Investigations of hypokalaemia

KCR (mmol/mmol) <1	Extrarenal
KCR >1, BP ↓ or normal	Tubular/renal
KCR >1, BP ↑	Mineralocorticoid axis

⚠ Check the ECG: small T waves, U wave (after T), PR interval ↑, ST segments ↓. ↓ in extracellular K^+ hyperpolarizes cell membranes → a cell less sensitive to stimuli.

Treatment

⚠ Is the patient on digoxin? Will potentiate digoxin's arrhythmogenicity. Note that diuretic-induced hypokalaemia is exacerbated if dietary Na^+ intake is high. Always aim to treat the underlying cause over time.

Mild (>2.5mmol/L):

- Oral slow-release potassium chloride 50–150mmol/day in divided doses (treatment limited by GI intolerance).
- Check K^+ regularly.
- Rule of thumb is to treat until *alkalosis* resolves.
- ↑ dietary K^+ and ? switch to/add in K^+ -sparing diuretic.
- Common options include Sando-K® (12mmol/tab), or Slow-K® (8mmol/tab). If acidotic, rather use $KHCO_3$.

⚠ Severe or symptomatic hypokalaemia ($K < 2.5$ mmol/L, arrhythmias, liver failure, or extreme weakness):

- Cardiac monitor.
- Check Mg^{2+} , and correct if need be (p. 808).
- Avoid glucose-containing solutions or sodium bicarbonate.
- I.V. 0.9% saline 1L with 20–40mmol KCl at no more than 10–20mmol KCl/h through peripheral cannula. If ↓ K^+ with hyperchloraemic acidosis (RTA, p. 824, or gut losses), avoid 0.9% saline, and rather use KCl as listed here.
- ► *Danger of rapid onset hyperkalaemia.* Recheck K^+ .
- In volume-restricted patients or those with profound and ongoing hypokalaemia, KCl can be given into a central vein as 20–40mmol/100mL 0.9% saline (NOT glucose, risk of hypokalaemia) at not >40mmol/h using a volumetric pump. Must be in high dependency surroundings.

Bartter's, Gitelman's and Liddle's syndromes

Bartter's syndrome


Autosomal recessive tubular hypomagnesaemia and a hypokalaemic metabolic alkalosis with hypocalciuria. Type 5 Bartter's is inherited in an autosomal dominant fashion.

At least six subtypes now detected, all sharing impaired Na^+ reabsorption in the thick ascending limb of the loop of Henle. Mutations in a number of channels on both the apical and basolateral membranes (including NKCC2, CLC-Ka and CLC-Kb, CaR, and ROMK) are responsible for salt wasting and mild volume depletion. It is, in effect, what is seen with *loop diuretic use*. Subsequent 2° hyperaldosteronism (and juxtaglomerular apparatus hyperplasia) leads to a hypokalaemic metabolic alkalosis. \uparrow luminal Na^+ impairs Ca^{2+} absorption, leading to normal to \uparrow u- Ca^{2+} .

Diagnosis

In children (or adolescents) with failure to thrive, polydipsia, polyuria, and cramps. Sensorineural deafness in type 4 Bartter's. Lower BP than general population, \downarrow K^+ , mild metabolic alkalosis, \uparrow u- Na^+ , \uparrow u- K^+ , \uparrow u- Ca^{2+} , \uparrow u-prostaglandin E2 (reduced NaCl entry into macula densa, leading to increased COX-2 expression), \uparrow renin, \uparrow aldosterone.

Treatment

Aim to *normalize* K^+ . Start with amiloride 5–40mg day (large doses may be needed!). Add on oral potassium supplementation as potassium chloride 25–100mmol/day (for drugs, see  p. 799).

Δ Recheck K^+ after 5–7 days to ensure that the dosing is appropriate.

NSAIDs (indometacin) if \uparrow u-PGE2. ACE-I may help normalize K^+ . Often difficult to treat and demanding of patient (child!) compliance.

Gitelman's syndrome

Autosomal recessive inheritance, characterized by hypomagnesaemia, hypokalaemia with hypocalciuria, and metabolic alkalosis.

Heterogeneous loss-of-function mutations largely affecting the *SLC12A3* gene encoding the thiazide-sensitive Na-Cl co-transporter in the DCT, with impaired Na^+ reabsorption. \uparrow Na^+ loss leads to 2° hyperaldosteronism and a hypokalaemic metabolic alkalosis. It is, in effect, what is seen with *thiazide diuretic use*. Increased urinary Mg^{2+} loss, with significant hypomagnesaemia, is thought to occur as a result of a reduction in TRPM6 (an epithelial magnesium channel) density in the DCT.

Diagnosis

In young adults, with often asymptomatic \downarrow K^+ (2.0–3.0mmol/L).

May be weakness and myalgia, and symptoms of \downarrow urinary concentrating ability (nocturia, in particular, polyuria, and polydipsia).

Investigations

Include \downarrow Mg^{2+} . Mild metabolic alkalosis. \uparrow renin, \uparrow aldosterone. Urinary u-PGE2 is not raised (unlike Bartter's). Genetic testing is available though not widely so.

Treatment

Generally good prognosis. Amiloride 5–40mg od \pm K^+ supplementation (p. 799). No role for NSAIDs.

Liddle's syndrome

Autosomal dominant inheritance. Caused by gain-of-function mutations in ENaC (epithelial sodium channel expressed on the apical surface of collecting duct cells), resulting in a failure to endocytose ENaC from the surface membrane of collecting duct cells. Constitutive overexpression leads to \uparrow Na^+ reabsorption which leads to \downarrow BP \pm oedema. Enhanced Na^+ uptake renders the lumen more electronegative, opening the transepithelial ROMK K^+ channel, leading to K^+ wasting and a hypokalaemic metabolic alkalosis. Aldosterone is appropriately suppressed.

Diagnosis

In young hypertensives (often with severe \uparrow BP and a +ve family history), with \downarrow K^+ (may be mild) and mild metabolic alkalosis. \downarrow renin, \downarrow aldosterone (see Table 10.3).

Treatment

Low-salt diet (<100mmol/day) \pm amiloride 5–10mg od (or triamterene—directly inhibits ENaC).

Table 10.3 Differentiating inherited channelopathies

	Bartter's	Gitelman's	Liddle's
BP	N/ \downarrow	N	\uparrow
K^+	\downarrow	\downarrow	\downarrow
Mg^{2+}	N or \downarrow	\downarrow	N
u-PGE2	\uparrow	N	N
Aldosterone	\uparrow	\uparrow	\downarrow
Age	Infancy	Early adulthood	Childhood

Calcium, magnesium, and phosphorus

Calcium

99% of total body Ca^{2+} (~1kg) is stored in bone. Extracellular Ca^{2+} accounts for a small fraction: of this; ~40% is bound to albumin, with 50% available as physiologically active, free (or ionized) Ca^{2+} . The remainder is complexed with anions, such as bicarbonate or phosphate. Free intracellular Ca^{2+} is found at 10^4 higher a concentration than in the extracellular space, a gradient maintained by an energy-dependent membrane Ca^{2+} ATPase. Intracellular Ca^{2+} is key to many signalling pathways within cells— Ca^{2+} is also important in skeletal health, membrane function, neuromuscular integrity, and coagulation.

The serum normal range is 2.1–2.5mmol/L (~1.2mmol/L ionized), with Ca^{2+} available from both the gut and bone stores. Gut Ca^{2+} absorption occurs via transcellular (uptake via TRPV6, the apical Ca^{2+} channel with subsequent energy-dependent basolateral efflux) and paracellular pathways. Uptake is under the control of (active) $1,25(\text{OH})_2$ vitamin D_3 .

The ionized fraction is freely filtered across the glomerulus and mainly reabsorbed in the PCT and loop of Henle. Most Ca^{2+} is resorbed paracellularly along a concentration gradient, but TRPV5 regulates (the final 10% of total) distal calcium uptake in a PTH- and vitamin D-dependent manner. Urinary Na^+ is able to strongly influence urinary Ca^{2+} excretion: in the thick ascending loop of Henle, $\uparrow \text{Na}^+$ delivery forces $\uparrow \text{Na}^+$ uptake, at the expense of Ca^{2+} resorption \rightarrow hypercalciuria. This is a key factor in stone formation (📖 p. 716).

Falling Ca^{2+} activates parathyroid calcium-sensing receptors (CaRs), leading to parathyroid hormone (PTH) release. PTH increases renal tubular Ca^{2+} reabsorption and hydroxylation of vitamin D_3 to the active metabolite, increasing intestinal uptake. PTH also enhances bone osteoclastic activity. There is also evidence that PTH receptors are present on cells not directly involved in calcium homeostasis (such as endothelial cells and cardiomyocytes), suggesting that PTH may have effects beyond its role in calcium/phosphate regulation.

Magnesium

Magnesium (Mg^{2+}) is the fourth most common cation in the body and is found largely in the intracellular compartment or stored in bone. Only 1% of the 25g total body Mg^{2+} is in the ECF, with the majority found in bone or muscle. It is a key component of ATP-requiring reactions and is necessary for the synthesis of protein and maintaining membrane function, nerve conduction, and muscle contraction.

Mg^{2+} , like Ca^{2+} , also regulates PTH secretion— $\downarrow \text{Mg}^{2+}$ leads to PTH release and vice versa. Profound $\downarrow \text{Mg}^{2+} \rightarrow$ symptomatic $\downarrow \text{Ca}^{2+}$.

The normal range is 0.75–0.95mmol/L in plasma. The kidney dominates the control of Mg^{2+} homeostasis. Mg^{2+} is absorbed from the gut and freely filtered across the glomerulus. In health, 70% is then reabsorbed in the thick ascending loop of Henle (TALH)—the strongly negative paracellular

protein paracellin-1 allows efficient absorption of the cations Mg^{2+} and Ca^{2+} under control of both PTH and the calcium-sensing receptor. Fine control is achieved in the DCT where the transmembrane (transcellular) protein TRPM6 allows further uptake. Loss of function of either paracellin-1 or TRPM6 leads to urinary Mg^{2+} wasting and $\downarrow Mg^{2+}$.

Phosphorus

Phosphorus occurs largely as the inorganic fraction phosphate in the circulation. Organic phosphorus exists as protein-bound phospholipids and is not measured in clinical practice. Phosphate is essential to almost all biochemical systems.

Absorbed by the type II sodium/phosphate co-transporter (NaPi) from the intestine, again in a vitamin D_3 -dependent manner, 80% is found in bone. The normal range for plasma phosphate is 0.8–1.4mmol/L (higher in children). Freely filtered in the kidney, it is largely reabsorbed in the PCT (depending on oral intake) by the type II NaPi.

Tubular reabsorption of phosphate is controlled by PTH (which inhibits reabsorption) and also by fibroblast growth factor 23 (produced by osteocytes which leads to lower levels of serum phosphate by reducing tubular reabsorption and by inhibition of 1α -hydroxylation of vitamin D).

Hypocalcaemia

Total serum Ca^{2+} is low with \downarrow albumin, though the free fraction may be normal. Always correct for albumin:

$$\text{Corrected Ca}^{2+} = \text{measured Ca}^{2+} + [40 - \text{serum Alb}] \times 0.02$$

Causes of hypocalcaemia

- Vitamin D deficiency:
 - Malnutrition (osteomalacia).
 - Malabsorption (gastrectomy, short bowel, coeliac disease, chronic pancreatitis).
 - CKD (loss of 1α -hydroxylase).
 - Vitamin D-dependent rickets (anticonvulsants, nephrotic or Fanconi syndrome).
- Hypoparathyroidism:
 - Post-parathyroidectomy—'hungry bone syndrome' (📖 p. 254).
 ▲ Inadvertent after thyroidectomy!
 - Inherited, pseudohypoparathyroidism.
- Hyperphosphataemia (\uparrow phosphate increases bone Ca^{2+} deposition):
 - Tumour lysis (📖 p. 160).
 - Rhabdomyolysis (📖 p. 152).
 - Administered or ingested.
- Acute pancreatitis.
- $\downarrow \text{Mg}^{2+}$.
- Acute alkalosis (reduction in ionized calcium).

Symptoms and signs

Depression and anxiety, (perioral) paraesthesiae, carpopedal spasm, tetany, respiratory depression, convulsions, hypotension, and arrhythmias. Examine for Chvostek's sign (tap over the parotid for facial muscle twitching, as CN VII excited) and Trousseau's sign (occlude brachial artery with BP cuff inflated $>$ SBP; observe wrist and finger flexion). If chronic, cataracts, dry skin, dental changes, bone pain, and muscle weakness \pm skeletal deformities.

Investigations

► ECG: prolonged QT interval. U&E, Ca^{2+} , phosphate, Mg^{2+} , alkaline phosphatase, and intact PTH. If appropriate, amylase, CK, urate. Consider 25-(OH) vitamin D_3 and 1,25-(OH) $_2$ vitamin D_3 . Consider X-ray long bones and hands.

Treatment

► Only treat if symptomatic \pm acute.

If mild (>1.9): increase dietary Ca^{2+} . Add in oral Ca^{2+} (e.g. calcium carbonate) 0.5–1.5g tds 2 hours after meals. If vitamin D-deficient, oral ergocalciferol (inactive vitamin D) or colecalciferol 10 micrograms–1mg od, usually in a preparation with Ca^{2+} . If \downarrow , Mg^{2+} supplement, as described on 📖 p. 808.

⚠ If acute or symptomatic, infuse Ca^{2+} at 2mg/kg/h: start IVI 10% calcium gluconate 60mL in 500mL 5% glucose or 0.9% saline at 125mL/h. Recheck Ca^{2+} at +4 hours, and adjust infusion rate accordingly.

⚠ If tetany, give 10mL 10% calcium gluconate 10mL (2.2mmol) IVI over 3 minutes (⚠ extravasation). Repeat, if necessary, or infusion as described.

Hypercalcaemia

Usually the result of increased absorption from gut, bone resorption, or both. Due to increased PTH or analogues, or osteolytic metastases. Mild \uparrow Ca^{2+} (2.6–2.9mmol/L) is usually asymptomatic, but rapidly evolving \uparrow Ca^{2+} >3.5 may be fatal.

Symptoms and signs

'Bones, stones, groans, and psychic moans'. Nausea, abdominal pain, anorexia, constipation, depression, confusion, polydipsia, and polyuria. Dehydration (? postural drop), renal calculi, nephrocalcinosis. Signs from associated malignancy. Take a full medication history (milk-alkali syndrome) (see Table 10.4).

Causes

- 1° hyperparathyroidism (10–20%)—less commonly tertiary with CKD.
- Malignancy:
 - Local osteolytic bone lesions.
 - Humoral hypercalcaemia (tumour-derived PTH-related protein PTHrP has similar actions to PTH).
 - Common cancers include breast, lung, myeloma, ovary, lymphoma, oesophagus, renal, prostate, and head and neck primaries.
- Granulomatous diseases (sarcoidosis, TB) activated macrophages 1α -hydroxylase vitamin D.
- Drugs (vitamin D, vitamin A, lithium, thiazide diuretics).
- Immobilization (repetitive mechanical skeletal stress prevents bone and mineral loss).
- Thyrotoxicosis, (phaeochromocytoma), milk-alkali syndrome (antacids, calcium carbonate therapy).
- Familial hypocalcaemic hypercalcaemia: due to dysfunction of the calcium-sensing receptor.

Investigations

- U&E, Ca^{2+} , phosphate, alkaline phosphatase, albumin.
- PTH \pm PTHrP, 25-(OH) and $1,25\text{-(OH)}_2$ vitamin D_3 . If indicated, serum ACE, protein electrophoresis, urinary Bence-Jones proteinuria, serum free light chains, PSA. CXR. Plain KUB. Consider CT.
- ► ECG: short QT interval.

Treatment

- Treat the underlying cause:
 - Stop drugs which cause \uparrow Ca^{2+} .
 - 1° hyperparathyroidism: either cinacalcet or surgery if end-organ damage or uncontrolled hypercalcaemia.
 - Malignancy: surgical resection, radiotherapy, bisphosphonates.

Corticosteroids (prednisolone 30mg od) is effective when \uparrow Ca^{2+} is driven by increased extrarenal (macrophage or tumour) $1,25\text{-(OH)}_2$ vitamin D_3 synthesis.

Treat the calcium if symptomatic

- Mild hypercalcaemia (<3.0): increase fluid intake \pm salt intake (promotes u-Ca²⁺ loss). Aim to treat underlying cause.
- Δ Severe \uparrow Ca²⁺ (>3.0):
 - Vigorous rehydration with 0.9% saline, initially at 250–500mL/h, aiming for +2L positive balance (and giving 3–5L/day). \blacktriangleright Assess fluid balance regularly.
 - Furosemide (increases renal \uparrow Ca²⁺ wasting) 10–20mg 4-hourly, or as IVI infusion (5–40mg hourly). Do not dehydrate.

If urgent control required (and volume-resuscitated), calcitonin 4–8IU/kg SC/IM (inhibits osteoclast activity, promotes urinary calcium excretion). Repeat 12-hourly. Must add on bisphosphonate therapy, as tachyphylaxis develops.

- Bisphosphonates are powerful and prolonged inhibitors of osteoclasts. Options include zoledronic acid (4–8mg in 100mL in 0.9% saline over 30min, duration of effect 30 days) or pamidronate (60–90mg in 500mL 0.9% saline over 4h. Effect ~7 days). Monitor SCr.
- Treat \downarrow K⁺ or \downarrow Mg²⁺ with IVI supplements.

If significant hyperparathyroidism associated with hypercalcaemia, cinacalcet 30mg od, dose rapidly titrated upwards, if tolerated.

\blacktriangleright Hypercalcaemia in ESRD may need treatment by haemodialysis. Will rapidly lower Ca²⁺ and should be considered if Ca²⁺ >3.5 or depressed level of consciousness.

Table 10.4 Distinguishing 1^o hyperparathyroidism from malignancy

	HPT	Humoral Ca ²⁺ of malignancy	Metastases to bone
Phosphate	\downarrow	\leftrightarrow or \uparrow	\leftrightarrow or \uparrow
PTH	\uparrow	\downarrow	\downarrow
PTHrP	\downarrow	\uparrow	\downarrow
Albumin	\leftrightarrow	\downarrow	\downarrow
Chloride	\uparrow	\uparrow	\leftrightarrow
pH	\downarrow	\downarrow	\leftrightarrow

Hypomagnesaemia

Occurs in up to 12% of hospitalized patients. Often exacerbated by under-nutrition, chronic diarrhoea, diuretics, nephrotoxins. Those with diabetes are particularly prone to \downarrow Mg^{2+} . Causes include:

- Renal:
 - Diuretic use (loop or thiazide) or prolonged natriuresis.
 - Recovery phase of obstruction or ATN.
 - Nephrotoxins (aminoglycosides, cisplatin, ciclosporin, amphotericin, foscarnet, pentamidine).
 - Hypercalciuria or phosphate depletion.
 - Gitelman's or Bartter's syndromes (📖 p. 800) or familial hypomagnesaemia-hypercalciuria.
- Gut:
 - Gut losses due to diarrhoeal disease, prolonged NG suction, intestinal surgery, or malabsorption.
 - Pancreatitis (saponification in necrotic fat).
 - Alcohol abuse.

Symptoms and signs

\downarrow Mg^{2+} occurs in conjunction with \downarrow K^+ (50% of cases), \downarrow Ca^{2+} , and a metabolic alkalosis. Weakness, cramps, carpopedal spasm, positive Chvostek's and Trousseau's signs (📖 p. 804), tetany, and convulsions may occur. Delirium, movement disorders, vertigo, and nystagmus also occur. Significant \downarrow Mg^{2+} may induce supra- or ventricular arrhythmias.

Investigations

\downarrow Mg^{2+} , \downarrow K^+ (<3.0 mmol/L). Hypokalaemia is often resistant to K^+ supplementation until Mg^{2+} is normalized. \downarrow Ca^{2+} (if $Mg^{2+} <0.5$ mmol/L), with inappropriately low/normal PTH.

△ ECG changes: \uparrow QRS width, \uparrow PR interval, flattened T waves. Fatal ventricular arrhythmias in the context of underlying heart disease (esp. acute coronary syndromes and CCF).

24h urinary Mg^{2+} (NR <10 – 30 mg/day) or fractional excretion of Mg^{2+} will distinguish renal losses from other causes of \downarrow Mg^{2+} but is not usually required for diagnosis.

Treatment

- *Asymptomatic* with modest \downarrow Mg^{2+} (>0.4 mmol/L): oral slow-release Mg^{2+} 6–18mmol/day in four divided doses. Preparations include Mg glycerophosphate or Mg oxide.
 - *Symptomatic*, or with hypocalcaemia or hypokalaemia: 10mmol $MgSO_4$ IVI bolus over 5min, then 20mmol $MgSO_4$ in 100mL 0.9% saline IVI over 4 hours. Repeat, as required. ► Can be given as a *painful* IMI. Oral supplementation once $Mg^{2+} >0.5$ mmol/L with 18–24mmol Mg^{2+} /day in four divided doses. Diarrhoea may limit use of oral Mg^{2+} .
- *With arrhythmias* (e.g. torsade de pointes): IVI $MgSO_4$ 4–8mmol stat, then 20mmol/12-hourly against plasma Mg^{2+} . Aim for >0.4 mmol/L.

50% of administered Mg^{2+} will be lost in the urine, so prolonged therapy may be needed. The total body deficit in symptomatic $\downarrow \text{Mg}^{2+}$ may be 0.5–1mmol/kg body weight, so up to 150mmol may be required over 5 days (with urine losses). In diuretic-induced chronic Mg^{2+} wasting states, add-on amiloride 5mg od may limit Mg^{2+} losses.

Hypermagnesaemia

Urine losses of Mg^{2+} can compensate for rising plasma Mg^{2+} , so $\uparrow Mg^{2+}$ is unusual. Occurs usually if excess Mg^{2+} administered IVI (as in treating pre-eclampsia) or in patients with impaired renal function given exogenous Mg^{2+} . Mg^{2+} -containing preparations include: antacids (Mg^{2+} hydroxide or carbonate), $MgSO_4$ enemas.

Clinically

$\uparrow Mg^{2+}$ depresses the CNS and reduces neuromuscular function through increasing resistance to acetylcholine-induced depolarization at the neuromuscular junction. Paraesthesiae and hyporeflexia ($Mg^{2+} > 2.0 \text{ mmol/L}$) progress to weakness, swallowing difficulty, and respiratory depression ($Mg^{2+} > 3.5 \text{ mmol/L}$).

Bradycardia and \downarrow BP with severe toxicity ($> 3.5 \text{ mmol/L}$). ECG: \uparrow PR and QT interval.

May also see mild hypocalcaemia due to Mg^{2+} -induced inhibition of PTH secretion.

Treatment

If clinically stable, with a good UO and normal renal function, stop Mg^{2+} -containing preparation, and monitor. Excess Mg^{2+} will be rapidly renally excreted.

► If respiratory depression, cardiac arrhythmias or $Mg^{2+} > 5 \text{ mmol/L}$, give IVI calcium gluconate 10% 10mL as slow IVI bolus. May require repeated doses.

Consider forced Mg^{2+} diuresis with IV furosemide 40–80mg, replacing UO on a mL/mL basis with 0.45% NaCl.

In patients with impaired renal function, haemodialysis provides rapid and effective normalization of Mg^{2+} . Expect normalization of Mg^{2+} within 4 hours.

Hyperphosphataemia

Almost always occurs in patients with renal impairment. Calcium and phosphate are at the limits of solubility in plasma, so \uparrow calcium \times phosphate product leads to precipitation and ectopic calcification. Over time, this leads to vascular calcification (and is associated with \uparrow mortality in CKD). 2° hyperparathyroidism will attempt to \uparrow renal losses as compensation.

Usually asymptomatic, causes include:

- CKD.
- Tumour lysis (📖 p. 160) and rhabdomyolysis (📖 p. 152).
- Hypoparathyroidism.
- Phosphate-containing enemas (usually with renal impairment).
- Vitamin D toxicity.

No treatment is usually required in the acute setting though, if with \downarrow Ca^{2+} (tumour lysis, rhabdomyolysis), can be life-threatening.

▶ If so, give 10IU soluble insulin in 100mL 50% glucose over 30 minutes. This works by redistributing PO_4^- into cells. Promote diuresis through volume resuscitation (0.9% NaCl).

If chronic, aim to restrict dietary phosphate; use oral phosphate binders to limit uptake and in those with ESRD and dialysis.

For a fuller discussion, see 📖 p. 246.

Hypophosphataemia

Important hypophosphataemia occurs in \pm 1% of hospitalized patients, particularly chronic abusers of *alcohol*, *diabetics*, and those on *TPN*.

► Becomes clinically meaningful $<0.4\text{mmol/L}$.

Causes include:

- Redistribution:
 - Refeeding in malnourished (alcoholic) patients.*
 - Respiratory alkalosis (\uparrow pH intracellularly stimulates glycolysis).*
 - Exogenous insulin administration (DKA, critical care).*
 - Hungry bone syndrome (massive Ca^{2+} and PO_4^- deposition).
- \uparrow renal losses:
 - Hyperparathyroidism.
 - Impaired vitamin D metabolism.
 - Renal tubular disorders (Fanconi syndrome), ATN, or resolving obstructive uropathy.
- Gut uptake:
 - Malnutrition or vitamin D deficiency.
 - Chronic diarrhoea or malabsorption.
 - Antacid abuse.
 - Inappropriate use of phosphate binders (calcium carbonate, sevelamer, or lanthanum).

Note: reduced phosphate intake alone rarely causes hypophosphataemia due to compensatory increased renal phosphate reabsorption.

Symptoms and signs

Largely due to falling intracellular ATP levels and red cell 2,3-DPG (with impaired O_2 release from haemoglobin). Proximal muscle weakness \rightarrow spontaneous rhabdomyolysis (\pm diaphragmatic weakness and underventilation), ileus, myocardial depression (even heart failure), haemolysis, thrombocytopenia. altered mental state and fits, if prolonged, osteomalacia.

Investigations

Urine pH, U&E, bicarbonate, Ca^{2+} , phosphate. If indicated, PTH, FGF-23, 25-(OH) vitamin D_3 , calcitriol. Urine phosphate determines if low phosphate is due to renal losses or due to redistribution/reduced gut uptake. 24h urine phosphate $<16\text{mmol/day}$ = non-renal cause.

Treatment

If phosphate $>0.4\text{mmol/L}$, \uparrow dietary phosphate (milk and dairy products). Oral phosphate (e.g. Phosphate-Sandoz[®]) 1g tds (3g = $\sim 100\text{mmol}$).

► If $<0.4\text{mmol/L}$ or, if critically unwell, IVI phosphate (eg Addiphos[®]) 0.15mmol/kg in 500mL 5% dextrose or feed over 12 hours. Calcitriol PO or IVI may reduce urinary phosphate losses. Check Ca^{2+} repeatedly (as phosphate may precipitate sudden hypocalcaemia and tetany).

* Glycolysis = intracellular shift of phosphorylated glucose metabolites.

Acid–base

Understanding normal physiology

The concentration of hydrogen ions ($[H^+]$) is tightly controlled within and without cells, in various tissues and fluid compartments of the body. A key function of the kidneys is to regulate the blood $[H^+]$ and consequently total body $[H^+]$. pH is the negative logarithmic expression of the concentration of hydrogen ions in any fluid. In the ECF, pH is maintained within a normal range of 7.38–7.42 where $[H^+]$ at pH 7.40 is 40nmol/L—at pH 7.0 (the intracellular pH), $[H^+] = 100\text{nmol/L}$. Remember the pH of water is 6.8—note the role of buffers in biological fluids.

Intake and generation

Acid loads can be categorized as volatile (CO_2) and non-volatile. Non-volatile acid loads can be subdivided into metabolizable (via intermediary metabolism, e.g. lactic acid) and non-metabolizable (e.g. HCl). Non-metabolizable acid amounts to 1mmol/kg acid/day in adults, largely derived from the breakdown of ingested protein (sulphur-containing amino acids $\rightarrow \text{H}_2\text{SO}_4$) and by-products of cellular metabolism.

Metabolizable acids are eventually metabolized to CO_2 and H_2O , so eliminating the acid. The addition of salts of metabolizable acids (e.g. sodium lactate) to the body are equivalent to the addition of bicarbonate, as a proton will be used to metabolize lactate to CO_2 and H_2O (resulting in a net generation of bicarbonate). It is this principle that allows for the use of acetate and lactate as buffers in various forms of renal replacement therapy.

Buffering

To prevent rapid changes in pH with \uparrow dietary intake or excess production of $[H^+]$, e.g. during exercise, a system of local (tissue) and systemic buffers has evolved. These buffers include:

- Bicarbonate (HCO_3^-).
- Bone salts (calcium carbonate and calcium phosphate).
- Blood proteins (albumin, haemoglobin, and other globulins).

In the short term, bicarbonate is, by far, the most important, though bone buffers play a more significant role in chronic acidosis.

Acid maths



Adding H^+ (acidosis) consumes bicarbonate and generates CO_2 , as the reaction is driven rightwards. Removing CO_2 (hyperventilation) returns the pH toward normal, according to the Henderson–Hasselbach equation:

$$\text{pH} = \text{pK} \log[\text{HCO}_3^-]$$

where $\text{pK} = 6.1$, the dissociation coefficient of carbonic acid (H_2CO_3).

This does not generate more bicarbonate, so the kidney has to $\uparrow \text{H}^+$ excretion to balance the system.

Models of acid–base balance

There are two principal models to explain the physiological acid–base balance.

- The traditional ‘base excess’ model (see Fig. 10.1).
- Stewart’s theory—see <http://www.acidbase.org>.

Base excess (traditional method)

Building on the work of Singer and Hastings, Siggaard–Andersen introduced the concept of ‘base excess’ (BE) in 1960. Defined as the number of mmol of acid or base that are needed to titrate 1L of blood to pH 7.40 at 37°C in the presence of a $p\text{CO}_2$ of 5.33kPa (40mmHg). The base excess allows differentiation between metabolic and respiratory acidosis/alkalosis. The term ‘base deficit’ is synonymous with negative values of base excess (i.e. metabolic acidosis).

Values for HCO_3^- and BE are derived from the directly measured variables of pH, $p\text{CO}_2$, and Hb.

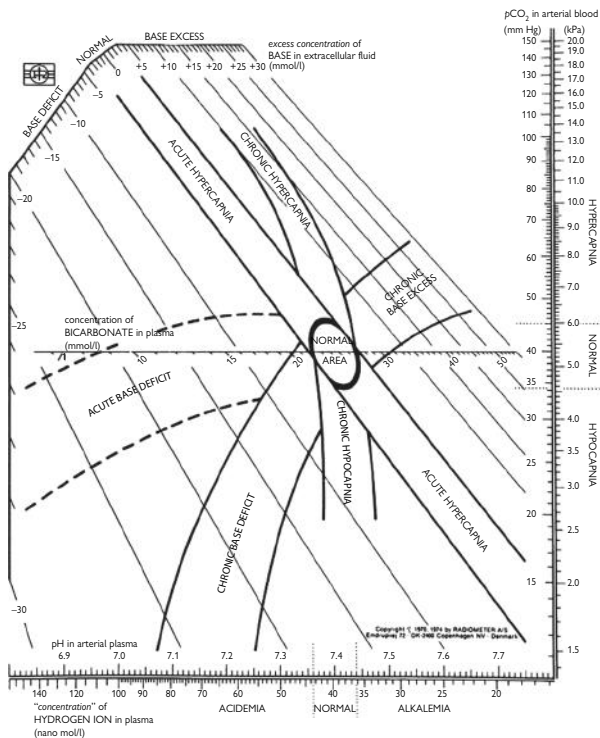


Fig. 10.1 Siggaard-Andersen acid-base chart. Reproduced with permission from Astrup P, Severinghaus JW: *The History of Blood Gases, Acids and Bases*. Copenhagen, Munksgaard, 1986.


Excretion: the kidney in acid–base

Preventing bicarbonate loss

80–90% of filtered HCO_3^- is actively reabsorbed in the proximal tubule:

- Proximal tubular cell Na^+ is pumped basolaterally into the interstitium, creating an inward gradient $\rightarrow \text{Na}^+$ movement from the lumen.
- NHE-3, the Na^+/H^+ antiporter, allows Na^+ entry from the lumen, exchanged for H^+ .
- In the lumen, $\text{H}^+ + \text{HCO}_3^- = \text{H}_2\text{CO}_3$ (carbonic acid).
- Luminal carbonic anhydrase then $\rightarrow \text{CO}_2$ and H_2O , taken up into cells.
- Intracellular carbonic anhydrase then $\rightarrow \text{H}^+ + \text{HCO}_3^-$.
- Intracellular HCO_3^- is then transported into the peritubular capillaries.
- The remaining H^+ is available for recycling.

Excreting proton

- Almost all H^+ in the proximal tubule is reabsorbed with HCO_3^- .
- Acid excretion occurs in the collecting duct.
- Na^+ absorbed under the influence of aldosterone (in the principal cells,  p. 931) means the tubular lumen becomes increasingly electronegative.
- K^+ is secreted from principal cells, and H^+ is secreted from α -intercalated cells into the lumen (aldosterone acts directly on this cell's H^+ -ATPase to effect this) to maintain electrical neutrality.

Buffering urinary proton

The luminal pH rapidly falls to <4.0 , inhibiting α -intercalated cell H^+ -ATPase. For ongoing net acid excretion, urinary H^+ is buffered (to keep u-pH >4.0) by:

- Titratable acids (H^+ incorporated into phosphoric acid H_3PO_4 or sulphuric acid H_2SO_4).
- Ammonium (NH_4^+).


In health, titratable acids and ammonium carry $\pm 50\%$ of the dietary H^+ load, but, with metabolic acidosis, more ammonium is needed for acid excretion.

Ammonium

Proximal tubular cells deaminate glutamine to form bicarbonate and ammonia (NH_3), then released and acidified in the lumen as NH_4^+ .

- NH_4^+ is absorbed into the medullary interstitium from the ascending limb of the loop of Henle where it dissociates to form NH_3 and H^+ once more.
- NH_3 can now move down a concentration gradient into the lumen of the collecting duct, available to buffer H^+ , and is then excreted as NH_4Cl in the urine.
- Ammonia synthesis is enhanced by acidosis and $\downarrow \text{K}^+$.

The urine anion gap (UAG) = $u\text{-}[\text{Na}^+ + \text{K}^+] - u\text{-}[\text{Cl}^-]$.

This difference is urinary NH_4^+ . If the kidney responds normally to acidosis (non-renal acidosis), it will $\uparrow \text{NH}_4^+$ excretion to waste H^+ into the urine. The UAG will then be negative (as $\uparrow \text{Cl}^-$ will accompany $\uparrow \text{NH}_4^+$). If the renal response is inappropriate (e.g. RTA,  p. 824), the UAG will be 0 or positive.

Metabolic acidosis

Acidosis occurs if the systemic pH falls <7.35 and is considered metabolic in origin if $\downarrow [\text{HCO}_3^-]$. This occurs through:


- \uparrow bicarbonate losses (gut or kidney).
- \uparrow acid retention.
- Excessive acid production or administration (HCl).
- Administration of Cl^- -rich solutions during resuscitation.

With pure metabolic acidosis, compensation occurs through increasing ventilation and blowing off CO_2 ($\downarrow p\text{CO}_2$).


Why do chloride-rich solutions lead to acidosis?

Solutions, such as 0.9% NaCl, normal saline, are bicarbonate-free. Falling bicarbonate is replaced by chloride (Cl^-) without a proportional \downarrow in $p\text{CO}_2$.

This is a so-called 'dilution acidosis'.

In determining the cause of a metabolic acidosis, it is helpful to estimate the anion gap—this may be calculated for both the plasma and urine (UAG,  see below). In health, the difference between cations and anions is made up of organic (negatively charged) acids. An \uparrow AG occurs if acids, other than carbonic acid (\rightarrow phosphate, lactate, or sulphate), accumulate or \uparrow exogenous acids are added to plasma.

Calculating the anion gap

- $\text{AG} = [\text{Na}^+ + \text{K}^+] - [\text{Cl}^- + \text{HCO}_3^-] = 8\text{--}16$ in health.
- Albumin is negatively charged: \downarrow Alb \rightarrow underestimates the AG.
- To correct for hypoalbuminaemia, add $0.25 \times (44 - s\text{-Alb})$ to the AG.
- In the USA, the contribution of $[\text{K}^+]$ to the anion gap is frequently ignored.
- $\text{UAG} = u[\text{Na}^+ + \text{K}^+] - u[\text{Cl}^-]$.
- As $u\text{Cl}^-$ usually exceeds $u\text{Na}^+$ and $u\text{K}^+$, this should return a negative value.
- UAG is an estimate of renal ammonia production ( p. 819).

Clinical features of an acidosis

Systemic effects of severe metabolic acidosis (pH <7.1):

- Air hunger (Kussmaul's breathing, an increase in tidal volume, with deep, sighing respiration) and hyperventilation (to blow off CO_2).
- \downarrow myocardial contractility (\downarrow Ca^{2+} release from sarcoplasmic reticulum), arteriodilatation, and venoconstriction (central blood pooling).
 - Shifts oxygen dissociation curve rightwards (more O_2 release).
 - Reduced binding of noradrenaline (norepinephrine) to receptors.
- Resistant arrhythmias (esp. VF).

The associated underlying cause may be apparent.

Investigations

- U&E, venous pH (in a blood gas syringe), or ABG.
- Urine pH. In health, the urine pH <5.3 in the face of acid loading.
- Lactate, ketones, blood glucose.
- Urinary dipstick, electrolytes (UAG), and ketones.
- Microscopy for crystals. Toxicology screen, including salicylates.

Normal AG acidosis

Due to retained H^+ or HCO_3^- loss. Both Cl^- and H^+ are increased, so a normal AG acidosis is also referred to as 'hyperchloraemic'.

Cl^- displays a reciprocal relationship with HCO_3^- , increasing when bicarbonate is lost to maintain electrical neutrality.

The UAG is useful in evaluating a normal AG acidosis:

- Non-renal losses of bicarbonate (▶ negative UAG):
 - Diarrhoea or high-output ileostomy.
 - Uretersigmoidostomy (gut absorption of urinary NH_4^+ and Cl^-).
- Renal bicarbonate losses (UAG >0):
 - Impaired reabsorption (acetazolamide).
 - Proximal RTA (📖 p. 824) or Fanconi-like syndromes (📖 p. 825).
 - Hypoaldosteronism or mineralocorticoid receptor blockade.
- Failure of renal acid excretion (UAG >0):
 - RTA (distal or type 4, 📖 p. 825).
- Increased acid production/load:
 - Toluene poisoning, lysine or arginine administered in TPN (metabolized to HCl), or NH_4Cl administration.

Increased AG acidosis

('Hypo-' or 'normochloraemic' acidosis).

Causes remembered, using the mnemonic KUSMAL:

- K—ketoacidosis (acetoacetate or β -hydroxybutyrate).
- U—uraemia/CKD; acidosis uncommon until eGFR <20–25mL/min.
- S—salicylates (aspirin).
- M—methanol (and other alcohols, e.g. ethylene glycol).
- A—aldehydes.
- L—lactic acidosis.

Causes of a ketoacidosis include diabetes, starvation, and alcohol—all induced by insulin deficiency and relative glucagon excess → ↑ fatty acid mobilization and subsequent oxidation to keto-acids.

Treating severe acidosis with IVI $NaHCO_3$ is controversial

- Corrects extracellular pH.
- May worsen intracellular acidosis (normal intracellular pH is 7.1), as generated CO_2 crosses the cell membrane faster than HCO_3^- so ↑ intracellular acidosis.
- Generates CO_2 that must be blown off (△ fixed or ↓ respiratory rate).

- Ionized calcium can fall abruptly.
- Na^+ load is substantial (150mmol in 500mL 1.26% NaHCO_3 and 1mmol Na^+ /mL of 8.4% NaHCO_3) and poorly tolerated in volume-overloaded patients.
- Studies of bicarbonate supplementation in severe acidosis have consistently failed to demonstrate a benefit—and some have suggested an association with mortality (as BP and cardiac output fall with correction).

Reduced CO_2 -generating buffers (such as Carbicarb[®]) are promising but have not been adequately assessed clinically.

Managing severe and life-threatening acidosis

Consider NaHCO_3 if pH <7.0 in patients with impaired cardiac performance. If correcting, aim to correct to pH >7.2 or a minimum $[\text{HCO}_3^-]$ >10, at which pH life-threatening complications of acidosis would be unusual.

- HCO_3^- deficit = (target – measured $[\text{HCO}_3^-]$) × bicarbonate space.
- Bicarbonate space = $(0.4 + 2.6/[\text{HCO}_3^-]) \times \text{weight (kg)}$.

For example, in a 70 kg ♂ with pH 6.9 and $[\text{HCO}_3^-] = 4\text{mmol/L}$ with cardiac instability: deficit = $(10 - 4) \times ((0.4 + 2.6/4) \times 70) = 420\text{mmol HCO}_3^-$.

⚠ Note that the target bicarbonate is 10mmol/L and NOT normal (24mmol/L).

Aim to give as 1.26% NaHCO_3 (1,000mL = 150mmol HCO_3^-) IVI over 4–6 hours. 50mL 8.4% NaHCO_3 contains 50mmol HCO_3^- .

▶ IVI bicarbonate is almost never needed in diabetic ketoacidosis—it delays the removal of blood ketone bodies.

Respiratory acidosis

Occurs if pH <7.35 and $\uparrow \text{pCO}_2$ —may be metabolic compensation if chronic ($\uparrow [\text{HCO}_3^-]$). Causes include advanced pulmonary disease, respiratory muscle fatigue, impaired central ventilatory control (drugs or stroke), or as a result of mechanical ventilation.

Treatment (if warranted) usually involves mechanical ventilation.

Oral bicarbonate supplementation in progressive CKD

Emerging evidence supports the use of oral bicarbonate salts in slowing the progression of renal failure and improving the nutritional status of patients with CKD stages 4–5.

The optimal bicarbonate level in CKD has yet to be defined. However, a level between 23 and 29mmol/L is associated with a reduced rate of deterioration in renal function, and observational studies suggest it may be associated with reduced mortality.

Aim to treat with oral NaHCO_3 1.5–4.5g/day in 2–3 divided doses. Alternatives include Na citrate or a diet in fruit and vegetables (rich in alkali). Advantages in not using NaHCO_3 include lowering the salt load.

Other benefits in treating chronic acidosis include:

- Reducing bone demineralization.
- Improving appetite.
- Reducing muscle wasting and malnutrition.

Renal tubular acidosis

A group of disorders characterized by impaired renal handling of acid, usually with normal renal function. The basis for the, often confusing, terminology used for RTA revolves around physiology: almost all filtered bicarbonate (HCO_3^-) is reabsorbed in the proximal tubule, with no net acid excretion. All net acid excretion occurs in the distal nephron (📖 p. 930). See Table 10.5 for distinguishing types of RTA.

Distal RTA (type 1)

Disordered excretion of acid (H^+) from the α -intercalated cell in the collecting duct leads to acidosis. Presents as a hyperchloraemic, hypokalaemic metabolic acidosis, with hypophosphataemic metabolic bone disease, renal stones, or diffuse nephrocalcinosis (requirement to chronically buffer acidosis \rightarrow bone buffering). Is (rarely) inherited or, more commonly, acquired secondary to:

- Sjögren's syndrome, RA, SLE, and other autoimmune diseases.
- Nephrocalcinosis (distal RTA is confusingly both a cause and result of nephrocalcinosis) of any cause.
- Drugs (analgesic nephropathy, ifosfamide, amphotericin, lithium).
- Chronic tubulointerstitial disease (of any cause, 📖 p. 582).
- Dysproteinaemias (hypergammaglobulinaemia, amyloidosis).

Investigations

- \uparrow u-pH (>5.3 in the face of acidosis).
- \downarrow K^+ , \downarrow $\text{HCO}_3^- <12\text{mmol/L}$, normal AG (\uparrow Cl^-).
- Positive urinary AG (📖 p. 820), \uparrow u- Ca^{2+} , \downarrow u-citrate (absorbed to buffer acidosis).
- Plain KUB or USS may show nephrocalcinosis.
- ANF, anti-Ro/La, rheumatoid factor.

If partial RTA suspected, either:

- Acid loading test: $0.1\text{g/kg NH}_4\text{Cl PO}$, with u-pH hourly, HCO_3^- at +3 hours. If $\text{HCO}_3^- <21$ and u-pH >5.3 , diagnose RTA.
- Furosemide (40mg PO) and fludrocortisone (1mg PO) test: stat simultaneous dose, then hourly urine pH to 6 hours. At +6 hours, if $\text{HCO}_3^- <21$ and u-pH >5.3 , diagnose RTA.

Treatment

Potassium citrate 3–10g/day in three divided doses (citrate generates two bicarbonate molecules) or sodium bicarbonate 4–12g/day in four divided doses, aiming for s- $\text{HCO}_3^- >22\text{mmol/L}$.

Proximal RTA (type 2)

Impaired retention of HCO_3^- in the proximal tubule leads to bicarbonate wasting and a systemic acidosis. Presents as a hyperchloraemic metabolic acidosis, usually with other features of proximal tubular dysfunction (so-called Fanconi syndrome, see 📖 p. 825). Commoner causes include:

- Myeloma and amyloidosis.
- Cystinosis, Wilson's disease, or heavy metal toxicity (lead, cadmium).
- Drugs (acetazolamide, antiretroviral drugs, aminoglycosides).

Investigations

Although the u-pH may be >5.5 , usually \downarrow u-pH <5.3 , once steady state achieved with chronic acidosis (as falling filtered bicarbonate means less bicarbonate wasting).

- ▶ If IVI NaHCO_3 1mmol/kg/h given, distal reabsorption is overwhelmed and u-pH $\uparrow >7$.
- $\downarrow \text{K}^+$, with \uparrow distal Na^+ delivery and hyperaldosteronism $\rightarrow \text{K}^+$ wasting.
- $\downarrow \text{HCO}_3^-$ (12–20mmol/L), normal AG ($\uparrow \text{Cl}^-$), negative u-AG (see below). Findings of Fanconi.

Treatment

△ High-dose bicarbonate merely $\uparrow \text{HCO}_3^-$ wasting and increases Na^+ delivery to the distal nephron (and so worsens $\downarrow \text{K}^+$). Aim to allow mild acidosis: potassium bicarbonate 1.5–3g/day in three divided doses (KHCO_3^- is less calciuric, replenishes K^+ and Na^+ load). Thiazide diuretics may also be helpful.

Fanconi syndrome

A descriptive term for generalized proximal tubular dysfunction. It is marked by failure of proximal reabsorption of many filtered substances and classically describes glucosuria, aminoaciduria, and phosphaturia. Excretion of uric acid and LMW proteins is also increased. Commonly seen in association with type 2 RTA.

- May present with bone pain \pm osteomalacia. Causes as for proximal RTA.
- Investigations: metabolic acidosis, \downarrow s-phosphate, \downarrow s-urate. Glycosuria and proteinuria (amino acids), \uparrow u-phosphate, and \uparrow u-citrate.

Drug-induced Fanconi

Occurs with antivirals (tenofovir, adefovir, and cidofovir), didanosine, out-of-date tetracyclines, aminoglycosides, sodium valproate, or ifosfamide.

Hyperkalaemic distal RTA (type 4)

Is much more common than proximal RTA or distal RTA and is due to hypoaldosteronism, usually hyporeninaemic hypoaldosteronism. Aldosterone promotes urinary K^+ loss, so its absence \rightarrow hyperkalaemia. $\uparrow \text{K}^+$ impairs NH_3 secretion, limiting net acid excretion \rightarrow acidosis. Causes include:

- Diabetes mellitus (often with mild renal impairment).
- Drugs (NSAIDs, ciclosporin, heparin, co-trimoxazole).
- Obstructive uropathy.
- Chronic tubulointerstitial disease of any cause (📖 p. 582) \pm CKD.
- Addison's or selective aldosterone deficiency.

Investigations

- ↑ K⁺, ↓ HCO₃⁻ (rarely <16mmol/L).
- Normal AG (↑ Cl⁻), negative u-AG (📖 p. 820), ↓ u-citrate. Urine pH variable but often <5.3.

Treatment

If due to hypoadrenalism, mineralocorticoid replacement (fludrocortisone 100–300 micrograms/day) will rapidly reverse the problem.

⚠ Often revealed in patients taking ACE-I and increasingly spironolactone for treatment of heart failure. Advise low K⁺ diet (📖 p. 259). Mineralocorticoids rarely useful because of significant Na⁺ retention in at-risk patients (CKD, heart failure). Trial of furosemide 40–120mg od. Review drugs.

Table 10.5 RTA by numbers

Type	Distal RTA	Proximal RTA	Hyperkalaemic distal
Defect	Impaired net acid excretion	Impaired HCO ₃ ⁻ uptake	Hypoaldosteronism
K ⁺	↓	↓	↑
Bicarbonate	<10	12–20	>16
Urine pH	>5.3	<5.3, ↑ + bicarbonate	Variable
UAG	Positive	Negative	Positive
Urine citrate	↓	↑ or normal	↑ or normal
Nephrocalcinosis	Yes	No	No

Lactic acidosis

L-lactate is an end-product of anaerobic glucose metabolism: glucose is metabolized to pyruvate. In hypoxic tissue, oxidative regeneration of NAD^+ cannot occur, so pyruvate is used with NADH and H^+ by lactate dehydrogenase to produce NAD^+ (crucial earlier for glycolysis) and lactate. In health, lactate is usually rapidly oxidized by the liver. The normal plasma concentration is between 0.5 and 1.5mmol/L. Significant lactic acidosis is present if blood lactate is $>3.5\text{mmol/L}$, with an increased anion gap. Conventionally, lactic acidosis is divided into:

Type A lactic acidosis

Secondary to increased O_2 demand or inadequate O_2 delivery (tissue underperfusion), causes of which include:

- Shock:
 - Cardiogenic.
 - Septic.
 - Hypovolaemic.
- Severe anaemia.
- Localized tissue or organ ischaemia (infarcted gut, muscle).
- \uparrow energy-dependent work (usually in skeletal muscle):
 - Seizures.
 - Extreme exercise.
 - Malignant hyperthermia.
- Respiratory failure with severe hypoxaemia.
- Carbon monoxide poisoning.

Type B lactic acidosis

Secondary to abnormal lactate metabolism, the underproduction or over-utilization of ATP or other causes of defective gluconeogenesis (drugs!). Causes include:

- Mitochondrial dysfunction, either congenital or drug-induced (📖 p. 829).
- Thiamine deficiency.
- Metabolic derangements involving oxidation:
 - Diabetes mellitus—especially when poorly controlled.
 - Ethanol poisoning.
- Liver impairment.

D-lactic acidosis is a rare cause of an increased anion gap metabolic acidosis where bacterial overgrowth in intestinal blind loops leads to increased lactate absorption—the proliferating organisms (and not humans) are capable of producing the D-isomer.

Management of lactic acidosis

Treat the underlying cause—there is no role for systemic NaHCO_3 . So the treatment of type A lactic acidosis involves improving oxygenation: resuscitate shock; restore blood flow, and/or improve gas exchange.

Drugs and lactic acidosis

Metformin has long been thought to cause a type B lactic acidosis, particularly in diabetics with renal impairment. There is some doubt about this association. However, current NICE recommendations are to stop metformin if SCr $>150\mu\text{mol/L}$ (1.7mg/dL) or eGFR $<30\text{mL/min}/1.73\text{m}^2$.

Recently, reverse transcriptase inhibitors have also been found to cause an often severe lactic acidosis as a result of mitochondrial injury—in life-threatening cases (lactate $>10\text{mmol/L}$), consider L-carnitine.

Other drugs recognized as causes of type B lactic acidosis:

- Ethanol, cocaine, paracetamol, salicylate.
- Zidovudine, didanosine, stavudine, lamivudine, zalcitabine.
- Propofol, isoniazid.
- Niacin, nitroprusside, cyanide.
- Sorbitol and fructose.

Alkalosis

Metabolic alkalosis

Metabolic alkalosis is common (as might be expected from its causes) and, if severe ($\text{pH} > 7.55$), is associated with mortality as high as 45%. Either retention of base or loss of acid in the ECF leads to a rising serum bicarbonate and pH. To buffer such changes, patients can hypoventilate to $\uparrow \text{pCO}_2$ to as much as 7kPa ($\times 7.5$ for kPa \rightarrow mmHg). For each 1mmol/L rise in serum HCO_3^- above normal, the pCO_2 will rise by $\pm 0.08\text{kPa}$ to buffer the alkalosis (e.g. to buffer a serum HCO_3^- of 34mmol/L, the pCO_2 will need to rise by 0.8kPa).

Causes of a metabolic alkalosis include:

- With low chloride:
 - Gastric losses (vomiting, NG suction, self-induced vomiting).
 - Diuretics (thiazide, loop diuretics).
 - Diarrhoea (esp. chloride-secreting villous adenoma).
 - Cystic fibrosis.

Chloride-losing alkaloses

With vomiting or NG losses, the stomach generates replacement gastric HCl, in the process returning HCO_3^- to the ECF. NaCl loss into gastric fluids \rightarrow volume contraction as well.

Diuretics block NaCl uptake, with ECF depletion (2° hyperaldosteronism) and \uparrow salt delivery to the DCT ($\therefore \uparrow$ exchange of Na^+ for K^+ and H^+). Diuretic-induced $\downarrow \text{K}^+$ exacerbates alkalosis further.

- With low potassium:
 - 1° hyperaldosteronism (and, less commonly, 2°).
 - Drugs (carbenoxolone, liquorice, laxative abuse).
 - Bartter's, Liddle's, and Gitelman's syndromes (📖 p. 800).

Hypokalaemic alkalosis

Hyperaldosteronism leads to $\uparrow \text{Na}^+$ retention at the expense of K^+ and H^+ . $\downarrow \text{K}^+$ may increase net acid excretion.

The intracellular acidosis found with $\downarrow \text{K}^+$ leads to $\uparrow \text{HCO}_3^-$ retention in the kidney.

- Other:
 - Milk-alkali syndrome (or hypercalcaemia of other causes usually 2° to calcium and vitamin D-containing preparations, occasionally in association with thiazide diuretic use, the so-called calcium-alkali syndrome).
 - Overzealous bicarbonate therapy (esp. if with CKD).
 - Penicillins (cation load $\rightarrow \text{uHCO}_3^-$ wasting).
 - Massive transfusion (citrate load).

Symptoms and signs

Often due to associated hypovolaemia or hypokalaemia. With severe alkalosis, ↓ cerebral and myocardial blood flow: headaches, confusion, seizures, angina, arrhythmias. Compensatory hypoventilation and hypocapnoea may be important in critically ill patients (failure to wean off ventilator).

O₂ delivery to tissues is reduced (through alkalosis-induced vasoconstriction and reduced O₂ release—the dissociation curve is shifted leftwards).

Investigations

Only consider ABG if evaluating respiratory contribution to a mixed acid–base disorder.

- U&E (↓ K⁺, ↓ Cl⁻). ? ↑ Ca²⁺.
- Urinary electrolytes:
 - u-Cl⁻ <10mmol/L if gastric losses (▶ surreptitious vomiting).
 - u-Cl⁻ >30mmol/L if diuretic therapy (abuse), Bartter's, Gitelman's.
 - u-K⁺ >30mmol/L if diuretics, hyperaldosteronism.
 - u-K⁺ <20mmol/L if extrarenal K⁺ losses.

Diagnosis usually obvious: urinary diuretic/laxative screen, renin and aldosterone, if indicated.

Treatment

Depends on the cause:

- Treat ↓ Cl⁻ alkalosis with chloride.
 - Replacement of lost Cl⁻ is the mainstay of treatment.
 - If volume-deplete: 0.9% saline (NaCl) 3–5L/day IVI.
 - If volume-overloaded: KCl, rather than NaCl (unless ↑ K⁺).
- Treat ↓ K⁺ alkalosis with KCl (📖 p. 799).
- Reverse the underlying cause:
 - Stop alkali therapy.
 - Stop diuretics, if possible, or add K⁺-sparing agent, esp. if hyperaldosteronism present (spironolactone).
 - Antiemetics (e.g. metoclopramide 10mg IMI/IVI).
 - If NG drainage needed, H₂ receptor antagonist or proton pump inhibitor.
- Acetazolamide 250–500mg daily will cause NaHCO₃⁻ wasting. Particularly useful in those with chronic lung disease (and need their respiratory drive) or with acute unstable cardiac syndromes.

Respiratory alkalosis

Always a result of overventilation (due to mechanical ventilation), increased central respiratory drive (anxiety, pregnancy, stroke, or CNS infection), or hypoxaemia (mild asthma, pulmonary oedema, or emboli). Treatment can be difficult if alkalosis severe.

Urgent reversal of severe metabolic alkalosis (in ITU)**Indications**

- Bicarbonate $>45\text{mmol/L}$ (or $\text{pH} >7.55$), and
- Hepatic encephalopathy, or
- Arrhythmias (including digoxin toxicity), or
- Confusion, seizures.

Correct K^+

IVI hydrochloric acid (HCl) via central line: $\text{body weight (in kg)} \times 0.5$ (bicarbonate space = 50% body weight) \times required $\downarrow \text{HCO}_3^-$ (mmol/L) = mmol HCl infused at 0.2mmol/kg/h .

Example: in a 70kg male, to $\downarrow \text{HCO}_3^-$ by 10mmol/L , 0.1M HCl solution ($10 \times 70 \times 0.5 = 350\text{mmol}$) at 35mmol/h for 10 hours to reduce plasma bicarbonate by 10mmol/L . Alternatives include NH_4Cl or arginine HCl. HD or CVVHF also provide rapid correction of severe alkalosis.

Mixed disturbances

As a rule of thumb, pH will rise or fall by 0.1 if:

- $[\text{HCO}_3^-]$ changes by 6mmol/L, or
- pCO_2 changes by 1.58kPa.

For example, a fall in $[\text{HCO}_3^-]$ from 24 to 12 = pH from 7.4 to 7.2, or a rise in pCO_2 from 5.5 to 7.9 = pH from 7.4 to 7.25.

See Table 10.6 for normal ranges.

Table 10.6 Normal ranges

pH	7.38–7.42
pO_2	10–13kPa (1kPa = 7.6mmHg)
pCO_2	4.7–5.9kPa (mixed venous pCO_2 usually 1kPa higher)
HCO_3^-	22–26mmol/L

Table 10.7 Characteristics of pure acid–base disturbances

	pH	pCO_2	$[\text{HCO}_3^-]$
Metabolic acidosis	↓	Ⓣ	↓
Metabolic alkalosis	↑	Ⓢ	↑
Respiratory acidosis	↓	↑	Ⓢ
Respiratory alkalosis	↑	↓	Ⓣ

Circled arrows = compensatory mechanism.

Mixed acid–base disturbances are not uncommon in hospitalized patients: the key to diagnosis is recognizing when compensation is inappropriate. Using Table 10.7, the following should be expected:

- Metabolic acidosis: pCO_2 falls by $[24 - \text{actual } \text{HCO}_3^-] \times 0.17$.
- Metabolic alkalosis: pCO_2 rises by $[\text{actual } \text{HCO}_3^- - 24] \times 0.08$.
- Acute respiratory alkalosis: $[\text{HCO}_3^-]$ falls to not less than 18mmol/L.
- Acute respiratory acidosis: $[\text{HCO}_3^-]$ rises by $[0.75 \times \text{pCO}_2 - 5.3] \pm 3$.
- Chronic respiratory alkalosis: $[\text{HCO}_3^-]$ falls to not less than 14mmol/L.
- Chronic respiratory acidosis: $[\text{HCO}_3^-]$ rises by $[3 \times \text{pCO}_2 - 5.3] \pm 4$.

If compensation does not fall roughly within these limits, there is likely to be a mixed component to the disturbance:

- What is the pH (acidotic or alkalotic)?
- Is predominant cause metabolic or respiratory?
- Is compensation appropriate?
- If not, a mixed acid–base disturbance is present.

See Fig. 10.2 for the acid–base nomogram.

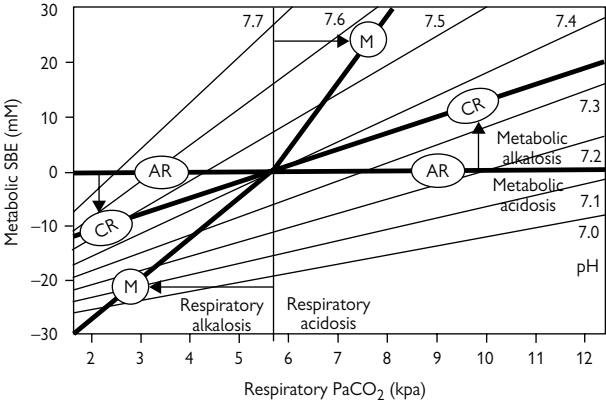



Fig. 10.2 The acid–base nomogram. Plot PaCO_2 on the x-axis. The left-hand scale predicts the base excess/deficit from the intersection with the measured pH. Changes in PaCO_2 (i.e. in ventilation) will lead to horizontal shifts, whilst changes in bicarbonate (i.e. administration) will lead to vertical shifts from the original intersection. Metabolic and respiratory changes move the patient along the appropriate axis without altering the other. Adapted from Schlichtig R, Grogono AW, Serveringhans JW (1998) Current status of acid–base quantitation in physiology. *Anesthesiology Clinics of North America* 16: 211–13, with permission from Elsevier.

Tubular rarities

Cystinuria (see p. 719)

Defective uptake of filtered cystine and other dibasic amino acids from the urine leads to cystine stone formation. Autosomal recessive inheritance of genes encoding tubular amino acid transporter proteins presents in childhood or adolescence with flank pain \pm haematuria (calculi).

Urine microscopy shows characteristic hexagonal crystalluria (see Fig. 10.3). \uparrow 24h urinary cystine excretion ($>2\text{mmol/day}$, NR <0.15), radio-opaque calculi on plain KUB or USS. Aim to increase oral fluids for UO of $>3\text{--}4\text{L/day}$. If u-cystine remains $>1\text{mmol/L}$ (cystine is insoluble much above this), add in penicillamine $1\text{--}2\text{g/day}$ in four divided doses. Alternatives include tiopronin up to 400mg daily or captopril. All work by increasing cystine solubility. For managing stones, see  p. 722.

Cystinosis

 *Is not the same disease as cystinuria*


Presents in childhood with growth failure, Fanconi syndrome, and progressive renal impairment. Eye involvement, hepatomegaly, hypothyroidism, and diabetes develop, as cystine deposits impair organ function. An adolescent variant with normal stature and tubular function, but renal impairment, offers a better renal prognosis. An autosomal recessively inherited defect in cystine export from intracellular lysosomes leads to accumulation and local injury. Oral cysteamine forms a complex with cystine that can leave lysosomes, ameliorating disease.

Hyperoxaluria

An autosomal recessive condition presenting in childhood marked by \uparrow u-oxalate excretion, calcium oxalate calculi, and nephrocalcinosis.

Defective synthesis or targeting of the enzyme AGXT, which converts glyoxalate to glycine, leads to compensatory shuttling of glyoxalate to oxalate. Heavy oxalate deposition in the heart, blood vessels, and joints causes significant morbidity. The treatment of choice is combined liver-kidney transplantation, although high-dose pyridoxine offers interim benefit. Rarely, hyperoxaluria and nephrocalcinosis may be associated with Crohn's disease. See Fig. 10.4 for radiography of the abdomen

Dent's disease

An X-linked inherited defect in the gene encoding CLC-5, a chloride channel responsible for endosomal acidification in the proximal tubule and elsewhere. This leads to impaired endocytosis and uptake of urinary proteins. Presents predominantly in σ (♀ may have urinary abnormalities) as Fanconi syndrome ( p. 825), hypercalciuria, nephrocalcinosis, and renal impairment. Rickets and osteomalacia are common. Renal transplantation is the treatment of choice for ESRD, and patients generally do well. Other syndromes, such as X-linked recessive nephrolithiasis, X-linked recessive hypophosphataemic rickets, and idiopathic low molecular weight proteinuria of Japanese children, are now known to be due to similar defects.

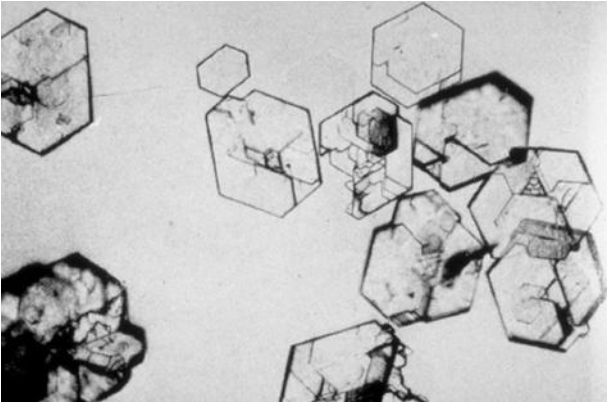


Fig. 10.3 Characteristic hexagonal urinary crystals of cystine. Reproduced from http://thiola.com/Kidney_Stone_Photos/Photo27-Cystine-Crystals.aspx, with permission from Mission Pharmacal Co.



Fig. 10.4 Plain abdominal radiograph demonstrating the cortical pattern of calcium oxalate crystal deposition seen in hyperoxaluria. Reproduced from Phang Boon Lim et al., *Nephrology Dialysis Transplantation*, 19: (5) 1325 (2004) with permission from Oxford University Press.

Pregnancy and the kidney

- Physiological changes during pregnancy [840](#)
- Urinary tract infection [842](#)
- AKI during pregnancy [844](#)
- Hypertension during pregnancy [846](#)
- Pre-eclampsia: pathophysiology [850](#)
- Pre-eclampsia: management [852](#)
- Pre-existing renal disease [856](#)
- Disorders of the urinary tract in pregnancy [860](#)
- Pregnancy on dialysis [862](#)
- Pregnancy after renal transplantation: introduction [864](#)
- Transplant function and pregnancy [865](#)
- Pregnancy after renal transplantation: management [866](#)

Physiological changes during pregnancy

Systemic changes

- Significant changes to cardiovascular function and volume homeostasis begin early in pregnancy.
 - Increased cardiac output (up to 50%).
 - Increased plasma volume (up to 30–40%).
 - Increased peripheral vasodilatation, with corresponding decrease in systemic vascular resistance (→ fall in BP and widening of pulse pressure during 1st and 2nd trimesters that normalizes during 3rd trimester).
 - The fall in BP is actually modest, in comparison to the increase in CO and intravascular volume, as there is a significant concomitant increase in vascular compliance.

Renal changes

- Increased renal blood flow, up to 70–80% in 2nd trimester (under the influence of NO, vasodilator prostaglandins and relaxin). Trans-glomerular capillary pressure remains the same, with matching dilatation of both afferent and efferent arterioles.
- Marked stimulation of RAAS.
- Increased GFR (40% by end of 1st trimester).
- Increase in proteinuria.
 - $\leq 300\text{mg}/24\text{h}$ is not significant in pregnancy.
 - It is important to quantify baseline pre-existing proteinuria at the start of pregnancy (uACR/uPCR).
 - Pre-existing proteinuria is likely to double.

Renal function

(See Table 11.1.)

- ⚠ eGFR is not validated in pregnancy: MDRD underestimates, and Cockcroft–Gault overestimates, true GFR.
- ► SCr $>80\mu\text{mol}/\text{L}$ (0.9mg/dL) or Ur $>5\text{mmol}/\text{L}$ (14mg/dL) during pregnancy may indicate renal impairment and warrant further evaluation.
- 24h urinary creatinine clearance (📖 p. 33) remains the gold standard for the measurement of renal function during pregnancy (NR: 125–150mL/min; 30% above range for non-pregnant women).

Table 11.1 Renal function in pregnancy

Mean serum creatinine values

Non-pregnant	Average $72\mu\text{mol}/\text{L}$ (0.8mg/dL)
1st trimester	52–68 $\mu\text{mol}/\text{L}$ (0.58–0.77mg/dL)
2nd trimester	44–64 $\mu\text{mol}/\text{L}$ (0.5–0.72mg/dL)
3rd trimester	55–73 $\mu\text{mol}/\text{L}$ (0.62–0.82mg/dL)

Tubular function

- Glycosuria does not necessarily indicate impaired glucose tolerance during pregnancy. If persistent, measure blood glucose.
- Tubular handling of bicarbonate and acid is unchanged, but hyperventilation in pregnancy leads to \downarrow $p\text{CO}_2$, a mild respiratory alkalosis (\uparrow pH from 7.4 to 7.43). HCO_3^- excretion increases and serum HCO_3^- falls to 18–22mmol/L to compensate.
- Urinary calcium excretion is increased.
- Serum urate falls in early pregnancy: as a *rough* guide the intrapartum urate should be 0 (gestational age in weeks), i.e. at 26 weeks, urate will be ~ 0.26 mmol/L.
- Plasma osmolality is reduced:
 - Women gain an average 9–14kg during pregnancy, with up to 8L as \uparrow total body water.
 - The threshold for arginine vasopressin (AVP or ADH) release is lowered, resulting in sustained AVP release in the face of plasma dilution and \therefore a true fall in plasma osmolality (~ 10 mOsm/kg).
 - Serum Na^+ falls to 132–140mmol/L (Δ $\text{Na}^+ > 140$ mmol/L may indicate hypernatraemia in pregnancy).
 - Rarely, transient diabetes insipidus of pregnancy (with polyuria) may develop in the 3rd trimester (the result of either incomplete cranial DI in susceptible women or increased AVP degradation).

Anatomical changes

- Increased kidney volume, size, and weight.
- Renal length increases by ~ 1 cm.
- Collecting system dilatation:
 - May begin at 8 weeks. Apparent in 90% of women by 20 weeks' gestation (~ 2 cm above normal diameter).
 - More obvious on right (uterine veins, enlarging uterus, and iliac artery compress the right ureter \rightarrow 'iliac sign' on IVU, with abrupt ureteric cut-off at the pelvic brim).
 - Assessments made during pregnancy should be interpreted with caution.
- Collecting system dilatation usually resolves within 48h of delivery in 50% of cases but can still be present up to 12 weeks post-partum.

Urinary tract infection

Introduction

Anatomical, functional, and hormonal changes in the urinary tract make UTI more common in pregnancy. Pyelonephritis is the most common renal complication of pregnancy, occurring in 1–2% of all pregnancies. In addition, preterm labour or low birthweight infants may be associated with asymptomatic bacteriuria or UTI (mechanism: possible amnionitis → ↑ inflammatory cytokine synthesis, provoking uterine contraction). Untreated UTI may be associated with subsequent developmental delay in the child and even increased risk of fetal death.

Bacteriology

80–90% due to *E. coli*. *Proteus* spp., *Klebsiella* spp., or Gram +ve organisms may also be implicated. Group B *Streptococcus* (GBS) infection near delivery may lead to vaginal colonization and serious neonatal sepsis, so penicillin prophylaxis should be given during labour.

Risk factors

- Asymptomatic bacteriuria ($>10^5$ cfu/mL urine) occurs in 4–7% of women and, in pregnancy, is associated with pyelonephritis in 30% of cases, if untreated.
 - Send urine for culture at first antenatal visit.
 - If asymptomatic bacteriuria is present, send a second sample.
 - If second sample positive, → treat.
- The absence of bacteriuria at antenatal booking is associated with <2% chance of UTI through pregnancy.
- Further risk factors for bacteriuria or frank UTI prior to delivery include:
 - UTI before falling pregnant or UTI in previous pregnancies.
 - An abnormal urinary tract.
 - Diabetes mellitus, HIV positivity, or sickle cell disease.
- Prolonged labour, Cesarean section, pre-eclampsia, placental abruption, and urinary catheters are all risk factors for post-partum UTI.

Diagnosis

- Dysuria, frequency, urgency, or offensive urine suggests UTI.
- Loin pain, backache, vomiting, and fevers often occur in pyelonephritis.
- Suprapubic or renal angle tenderness may be present.
- Dipstick for leucocytes or nitrites may suggest UTI but will often miss asymptomatic bacteriuria. ► Send MSU for M,C+S.
- If pyelonephritis suspected: blood cultures, FBC, U&E, CRP. Consider USS renal tract. Fetal well-being should be assessed.

►► Acute pyelonephritis

Pyelonephritis is more common in the second half of pregnancy and is a significant cause of fetal mortality and maternal morbidity. The increasing size of the uterus may cause ureteral obstruction and impaired urinary flow (particularly on the right), encouraging stasis and sepsis.

Recurrent UTIs in pregnancy

► After more than one UTI (or a single episode in ♀ with an abnormal urinary tract), women should be offered prophylactic antibiotics for the duration of the pregnancy.

Post-coital cefalexin 500mg PO stat or cefalexin 500mg nocte for 1 month, alternating with nitrofurantoin 100mg nocte, have proved safe and effective. Antimicrobial choice should ideally reflect sensitivities of organisms cultured. Post-partum investigation is recommended (📖 p. 708).

Treatment of UTI in pregnancy

Asymptomatic bacteriuria or cystitis

- First line, prior to sensitivities becoming available:
 - Nitrofurantoin 50mg PO qds × 7 days, or
 - Cefalexin 500mg PO bd (or 250mg qds) × 7 days.
 - Trimethoprim 200mg bd PO (⚠️ but give a folic acid supplement during the 1st trimester, and avoid if patient is folate-deficient or taking a folate antagonist, or if trimethoprim has been used in the preceding year).
 - Amoxicillin 250mg qds PO × 7 days (often first choice if sensitivities known).
 - Ampicillin 500mg PO qds × 7–10 days for group B *Streptococcus* infections—and inform the patient's antenatal service, as prophylactic antibiotics may be indicated during labour and delivery.
- Repeat MSU for M,C+S monthly to confirm eradication.

Pyelonephritis

- Admit.
- IV access and rehydration with 0.9% NaCl, as required.
- Ceftriaxone 1g IV od or cefotaxime 1–2g IV qds.
- Alternative: ampicillin 1g IV qds + gentamicin 1.5mg/kg tds.
- If the patient is immunocompromised and/or has incomplete urinary drainage, then seek urgent microbiological advice.

⚠️ Fluoroquinolones, such as ciprofloxacin, should be avoided, unless resistant organisms are cultured. Co-trimoxazole needs to be used with caution (sulfonamides should not be used in the 3rd trimester).

Safe antibiotics in pregnancy

- Penicillins.
- Cephalosporins.
- Nitrofurantoin (a recent large Norwegian population study suggests low teratogenic potential but increased risk of neonatal jaundice if used within 30 days of delivery).
- Trimethoprim (⚠️ safe after 1st trimester (📖 p. 843)).

AKI during pregnancy

Introduction

AKI during pregnancy remains a significant problem in the developing world, accounting for up to 20% of all AKI (usually in circumstances where there is no access to safe and sterile termination). ► In the developed world, pre-eclampsia is the commonest pregnancy-related cause of AKI.

Causes

Pre-renal

- Volume depletion:
 - Esp. 2° to hyperemesis gravidarum during the 1st trimester.
- Placental abruption:
 - Presents with abdominal pain and PV bleeding in 2nd or 3rd trimester. A classical cause of cortical necrosis (📖 p. 845).
- Post-partum haemorrhage (see also cortical necrosis, 📖 p. 845).
- Septic abortion (📖 p. 845). Common in the developing world. Presents with abdominal pain, fever, and shock.

Renal

- Pre-eclampsia (📖 p. 850).
- Acute fatty liver of pregnancy:
 - 3rd trimester. Presents with coagulopathy, abnormal LFTs, hypoglycaemia, and lactic acidosis. AKI common.
- HUS/TTP (📖 p. 845):
 - May present in either the antenatal or post-natal period.
- Exacerbation of existing renal disease, e.g. SLE:
 - Renal biopsy may be required to confirm diagnosis and is safe in early pregnancy in expert hands.
- Acute interstitial nephritis (📖 p. 580):
 - Often drug-related, e.g. NSAIDs, antibiotics, proton pump inhibitors.
- Nephrotoxic drugs (📖 p. 898).

Post-renal

- Acute urinary retention:
 - 3rd trimester. Relates to bulk of expanding uterus.
 - Also occurs following combined kidney/pancreas transplantation where the transplanted kidney is placed in an intraperitoneal location (unusual in renal transplantation alone where the transplant is in the false pelvis).

Investigations

SCr (► a SCr of $>80\mu\text{mol/L}$ (0.9mg/dL) may indicate of renal impairment in pregnancy). FBC, U&E, LFTs, calcium, clotting, urate, haemolysis screen, G&S, infection screen (MSU, blood cultures, vaginal swabs, as appropriate).

Management

Similar to non-pregnant patients. Careful assessment of fluid status, with correction of volume depletion. Treat underlying cause.

Septic abortion

Sudden onset (over hours) after attempted abortion. Fever (often $>40^{\circ}\text{C}$), rigors, myalgia, vomiting, and diarrhoea (may be bloody). Abdominal pain is common, but vaginal discharge is often absent. Progression to septic shock, with \downarrow BP, \uparrow HR, peripheral vasodilatation, oliguria, and DIC is rapid. Culpable organisms include *E. coli* and *Clostridia*.

Investigations

Blood cultures, Hb (haemolysis), \downarrow Plt (DIC) G&S, clotting, D-dimers, U&E, LFT. Perform VE for high vaginal swabs (\rightarrow M,C+S). Plain AXR may show intrauterine or intra-abdominal gas. Consider USS or CT to exclude pyometrium.

Management

Transfer to critical care. O_2 , resuscitate with IV fluids and blood products (📖 p. 168). \blacktriangleright Benzylpenicillin 1.2–2.4g IVI qds, metronidazole 500mg IVI tds + Gram -ve cover (e.g. cefuroxime 1.5g stat, followed by 750mg IVI tds or ciprofloxacin 200mg IVI bd, adjusted for SCr).

Acute fatty liver of pregnancy

Occurs late in pregnancy or immediately post-partum. Part of a spectrum of pregnancy-related diseases characterized by endothelial dysfunction with end-organ damage (which also includes pre-eclampsia). Presents with nausea, vomiting, jaundice, encephalopathy, acute hepatitis, and DIC. AKI is common. Management is supportive. Expedite delivery, if possible.

Cortical necrosis

Common historically, especially after placental abruption and post-partum haemorrhage. Sudden and profound renal vasospasm (often with marked \downarrow BP) causes patchy infarction of the renal cortex. Causes severe AKI (often with persistent anuria) and often irreversible renal failure. Contrast-enhanced CT scanning, Doppler USS or MAG-3 isotope scanning will demonstrate the perfusion defects.

HUS/TTP (📖 p. 574)

Very rare (~ 1 in 100,000 pregnancies). Presents with AKI (often requiring RRT), usually in the 3rd trimester or early puerperium (up to 10 weeks post-partum), but can occur throughout pregnancy. Endothelial dysfunction, with microangiopathic haemolytic anaemia, thrombocytopenia (both typically severe), and coagulopathy are present. \uparrow BP ($>70\%$) and proteinuria ($>80\%$) are common. May follow an otherwise unremarkable (normotensive and non-proteinuric) pregnancy.

Easily (and \therefore commonly) confused with other diagnoses, such as pre-eclampsia, HELLP, acute fatty liver of pregnancy, and antiphospholipid antibody syndrome. It is important to consider the diagnosis, as early treatment (FFP/plasmapheresis) is helping to improve historically poor outcomes for maternal morbidity and mortality. Pregnancy \downarrow ADAMTS13 levels (as does HELLP)—but they will be much lower in TTP and many cases of HUS (although usually not available to assist immediate management). Relapse may occur in subsequent pregnancies.

Hypertension during pregnancy

Introduction

Blood pressure falls in the early stages of a normal pregnancy and returns to pre-pregnancy baseline by term.

Hypertension is the most common medical problem encountered during pregnancy, affecting ~5–10% of women. Hypertensive disorders during pregnancy carry risks for the mother and are among the leading causes of maternal death in the developed world. Hypertensive disorders also carry a risk for the fetus in terms of higher perinatal mortality rates, preterm birth, and low birthweight.

Definition (NICE)

Diastolic blood pressure (DBP) of $>90\text{mmHg}$ on two separate occasions, more than 4 hours apart, and/or a single DBP reading of $>110\text{mmHg}$.

Degrees of hypertension

- *Mild*: DBP 90–99mmHg, SBP 140–149mmHg.
- *Moderate*: DBP 100–109mmHg, SBP 150–159mmHg.
- *Severe*: DBP $\geq 110\text{mmHg}$, SBP $\geq 160\text{mmHg}$.

Causes

- Pre-existing essential hypertension ('chronic hypertension') (📖 p. 847).
- Pregnancy-induced hypertension (PIH) ('gestational hypertension') (📖 p. 847).
- Pre-eclampsia (📖 p. 850).
- Hypertension complicating renal disease (either pre-existing or developing during pregnancy) (📖 p. 856) or other causes of secondary \uparrow BP (e.g. hyperaldosteronism or pheochromocytoma).

Measuring blood pressure in pregnant women

- Use a well-maintained mercury/aneroid sphygmomanometer or validated automated device.
- Use the stethoscope bell for auscultation.
- ► Always use the correct-sized cuff.
- Measure with patient sitting after a period of rest, with the arm supported at heart level.
- Either arm, but use higher value if $>10\text{mmHg}$ difference.
- Record SBP when sounds are first heard (*Korotkoff 1*) and DBP at the point of disappearance of sounds (*Korotkoff 5*).
- If the DBP is persistently below 40mmHg, use *Korotkoff 4* (and make a note).

Pre-existing essential hypertension ('chronic hypertension')

- Presents prior to conception or before 20 weeks' gestation (as BP tends to fall in the 1st and 2nd trimesters, a woman with ↑ BP before 20 weeks can be assumed to have pre-existing hypertension).
- Treatment targets for hypertensive women without pre-eclampsia remain controversial. Although treatment is likely to have maternal benefits, this must be balanced against potential harm to the fetus (particularly IUGR).
- Goals:
 - For uncomplicated ↑ BP, aim <150/100mmHg (but DBP no less than 80mmHg).
 - If evidence of target organ damage (e.g. renal disease), aim <140/90mmHg.
- Encourage to lower dietary salt intake.
- Ensure antihypertensives are altered appropriately, ideally, several months prior to conception (and that BP then stabilizes) or as soon as possible once pregnancy occurs (📖 p. 849). Treatment should be based on existing therapy, potential side effect profiles, and discussion with the patient.
- Seek specialist advice if known or suspected secondary ↑ BP.
- The majority of pregnancies are uncomplicated, although outcomes are worse than for pregnancy in normotensive patients. There is:
 - An increased incidence of placental abruption, AKI, cardiac events, and stroke in the mother.
 - Increased risk of growth retardation and unexplained mid-trimester fetal death.
 - A pre-eclampsia risk of ~20%. Warn about symptoms (📖 p. 852).
 - These risks correlate with maternal age, duration and degree of ↑ BP, obesity, and presence of end-organ damage.
- Recommend aspirin 75mg od from 12 weeks' gestation onwards to reduce pre-eclampsia risk.
- Calcium supplementation may have a small role in preventing serious adverse events, such as fetal death, associated with pre-eclampsia in populations with a low calcium intake (<600mg/day).
- If proteinuria develops after 20 weeks' gestation, treat as for pre-eclampsia.

Pregnancy-induced hypertension (PIH) ('gestational hypertension')

- Occurs *after* 20 weeks' gestation.
- Not associated with proteinuria.
- Usually no pre-existing diagnosis of ↑ BP.
- Risk factors include first pregnancy and maternal age >40 years.
- BP returns to normal post-partum (within 3 months).
- Increased risk of progression to pre-eclampsia (15–25%)—the earlier the development of PIH, the greater the risk. Warn the mother about potential symptoms (📖 p. 852).

- Aspirin 75mg until delivery in those with one high risk factor or two moderate risk factors for pre-eclampsia.
 - High risk: hypertensive disease during a previous pregnancy, CKD, diabetes, thrombophilia, or relevant autoimmune disease (such as SLE or antiphospholipid antibody syndrome).
 - Moderate risk: first pregnancy, age >40 years, pregnancy interval of 10 years, BMI >35, +ve family history, twin or multiple pregnancy).
- Calcium supplements may be beneficial in certain groups (📖 p. 852).
- Increased risk of both PIH (16–47%) and pre-eclampsia (2–7%) in subsequent pregnancies.
- Although the cause of gestational hypertension is unclear, it appears to identify women at risk of essential ↑ BP later in life.

Management

BP lowering is not an end in itself—maternal and fetal well-being are also important indicators of the underlying condition.

- Mild hypertension (BP 140/90–149/99mmHg):
 - Do not treat ↑ BP. Measure BP no more than weekly.
 - Test for proteinuria at each visit.
 - If <32 weeks or high risk of pre-eclampsia, test for proteinuria, and measure BP twice weekly.
- Moderate hypertension (BP 150/100–159/109mmHg):
 - Treat to keep BP <150/80–100mmHg (first-line agent: labetalol).
 - Measure BP; test for proteinuria twice a week.
 - Check SCr, U&E, FBC, and LFTs at presentation.
- Severe hypertension (BP ≥160/110mmHg):
 - ⚠ Admit until BP ≤159/109mmHg.
 - No role for 'bed rest'.
 - Treat to keep BP <150/80–100mmHg (first-line agent: labetalol).
 - Measure BP at least 4x per day.
 - Test for proteinuria daily.
 - Check SCr, U&E, FBC, and LFTs at presentation and then weekly.
- Fetal assessment includes USS for fetal growth, amniotic fluid volume assessment, and umbilical artery Doppler velocimetry. Fetal cardiotocography should be performed if there is any change in condition, such as a decrease in fetal movements.
- Early delivery is not usually required, unless severe refractory ↑ BP or other complications supervene.

Guidelines

The NICE guidelines for hypertension in pregnancy are a very useful resource. They are available at 📖 www.nice.org.uk

Drug treatment of hypertension in pregnancy

⚠ No drug is entirely 'safe' in pregnancy. However, experience has allowed an inference of low fetal risk for many agents (see Table 11.2).

⚠ ACE-I (and ARBs) are contraindicated during pregnancy: 1st trimester use is associated with an increased risk of cardiac and CNS malformations, and 2nd trimester use is associated with fetal death, oligohydramnios, growth restriction, and renal agenesis.

⚠ Diuretics should be avoided in pregnancy, as hypovolaemia may compromise placental blood flow. Occasionally, severe oedema, e.g. in the context of nephrotic syndrome, necessitates their use, but this should be under close specialist supervision.

Breastfeeding

Antihypertensive agents safe for breastfeeding in the post-natal period include enalapril, captopril, labetalol, nifedipine, atenolol, and metoprolol. ⚠ There is insufficient evidence to recommend other ACE-I, ARBs, or amlodipine.

Table 11.2 Antihypertensives in pregnancy

Drug	Dose	Comment
Labetalol	200mg bd–500mg tds	Low risk to fetus First line for PIH and pre-eclampsia Atenolol is no longer recommended, as low birthweights have been reported
Methyldopa	250mg bd–1g tds	Low risk to fetus SE: drowsiness, depression
Nifedipine	10mg bd–30mg bd	Low risk to fetus Limited data on other dihydropyridine CCBs, including amlodipine Non-dihydropyridine: limited data suggest verapamil is low risk, but diltiazem should be avoided
Prazosin	0.5mg tds–4mg tds	Limited data suggest low risk Limited data on other alpha-blockers, including doxazosin, but many authorities are happy to use in pregnancy
Hydralazine	25mg tds–75mg tds	Low risk to fetus Maternal SEs (including headaches, tachycardia, and palpitations) are common and may mimic the onset of pre-eclampsia

Pre-eclampsia: pathophysiology

Introduction

Pre-eclampsia (from the Greek *eclampsus* or lightning) is a pregnancy specific multisystem disorder, characterized by the development of \uparrow BP and proteinuria, usually, but not always, after 20 weeks' gestation. It affects 3–5% of pregnant women and is a leading cause of maternal and neonatal morbidity and mortality. The only cure is delivery, hence an association with prematurity. It is also associated with fetal growth restriction and oligohydramnios. Maternal complications include pulmonary oedema, cerebral haemorrhage, hepatic failure, AKI, and death. Seizures (2% of cases) herald the development of eclampsia.

Pathogenesis

The placenta plays a critical role in the pathophysiology of pre-eclampsia and the related conditions of PIH, acute fatty liver of pregnancy, HELLP syndrome, and pregnancy-induced HUS/TTP. All are associated with inadequate placental cytotrophoblast invasion and widespread maternal endothelial dysfunction (see Fig. 11.1).

Pre-eclampsia and the placenta

During normal placental development, cytotrophoblasts of fetal origin invade the uterine spiral arteries and remodel them from small, high-resistance vessels into larger, more dilated vessels able to provide an adequate blood supply to the developing fetus.

In pre-eclampsia, this remodelling is defective, with dysregulation of several angiogenic factors, including soluble Fms-like tyrosine kinase 1 (sFlt-1) (itself a receptor for placental growth factor (PlGF) and VEGF) and endoglin (sEng) (which impairs binding of TGF- β 1 to endothelial receptors and leads to \downarrow endothelial NO-dependent vasodilatation). High concentrations of sFlt-1 are present in the blood of women with pre-eclampsia, and the administration of sFlt-1 to animals produces a similar syndrome. Several studies of the utility of biomarkers, including sFlt-1, sEng, and PlGF, for the prediction and early diagnosis of pre-eclampsia are in progress.

Low placental L-arginine activity also reduces NO activity, thereby stimulating endothelial NO synthase to generate reactive oxygen species (e.g. peroxynitrite and OH radical) and worsen oxidative stress.

Subsequent release of vasopressive factors from the diseased placenta affects maternal endothelium, with increased sensitivity to vasopressors, such as angiotensin II and noradrenaline. This results in the widespread vasoconstriction, hypoperfusion, ischaemia, and vascular dysfunction, characteristic of the clinical syndrome.

Abnormalities of RAS, inflammation, immune maladaptation, and genetic susceptibility also appear to play a role.

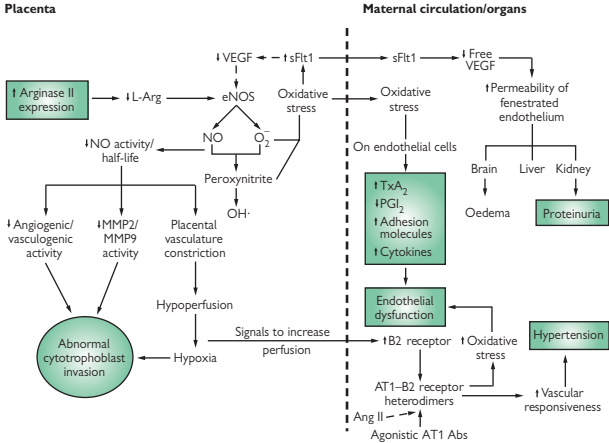


Fig. 11.1 The pathophysiology of pre-eclampsia. Abs, antibodies; Ang II, angiotensin II; AT1, angiotensin II type 1 receptor; eNOS, endothelial nitric oxide synthase; L-Arg, L-arginine; MMP2, matrix metalloproteinase 2; MMP9, matrix metalloproteinase 9; NO, nitric oxide; O₂⁻, superoxide anion; OH⁻, hydroxyl radical; PGI₂, prostacyclin; sFlt1, soluble Fms-like tyrosine kinase 1; TxA₂, thromboxane A₂; VEGF, vascular endothelial growth factor. Reproduced from Noris M *et al.* (2005). *Nat Clin Pract Nephrol*, 1: 98–114 with permission from Nature Publishing Group.

Organs affected

- Circulation: vasoconstriction → ↑ BP; capillary leak → oedema.
- Lungs: pulmonary oedema.
- Kidney:
 - Proteinuria.
 - AKI.
 - Glomerular endotheliosis is the term used to describe the ultrastructural changes seen in the kidney.
 - ↓ Renal blood flow → impaired tubular function → ↓ urate clearance → ↑ serum urate.
 - Pre-eclampsia increases the relative risk of developing ESRD.
- Liver: ischaemia → ↑ LFTs.
- Brain: ischaemia and oedema lead to seizures (eclampsia). Severe uncontrolled ↑ BP can lead to cerebral haemorrhage.
- Coagulation:
 - Platelet activation occurs early and may be associated with thrombocytopenia.
 - Several clotting factors are elevated beyond the raised levels already characteristic of pregnancy.

Pre-eclampsia: management

Introduction

► Pre-eclampsia has the potential to deteriorate rapidly. Seek specialist help. Near term, induction of labour is usually the therapy of choice, whereas a trial of stabilizing, or expectant, treatment may be more appropriate if the pregnancy is at an earlier stage.

Maternal risk factors for pre-eclampsia

- High risk: hypertensive disease during a previous pregnancy, CKD, diabetes, thrombophilia, or relevant autoimmune disease (e.g. SLE or antiphospholipid antibody syndrome).
- Moderate risk: first pregnancy, age >40 years, pregnancy interval of ≥ 10 years, BMI >35, +ve family history, twin or multiple pregnancy.

Prevention

- ♀ with one high-risk factor *or* two or more moderate risk factors should take aspirin 75mg od after 12 weeks' gestation (reduces risk by ~15%).
- ☛ Calcium supplementation may have a role in preventing serious adverse events, such as fetal death, associated with pre-eclampsia in populations with a low calcium intake (<600mg/day).

Diagnosis

- New onset \uparrow BP (SBP >140 or DBP >90mmHg), presenting after 20 weeks' gestation, with significant proteinuria (generally >300mg/24h; equivalent to uPCR >30mg/mmol).
- ► Classified as severe when there is significant \uparrow BP ($\geq 160/110$ mmHg) \pm symptoms \pm biochemical or haematological derangement.

Symptoms

► An explanation of the potential symptoms of pre-eclampsia should be given to all women at risk.

Advise them to seek immediate medical attention if they develop:


- Severe headaches.
- Visual disturbances (e.g. blurred vision, flashing lights, double vision, floating spots).
- New epigastric pain (or pain in the right upper quadrant).
- Vomiting.
- Breathlessness.
- Sudden swelling of the hands, feet, or face (Δ although oedema is a feature of pre-eclampsia, it also occurs in 60% of normal pregnancies).

Management

►► Admit to hospital, and undertake fetal monitoring. BP reduction is not the sole endpoint of management—additional assessments of maternal and fetal well-being are equally important.

Fetal assessment

- USS for fetal growth, amniotic fluid volume assessment, and umbilical artery Doppler velocimetry.
- Fetal cardiotocography should be performed if there is any change in maternal condition (e.g. decrease in fetal movements, vaginal bleeding, or abdominal pain).

- Mild hypertension (BP 140/90–149/99mmHg):
 - Do not treat ↑ BP.
 - Measure BP at least 4x/day.
 - SCr, U&E, LFTs, and FBC x2/week.
- Moderate hypertension (BP 150/100–159/109mmHg):
 - Treat to keep BP <150/80–100mmHg (first-line agent: labetalol,  p. 849).
 - Measure BP at least 4x/day.
 - SCr, U&E, LFTs, and FBC x2/week.
- Severe hypertension (BP ≥160/110mmHg):
 - Consider admission to high dependency environment.
 - Treat to keep BP <150/80–100mmHg (first-line agent: labetalol).
 - Measure BP at least 4x per day.
 - SCr, U&E, LFTs, and FBC at least x3/week.

Delivery

- *Before 34 weeks:* the decision to deliver can be very difficult. The rationale for delay is to improve neonatal outcome through delivery of a more mature fetus. It also affords the opportunity to administer corticosteroids to accelerate fetal lung maturity. However, it risks worsening organ damage in the mother. Delivery is generally recommended if any of the indications shown in Table 11.3 are present.
- *After 34 weeks:* delivery is generally recommended once BP has been controlled and a course of corticosteroids administered, depending on maternal and fetal condition. After 37 weeks, delivery within 24–48h is advocated. The choice between Cesarean or vaginal birth will need to be determined in each individual case.

Table 11.3 Indications for delivery in pre-eclampsia

Fetal	Maternal
No growth	Severe ↑ BP despite treatment
Abnormal CTG	AKI
Abnormal umbilical artery Doppler signal	Worsening liver function
	Thrombocytopenia
	Albumin <20g/L

Severe pre-eclampsia

▶▶ Characterized by severe \uparrow BP ($\geq 160/110$ mmHg) \pm symptoms \pm biochemical or haematological derangement.

- ▶ Features:

- Severe \uparrow BP and proteinuria (can be heavy).
- Mild to moderate \uparrow BP with one of: severe headache, visual disturbance, vomiting, epigastric or hypochondrial pain, liver tenderness, papilloedema, clonus, HELLP, platelet count $< 100 \times 10^9/L$, abnormal LFTs.

- ▶ Transfer to critical care if: eclampsia, HELLP, haemorrhage, AKI, electrolyte disturbances, coagulopathy, unstable or refractory \uparrow BP (including need for parenteral therapy), cardiac failure, or abnormal neurology.

- Continuous BP monitoring. Consider invasive monitoring.

- Careful fluid management:

- Chart input/output. Catheterize, and monitor UO.
- Limit maintenance fluids to 80mL/h, unless there are ongoing fluid losses (e.g. bleeding).
- Avoid volume expansion, unless hydralazine is used as antihypertensive therapy (📖 see below).

BP management

- ▶ Consult local guidelines.

- Aim to keep BP $< 150/80$ – 100 mmHg.

- Monitor maternal and fetal response, in addition to BP response.

- Continue antenatal antihypertensive therapy.

- If parenteral therapy is required:

- Labetalol 20mg IV (Δ contraindications: asthma, heart block); double the dose at 10min intervals to maximum cumulative dose of 200mg (or continuous infusion of 1–2mg/min).
- If inadequate response, give hydralazine 5mg IV, repeated every 15min, to a maximum cumulative dose of 20mg (or continuous infusion 0.5–10mg/h). Consider administration of 500mL crystalloid before, or at the same time as, the first dose of hydralazine.

Anticonvulsants

- Give IV magnesium sulfate (superior to phenytoin and benzodiazepines) if a mother with severe \uparrow BP or severe pre-eclampsia has a seizure (or has previously had an eclamptic seizure).

- Consider magnesium sulfate if delivery is planned within 24h in those with severe pre-eclampsia.

- Regimen:

- Loading dose of 4g IV over 5min.
- Further dose of 2–4g over 5min if recurrent seizures.
- Follow with an infusion of 1g/h for 24h.
- Monitor UO, respiratory rate, O_2 saturation, and reflexes. Measure serum magnesium level if toxicity is suspected (treatment for toxicity is 10% calcium gluconate).

Pre-eclampsia: follow-up and prognosis

Follow-up

- Do not discharge until all symptoms of pre-eclampsia have resolved, BP is <149/99mmHg, and biochemical and haematological parameters are improving.
- Post-discharge, measure BP every 1–2 days for 2 weeks.
- Those with persistent ↑ BP should be referred for specialist advice.
- Aim to keep BP <140/90mmHg. Reduce treatment if <130/80mmHg.
- If methyldopa has been used antenatally, withdrawal is recommended post-partum (⚠ risk of depression). The choice of alternative antihypertensive therapy, if required, will need to reflect the mother's desire to breastfeed.
- Repeat blood tests, as clinically indicated.
- If proteinuria persists at 3 months, seek nephrology advice.
- Women should be advised to keep their BMI in the healthy range prior to future pregnancies.

Prognosis

Women with pre-eclampsia have:

- An increased risk of gestational hypertension in future pregnancies (13–53%).
- An increased risk of pre-eclampsia in future pregnancies (16–25%) (⚠ >50% if pre-eclampsia led to delivery before 28 weeks).
- An increased risk of developing ↑ BP and CV disease in later life.
- An increased relative risk of CKD and ESRD (even if normotensive with no proteinuria at post-natal review), although this risk is low.

HELLP syndrome

- Refers to a syndrome of haemolysis, elevated liver enzymes, and low platelet count.
- Occurs in 0.1–0.2% pregnancies.
- Probably represents a severe form of pre-eclampsia.
- 15–20% of patients do not have ↑ BP or proteinuria.
- Often presents with nausea, vomiting, abdominal pain, and malaise.
- About 70% of cases develop prior to delivery (usually 27–37 weeks) and most of the remainder within 48 hours of delivery.
- The Martin/Mississippi classification grades severity as class I (most severe) to III, based on nadir platelet count, LDH, and liver function. This helps estimate the maternal morbidity risk (intracerebral haemorrhage is the principal cause of death).
- Management is similar to pre-eclampsia. 🧠 In addition, corticosteroids (dexamethasone, betamethasone, or prednisolone) are commonly used to increase platelet counts, although it remains unclear if this strategy improves overall outcomes.

Pre-existing renal disease

Introduction

The ability to conceive falls with ↓ GFR. ► However, once pregnant, the key determinant of pregnancy outcome in women with pre-existing renal disease is the degree of renal impairment.

Other factors that influence outcome include:

- Hypertension.
- Degree of proteinuria.
- Type of renal disease.

Obstetric complications include miscarriage, pre-eclampsia, preterm delivery, and low birthweight. Pregnancy can also result in a deterioration in renal function (see Table 11.4). This may be permanent and associated with progression to end-stage kidney disease.

△ Even with normal renal function, normal BP, and non-significant proteinuria, women with a history of renal disease have an increased risk of pre-eclampsia (~10%, compared to a background rate of 3–5% in the general population).

General rules

The following are helpful to remember when counselling women with renal disease that:

- Pre-pregnancy SCr <200µmol/L: (2.25mg/dL) although there is an increased risk of complications (see Table 11.4), the chances of a successful outcome and healthy baby are relatively good.
- Pre-pregnancy SCr >250µmol/L: (2.8mg/dL) high risk of a poor fetal outcome (including prematurity and significant developmental problems), together with a high risk of developing ESRD during (or soon after) pregnancy.
- The presence and degree of maternal ↑ BP and proteinuria are also important considerations.

Table 11.4 Approximate risks of obstetric complications and deterioration in renal function, based on pre-pregnancy renal function

Degree of renal impairment	Mild ↑ SCr <125µmol/L (1.4mg/dL)	Moderate ↑ SCr 125–180µmol/L (1.4–2.0mg/dL)	Severe ↑ SCr >180µmol/L (>2.0mg/dL)
Pre-eclampsia	10–20%	30–50%	60%
Preterm delivery	20–30%	60%	80–90%
Permanent deterioration in renal function	0%	20%	50%

Specific renal diseases

Diabetic nephropathy

Now the commonest renal condition encountered in pregnancy. It is essential that women with diabetes are educated about the importance of good pre-conception diabetic control for reducing the risk of congenital malformation (aim HbA1C $\leq 6.1\%$ (43mmol/mol)). There is an increased incidence of babies of higher birthweight. Otherwise, risks relate to both the degree of renal impairment and the degree of proteinuria, as shown in Table 11.4.

Reflux nephropathy

Women with reflux nephropathy should be screened for UTI during pregnancy, and, if present, infection should be treated promptly. Acute pyelonephritis is more common. Mothers should also be counselled regarding the potential risk of inheritance (~25–30%) and offered post-natal screening for their children (📖 p. 712).

Autosomal dominant polycystic kidney disease (ADPKD)

Cyst complications in pregnancy, such as haemorrhage or infection, may masquerade as obstetric complications. Patients with a family history of intracranial aneurysms should ideally be screened for aneurysms themselves prior to pregnancy.

Primary glomerular disease

The exact type of glomerular disease does not impact on pregnancy outcome, but renal impairment, proteinuria, and maternal \uparrow BP all can.

Relapse of a stable pre-existing glomerular lesion is generally unlikely (and usually very difficult to differentiate from pre-eclampsia when it occurs) (📖 p. 859). Wait until disease is in remission (ideally >6 months) before trying to conceive. The form of treatment is also a consideration. If relevant, wait until off cytotoxic agents and on lowest possible effective doses of corticosteroids. For other immunosuppressant drugs, see 📖 p. 866.

Proteinuria is likely to double during pregnancy. If $>3\text{g}/24\text{h}$ (PCR $>300\text{mg}/\text{mmol}$), then anticoagulation with low molecular weight heparin (LMWH) should be recommended, as there is an increased thrombotic risk.

In addition, significant proteinuria ($>3\text{g}/\text{day}$) is associated with ~ 2 increased risk of perinatal loss and preterm delivery, compared to no proteinuria.

Lupus nephritis

Renal impairment, proteinuria, and maternal \uparrow BP can all impact on pregnancy outcome. The risk of a disease flare increases in pregnancy (30%). Active lupus is associated with increased fetal loss, prematurity, and IUGR. In addition, there is a risk of a transient rash and fetal heart block (requiring pacing) in babies born to anti-Ro positive mothers. Those with antiphospholipid antibodies are at increased risk of spontaneous abortion and should be considered for LMWH from conception.

Management of renal disease in pregnancy

- Requires a multidisciplinary approach, including an obstetrician, a nephrologist, and, ideally, an obstetric physician.
- Pre-pregnancy counselling (including genetic counselling, if relevant) is extremely important.
- Folic acid 400 micrograms od 3 months before trying to conceive.
- Alter medications, including antihypertensives, to drugs that are safe in pregnancy (📖 p. 849).
- Recommend aspirin 75mg, particularly from 12 weeks onwards, to reduce the risk of pre-eclampsia.
- Patients should be booked early to antenatal clinic.
- Aim to see every 2–3 weeks until 28th week, thereafter weekly.
- BP every visit. Home BP monitoring may be helpful.
- Urinalysis every visit (MSU for M,C+S in those at particular risk of infection).
- SCr, U&E, Ca²⁺, LFT, urate, and uPCR or uACR every 2–4 weeks.
- FBC every 4 weeks (IV iron and ESAs are safe).
- If proteinuria >3g/24h (uPCR >300mg/mmol), then anticoagulation with LMWH should be considered.
- Monitor disease activity, where possible, e.g. SLE.
- Serial obstetric scans for those at higher risk (📖 p. 853).

Case study

A 27-year-old primigravid Chinese woman presents to antenatal clinic at 18 weeks' gestation with progressive oedema. She is found to be normotensive, but urinalysis reveals 3+ proteinuria. Her SCr is 54 μ mol/L (0.6mg/dL), uPCR 524mg/mmol, and serum albumin 26g/L.

Further investigations included: low C3 and C4, +ve ANA, +ve dsDNA, and +ve antiphospholipid antibody. Renal USS was normal.

After discussion, a renal biopsy was undertaken and revealed class V lupus nephritis (📖 p. 659).

Treatment options

Lupus nephritis (📖 p. 658) can be treated with corticosteroids. Azathioprine is also safe in pregnancy, as is tacrolimus (📖 p. 866). However, MMF (📖 p. 866) and cyclophosphamide are contraindicated. Rituximab may also be considered (🔮) but ideally not in the last 6 months of pregnancy so that fetal B cells have time to reconstitute prior to delivery. This patient should also be offered LMWH treatment in view of her proteinuria and antiphospholipid antibody status. If possible, diuretics should be avoided despite her oedema (📖 p. 849).

Learning point

If new-onset proteinuria (\pm renal impairment) occurs in early pregnancy (<20 weeks), it is important to attempt to diagnose the underlying renal lesion. Investigation will include immunological and serological testing (📖 p. 40) and potentially a renal biopsy. A histological diagnosis is likely to assist management in later pregnancy easier, as differentiating primary renal disease from pre-eclampsia becomes very difficult (see Table 11.5).

Table 11.5 Pre-eclampsia or active lupus nephritis?

	Pre-eclampsia	Lupus nephritis
BP	↑↑	↑↑
Proteinuria	+++	+++
Haematuria	±	+++
Red cell casts	–	++
ALT	↑	Normal
Complement	Normal	↓
dsDNA titres	Normal	↑
Symptoms of lupus	–	++
Response to steroids	–	+

Disorders of the urinary tract in pregnancy

Changes to the anatomy of the renal tract during pregnancy, particularly dilatation of the collecting system (📖 p. 840), need to be considered during the assessment of urinary tract symptoms and signs.

Haematuria

In the absence of proteinuria, haematuria is usually due to anatomical changes (bleeding from small venules in dilated collecting systems). On microscopy, 2–3 RBC/hpf is normal in pregnancy (unlike 1–2 in the non-pregnant population). If SCr is normal and no proteinuria, wait until 12 weeks after delivery for further assessment (📖 p. 66).

Obstruction

May occur 2° to mechanical pressure exerted by the uterus (usually on the right ureter, often where the ureter crosses the iliac artery) or 2° to pelvic or ureteric stone impaction.

Renal stones

Renal stones are uncommon in pregnancy and usually occur in women known to have pre-existing nephrolithiasis. However, collecting system dilatation, coupled with stasis and a 2–3-fold increase in urinary calcium excretion, may precipitate new stone formation in pregnancy. Ureteric stones are more common than stones in the renal pelvis, and most occur after the first trimester. The majority will pass spontaneously, but impacted stones may remain painful, and 2° urinary infection is a concern.

Women with cystinuria should be offered genetic counselling prior to conception, and proactive management of their stone disease should start pre-pregnancy (📖 p. 719).

⚠ The differential diagnosis of stone-induced colic must include obstetric problems, such as placental abruption

Investigation

Urine dipstick for haematuria and proteinuria. Microscopy: red cells (+ morphology), casts, pus cells, and organisms. Urine culture ± stone analysis. FBC, U&E, serum calcium, PTH.

USS is the first-line imaging modality. Ideally, ionizing radiation should be avoided during the 1st and 2nd trimesters. A limited IVU with fetal shielding is recommended in complex cases. Ureterscopy may be preferred to CT or multiple irradiations. MRI has limited utility.

Management

Hydration and analgesia (~75% stones will pass spontaneously). Obstruction, intractable pain, and urosepsis are indications for more definitive intervention. Standard treatment consists of nephrostomy placement and ureteric stent insertion (then changed at intervals until after delivery), but ureteroscopic methods are increasingly favoured. Extracorporeal shockwave lithotripsy should be avoided.

Pregnancy on dialysis

Introduction

♀ with ESRD rarely fall pregnant on dialysis: only 0.3–2.2% will conceive (reasons are complex, including hyperprolactinaemia, anaemia, polypharmacy, psychosocial issues, and the uraemic state per se). Nevertheless, contraception should be discussed with women who menstruate on dialysis (~40%). This is particularly true in the first few years after commencing dialysis.

β-HCG levels are high in dialysis patients, so if the level is high and pregnancy is a possibility, an USS should be performed.

If a pregnancy occurs and progresses beyond the 1st trimester, fetal outcomes have previously been poor and associated with significant maternal morbidity. However, better maternal and fetal care, coupled with improvements in dialysis efficiency and increases in dialysis frequency, have led to more optimism around pregnancy on dialysis.

In general, however, transplantation, if feasible, remains the favoured means for a patient with ESRD to conceive and undertake a pregnancy (📖 p. 864).

What dialysis patients of childbearing age should know

- 13–45% of pregnancies result in spontaneous miscarriage before 20 weeks' gestation.
- The outcomes of pregnancy on dialysis are improving. Available data suggest 23% of pregnancies resulted in a live infant in 1980, whilst this is now in excess of 70%.
- Maternal morbidity (e.g. hospitalization) remains significant, but mortality is rare.
- Maternal hypertension is very common.
- Preterm birth (70–100%, mean gestational age 32 weeks) and low birthweight (virtually 100%) are extremely common.
- Long-term outcomes for these infants are not yet known.
- Prolonged admissions to neonatal intensive care are common.
- Congenital abnormalities occur with the same frequency as in the general population.
- Pregnancy on dialysis is physically and emotionally demanding.
- Patients should be encouraged to dialyse as much as possible, preferably daily for long hours.
- It is worth re-exploring options for transplantation.

Dialysis prescription

There is no overriding reason for a modality switch: HD delivers a higher dialysis dose, but CAPD (esp. APD) offers less rapid metabolic changes and allows steady fluid removal whilst avoiding intradialytic hypotension. Residual renal function is important, as it improves pregnancy outcomes.

Haemodialysis

Aim for urea consistently ≤ 15 mmol/L (~ 40 mg/dL) through daily dialysis for at least 20h/week (~ 6 treatments). Titrate dialysate K^+ , Ca^{2+} , and HCO_3^- against serum levels (may require reduction in dialysate HCO_3^- to prevent maternal alkalaemia). Heparin requirements may increase. Δ Avoid hypotension. Allow for additional 0.5kg/week weight gains from mid-pregnancy onwards.

Peritoneal dialysis

As pregnancy progresses and intra-abdominal PD fluid volume is less well-tolerated and automated PD, with more frequent lower volume exchanges, is preferable. PD-related peritonitis should be treated promptly and assiduously, bearing in mind the potential teratogenicity of many antibiotics.

Diet, calcium, and vitamin D

Involve your dietetic staff from the outset. \uparrow protein intake to 1.2–1.4g/kg pre-pregnant weight + 10g per day. For CAPD, take dialysate protein losses into account and replace. Offer a daily multivitamin preparation, containing water-soluble vitamins. Increase folate to 1.6mg/day. The placenta produces calcitriol, so vitamin D analogue doses may require adjustment. Supplemental K^+ may be necessary.

Anaemia

Erythropoietin is not teratogenic. Dose requirements will increase by 50–100% in pregnancy. IV iron is safe and effective.

Labour and delivery

- Most units will deliver pregnant dialysis patients early (usually prompted by worsening \uparrow BP, IUGR, or both). Pregnancies rarely progress beyond 38 weeks.
- Monitoring of uterine activity should begin as early as the 26th week, as dialysis may induce contractions.
- Cesarean section is performed for standard obstetric indications.
- PD patients should be drained out for delivery—dialysis can resume 24h after delivery, with small-volume exchanges. Temporary HD may be necessary for a period in cases of PD fluid leakage.
- Assess fluid status carefully: Δ avoid volume overload.
- Beware infection.
- Neonates will need specialist input, including regular electrolyte assessment.

Pregnancy after renal transplantation: introduction

Improvement in renal function following successful transplantation, usually restores menstruation and fertility. Post-transplantation, 12% of women of childbearing age will become pregnant.

Advice regarding contraception should be accessible (key points: avoid oestrogen-containing contraceptives, as they can ↑ BP and they also have an unpredictable effect on CNI metabolism. Progesterone-only preparations and IUCDs are safe and more effective than barrier methods).

All renal transplant recipients contemplating pregnancy should be offered appropriate pre-pregnancy counselling (this may include genetic counselling, depending on underlying renal disease).

Outcomes


A number of international registries have recorded the outcomes of pregnancy in renal transplant patients around the world. A recent meta-analysis of available data from 4,706 pregnancies in 3,570 transplant recipients reported a live birth and miscarriage rate of 73% and 14%, respectively. Both these figures are similar to those seen in the general population. In ♀ with good graft function, >95% pregnancies that progress beyond 12 weeks are likely to have a successful outcome.

Complications

The key renal factors that affect the incidence of complications are:

- SCr pre-conception.
- ↑ BP.
- Degree of proteinuria.

Important complications (the incidence range reflects the presence and severity of the above factors) include:

- ↑ BP (30–60%):
 - ~50% of ♀ transplant recipients are taking antihypertensive drugs.
 - ↑ BP is associated with premature birth and pre-eclampsia.
 - For safe antihypertensive medications, see  p. 849.
- Pre-eclampsia (22–45%).
- IUGR (20–40%).
- Preterm delivery (20–60%), with associated low birthweight.
- Gestational diabetes (~8%).

There is also an increased incidence of UTI (~40%) (and graft pyelonephritis) during pregnancy.

Cesarean section rates are increased, reflecting the complex nature of the pregnancies, rather than presence of the transplant itself (which lies in the false pelvis).

There is no increase in incidence of congenital abnormalities above that in the general population. The incidence of longer-term developmental delay is also probably low.

Transplant function and pregnancy

The effect of renal transplant function on outcomes is shown in Table 11.6.

Table 11.6 Pregnancy outcome based on pre-conception SCr

SCr (μmol/L)	Complicated pregnancy ¹	Successful outcome ²	↓ GFR during pregnancy	↓ GFR persisting post-partum	Graft loss within 2 years
<125	30%	97%	15%	<5%	<5%
125–159	60%	90%	15%	5%	10%
160–199	90%	80%	30%	20%	60%
>200	100%	70%	60%	40%	90%

Outcome estimates based on literature review (1988–2004) from 613 women in 849 pregnancies that attained at least 24 weeks' gestation.

¹ Complicated pregnancy means ↑ BP, pre-eclampsia, IUGR, or premature delivery.

² Successful outcome means delivery of a live child.

Reproduced from Nicholas Torpey et al. (Oxford Specialist Handbook) *Renal Transplantation* (2010), with permission from Oxford University Press.

Pre-pregnancy transplant function predicts the risk of graft dysfunction both during and after pregnancy. For ♀ with good graft function (SCr ≤125 μmol/L (1.4 mg/dL)), the risk of deterioration in function due to pregnancy is low. For those with poor function (SCr >160 μmol/L (1.8 mg/dL)), renal function post-pregnancy is likely to be worse than pre-, and there is a significant incidence of premature graft loss.

Rejection

The risk of allograft rejection does not appear to be increased during pregnancy, with a reported rate of ~4%. However, when it occurs, it is associated with poorer outcomes.

Risk factors: shorter interval between transplantation and pregnancy, low CNl levels.

⚠ Pregnancy enhances CNl metabolism. Diligent therapeutic monitoring is necessary, often with significant dose increases.

The cause of graft dysfunction (📖 p. 404) can be difficult to diagnose in pregnancy. Transplant biopsies are often required and are safe in expert hands.

Pregnancy after renal transplantation: management

Transplant drugs during pregnancy

In the transplant setting, there is no other choice but to expose the fetus to immunosuppressive agents, as all the relevant drugs pass through to the fetal circulation to some degree. Reassuringly, however, the incidence of major congenital malformations does not appear different from the non-transplant population. Δ There are specific concerns regarding the use of MMF in pregnancy, and there are too little data on sirolimus to currently recommend its use (see Table 11.7).

Table 11.7 Safety of common immune suppressant agents in pregnancy

Immunosuppression	
Safe	Unsafe
Ciclosporin	Mycophenolate
Tacrolimus	Sirolimus (limited data)
Azathioprine	
Corticosteroids*	

Mycophenolate has been shown to cause a specific pattern of malformation in 20–25% of cases (hypoplastic nails, shortened fifth finger, ear defects, including deafness and cleft palate).

* Neonates should be monitored for adrenal suppression.

Δ Pregnancy enhances the metabolism of CNIs. Careful therapeutic monitoring is essential, and significant dose adjustments are often required.

☹ Breastfeeding is not generally advocated on maintenance immunosuppression, but many authorities do not believe it is absolutely contraindicated.

▶▶ Also unsafe in pregnancy: valganciclovir, co-trimoxazole, statins, fluconazole, and other -azole antifungal drugs.

Pre-pregnancy and antenatal care

- Optimize BP management (aim <140/90mmHg).
- Optimize immune suppression (prior to conception).
- Folic acid 400 micrograms od (to prevent neural tube defects), and consider aspirin 75mg od (to reduce the incidence of pre-eclampsia).
- Hepatitis B and C, HSV (cervical cultures if +ve), CMV, HIV, toxoplasmosis, and rubella status, if not already known.
- Rubella antibodies should ideally be tested prior to transplantation (rubella is a live vaccine, so administration is contraindicated post-transplantation).
- Rhesus compatibility of the patient and transplant: if the patient is Rh -ve and the kidney Rh +ve, there is a theoretical risk the patient could be sensitized to Rh, which could prove problematic for a Rh +ve baby.

- Antenatal clinic visit every 2–3 weeks. Weekly after 28 weeks.
- BP check every visit. Home BP monitoring may be helpful.
- Urinalysis and MSU for M,C+S every visit.
- If proteinuria >2g/24h (uPCR >200mg/mmol), then anticoagulation with LMWH should be considered.
- Check ciclosporin or tacrolimus levels frequently (every 2–4 weeks and more frequently if dose adjustments).
- Glucose tolerance test in each trimester.
- Monitor for CMV viraemia monthly (risk of congenital infection).
- SCr, U&E, Ca²⁺, LFT every 2–4 weeks.
- FBC every 2–4 weeks (IV iron and ESAs are safe).

Delivery

- Vaginal delivery is safe. Caesarean section for obstetric indications.
- Perform all VEs with strict aseptic technique.
- Consider additional hydrocortisone 100mg IVI or IMI (or increase oral prednisolone to 15mg od over labour).

Case study

A 35-year-old lady with ESRD secondary to membranous nephropathy underwent a live related transplant from her husband 9 months ago. At a visit to transplant clinic, she expresses her desire to try for pregnancy. She has had one episode of cellular rejection (Banff category 2A) 3 months previously, treated with pulsed corticosteroids.

Medications: tacrolimus, mycophenolate, prednisolone, enalapril, amlodipine, simvastatin, alendronic acid.

Blood pressure: 140/80mmHg. SCr presently stable at 130–140µmol/L.

What advice would you give her about pregnancy, and what changes to her medications would you suggest?

Recommendations

- Offer appropriate detailed counselling and planning, ideally in a multidisciplinary obstetric-renal clinic.
- Wait for 1 year post-transplantation (some advocate 18–24 months) and, preferably, 6 months after an episode of rejection.
- Ensure stable graft function, and document degree of any proteinuria.
- Immune suppression: needs to be stable. This patient should be changed to azathioprine under careful supervision and monitored for 3 months.
- Stop ACE-I (monitor BP, and consider safe alternative), statin, and bisphosphonate.
- Start folic acid at least 3 months prior to conception to reduce the risk of neural tube defects.
- Consider aspirin 75mg od once pregnant (particularly after 12 weeks) to reduce the risk of pre-eclampsia.
- Assess thromboembolic risk (particularly if proteinuria).
- Give advice regarding appropriate contraception until safe to conceive.

Drugs and the kidney

- Prescribing in renal impairment [870](#)
- Prescribing for dialysis patients [876](#)
- Sepsis and antimicrobials [878](#)
- Cardiovascular drugs [892](#)
- Prescribing in specific situations [894](#)
- Drug-related nephrotoxicity [898](#)
- NSAIDs and the kidney [902](#)
- Lithium and the kidney [904](#)
- Dialysis treatment of poisoning [906](#)
- Salicylate poisoning [908](#)
- Ethylene glycol poisoning [910](#)

Prescribing in renal impairment

▶▶ Always verify the recommended dose and dosing schedule when prescribing for a patient with renal impairment. Ask yourself, 'Is the drug still warranted, given the potential increased risk?'

Principles

- The kidneys have a fundamental role in the elimination of drugs, even those partially metabolized in the liver.
- Renal elimination may be either by glomerular filtration or tubular secretion.
- Renal impairment may necessitate a dose reduction, an extension in the dosing interval, or a combination of both.
- Such alterations will depend on the degree of renal dysfunction (or form of renal replacement therapy).
- Impaired renal function is common in elderly patients and those with multiple comorbidities, so the potential effects of polypharmacy and drug interactions are particularly relevant in these groups.
- Individuals who have been taking a drug at the same dose over a long period may need a dose alteration, as renal function changes with time.
- In practice, particular care is needed when using those drugs where:
 - There is a narrow therapeutic index, i.e. the toxic and therapeutic ranges overlap or are close to each other (e.g. digoxin, aciclovir).
 - Renal toxicity is a potential effect of the drug. ⚠ Beware the vicious cycle of worsening renal function, decreasing drug clearance, and rising drug levels (e.g. aminoglycosides).
 - ⚠ The consequences of accumulation are serious (e.g. metformin, opiates).
- The monitoring of therapeutic drug levels may be helpful in these situations.
- If there is a relatively wide therapeutic window, it may be possible to use a drug safely with a simple dose reduction (e.g. half the 'standard dose'). This is the case with many antibiotics. ⚠ However, never estimate—always confirm the appropriate dosing schedule.

Pharmacodynamics

Renal impairment may alter the sensitivity of target tissue to the effects of drugs. Examples: higher incidence of statin-induced myopathy, more pronounced effect of antiplatelet drugs, increased sensitivity to benzodiazepines, and increased risk of hyperkalaemia with potassium-sparing diuretics.

Pharmacokinetics

Renal impairment influences the pharmacokinetics of most drugs to some degree. Understanding why can help select drugs, doses, and dosing intervals that achieve therapeutic plasma concentrations but avoiding toxicity.

Absorption. Describes the passage of drug from site of administration into the plasma volume. Renal impairment may affect oral administration and enteral absorption via alterations in:

- Gastric pH:
 - Passive drug transfer across intestinal epithelial barriers is dependent on ionization. \uparrow gastric pH \rightarrow \downarrow ionization \rightarrow \downarrow absorption (e.g. ferrous sulphate, ketoconazole, itraconazole).
 - \uparrow gastric pH may be 2° to drugs (phosphate binders, H₂ antagonists, and proton pump inhibitors) as well as the excess urea hydrolysis to ammonia (to buffer HCl) present in renal failure.
- Gastric motility:
 - Gastric emptying can be delayed in uraemia (and diabetes mellitus).
 - Vomiting.
- Drug–drug interaction:
 - Interaction in the GI tract \rightarrow altered bioavailability (e.g. phosphate binders and ferrous sulphate should not be taken together).
 - Grapefruit juice inhibits the CYP3A4 isoform of the cytochrome P450 enzyme in liver and gut \rightarrow \downarrow first-pass metabolism of many drugs, including dihydropyridine calcium channel blockers and ciclosporin.
- GI tract oedema:
 - Nephrotic syndrome and CCF \rightarrow \downarrow loop diuretic absorption.

Distribution. Measures the (theoretical) volume (V_d) occupied by the total amount (Q) of drug, assuming uniform concentration (C_p) in all body compartments ($V_d = Q / C_p$). Several parameters are subject to change in renal insufficiency.

- Protein binding:
 - Changes in albumin concentration will affect the free (and \therefore active) concentration of highly protein-bound drugs.
 - Nephrotic syndrome \rightarrow hypoalbuminaemia \rightarrow \downarrow albumin binding \rightarrow \uparrow free drug.
 - Competitive binding of acidic uraemic toxins to albumin will also increase free drug.
 - Example: phenytoin is less protein-bound in renal failure, and signs of toxicity may occur at ‘therapeutic’ levels. (Δ Many assays used for therapeutic monitoring will not reflect this, as they measure total drug.) Warfarin and diazepam may also be affected. \blacktriangleright Be cautious with dose adjustments.
- Altered body composition:
 - Impaired renal function is associated with significant changes in body water, muscle, and adipose tissue.
 - Fluid overload will increase V_d for protein-bound and water-soluble drugs (e.g. atenolol, vancomycin).
 - Reduced muscle and adipose tissue may affect V_d for hydrophilic drugs (e.g. statins, morphine, codeine).
- Altered drug tissue binding:
 - Uraemia reduces tissue binding. Digoxin is the most clinically relevant, with a significant reduction in V_d .

Metabolism. Two important examples of the kidney’s involvement in drug metabolism are: (i) activation of vitamin D compounds through 1 α -hydroxylation; (ii) metabolism of insulin— Δ insulin requirements often decrease significantly as renal failure progresses.

Clearance

Clearance depends on glomerular filtration, tubular secretion, and tubular reabsorption.

$$\text{Clearance} = (F_{\text{unbound}} \times \text{GFR}) + \text{Secretion} - \text{Reabsorption}$$

where F_{unbound} is the fraction of unbound drug in the plasma.

Some drugs are eliminated unchanged by the kidney and are \therefore particularly susceptible to accumulation in renal failure. A more common scenario is that drugs are cleared via conversion to water-soluble (polar) metabolites prior to urinary excretion.

This initial breakdown to inactive, more polar metabolites usually occurs in the liver via conjugation (to glucuronide or sulphate) or oxidation/reduction.

In general, as GFR falls, drug elimination by all the following mechanisms is reduced.

- *Glomerular filtration.* Smaller molecules (MW <60,000) are filtered at the glomerulus unless protein-bound. Water-soluble (polar) molecules are more freely filtered than lipid-soluble (non-polar) ones.
- *Tubular secretion.* Non-polar drugs diffuse more readily across tubular membranes. In addition, many polar drugs undergo active excretion by the same mechanisms as organic acids and bases.
 - Organic acids: penicillins, cephalosporins, salicylates, loop and thiazide diuretics.
 - Organic bases: amiloride, quinidine, procainamide.
 - Acidic drugs are more effectively secreted into alkaline urine and vice versa. This can be exploited therapeutically, e.g. urinary alkalization in salicylate poisoning.
- *Tubular reabsorption* of non-polar drugs may be significant.

First-order kinetics

- Most drugs excreted by the kidneys exhibit first-order kinetics, i.e. the rate of elimination is proportional to the concentration of the drug.
- Drugs that demonstrate such kinetics can be described by their half-life ($t_{1/2}$). This is the time taken for the drug concentration to halve after absorption and distribution.
- $t_{1/2}$ determines steady state concentration, appropriate dosing interval, and persistence after cessation of treatment.
- The majority of drugs are given at regular intervals and reach steady state after $\sim 5 \times t_{1/2}$ when rate of intake equals rate of excretion.
- Increases in dose or dose frequency result in a higher steady state concentration.
- $t_{1/2}$ will itself depend on GFR for drugs excreted by the kidney.
- $\downarrow \text{GFR} \rightarrow \downarrow \text{clearance rate} \rightarrow \uparrow t_{1/2} \rightarrow$ accumulation and increased steady state drug concentration.
- This necessitates either a \downarrow in dose or \uparrow in dose interval.
 - Dose reductions \rightarrow lower peak concentrations but maintained trough levels (ideal when constant exposure required, e.g. many antibiotics, antihypertensives).

- Increased dose intervals → maintain peak concentrations but permit lower trough levels (e.g. aminoglycosides—high peak concentrations are required for bactericidal activity; low troughs avoid toxicity).
- See Fig. 12.1.

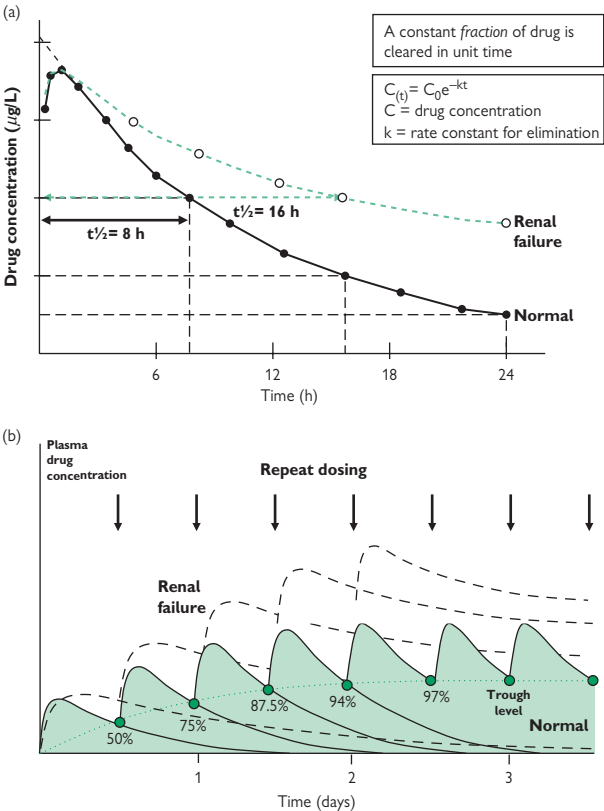


Fig. 12.1 Dose response curves following (a) single dose administration or (b) repeated dosing in the presence and absence of renal impairment. Note the effect of reduced renal clearance on $t_{1/2}$, time to steady state, and the steady state plasma concentration. Reproduced from *Oxford Desk Reference; Nephrology*, J. Barratt, K. Harris, P. Topham, with kind permission Oxford University Press, p. 692.

Assessing kidney function prior to prescribing

- The most important measure is GFR, not serum creatinine.
- A formal creatinine clearance is ideal but cumbersome (requires 24h urine collection) and \therefore rarely performed.
- \triangle MDRD eGFR was never intended to guide drug dosing. In particular, it may lead to overdosing of small patients and underdosing of large ones.
- Cockcroft–Gault estimation of CrCl incorporates body weight and is better suited to this purpose.
- \blacktriangleright GFR may be rapidly changing, particularly in AKI or a critical care setting. This makes drug selection and dosing a key component of management that requires constant attention and review.
- If in any doubt, discuss with a renal pharmacist—they are an invaluable resource on all specialist units.

Prescribing for dialysis patients

Patients on renal replacement therapy (RRT) will normally have an insignificant 'native' GFR, and the removal of drugs usually dependent on renal excretion will \therefore be negligible. ► It is vital to know whether such drugs will be removed by dialysis.

Drug clearance will vary, according to modality of dialysis. Clearance by haemodialysis and peritoneal dialysis is contingent on diffusion down a concentration gradient between plasma and dialysate. Clearance during haemofiltration is reliant on convection alone.

Two important factors that may influence drug removal require consideration when prescribing for patients on RRT:

- Characteristics of the drug.
- Characteristics of the type of RRT.

Drug characteristics

- Molecular weight (MW):
 - Haemodialysis membranes have relatively small pore sizes and will only clear molecules $<500\text{Da}$.
 - Haemofilters have larger pore sizes and can clear much larger molecules $<5,000\text{Da}$.
 - Protein binding:
 - Heavily protein-bound drugs are not well removed (even if low MW).
 - Volume of distribution:
 - Large volumes of distribution result in low plasma drug concentrations and reduced availability for removal by dialysis.
 - Water solubility:
 - Water-soluble drugs pass through filters more readily than lipid-soluble ones.
-
- For patients receiving RRT, GFR cannot be calculated using standard equations.
 - Even though clearance may be higher during treatment, dosing at $\text{CrCl} < 10\text{mL/min}$ is common for haemodialysis, as the treatment is generally intermittent.
 - Clearance is higher in continuous techniques, such as continuous veno-venous haemofiltration (CVVHF) or continuous veno-venous haemodiafiltration (CVVHDF) where clearances can be in the range $30\text{--}40\text{mL/min}$. This allows larger doses to be prescribed.
 - Generally, the manufacturer of machines and dialysers/filters will provide an estimate of CrCl by their system.
 - Drugs will have a sieving coefficient that indicates the proportion of drug that will pass through a membrane during treatment. A drug that passes freely has a sieving coefficient of 1, and one does not pass at all will have a coefficient of 0.
 - It is the knowledge of the system clearance and the drug-sieving coefficient that informs guidance for drug prescription.

- There are several comprehensive resources, such as renal formularies, that could, and should, be frequently consulted.
- Clinical decision support alerts within electronic prescribing systems can help reduce errors.
- Specialist renal and critical care pharmacists are an invaluable source of information and essential members of the relevant clinical teams.

RRT characteristics

- Properties of the dialyser or filter (pore size, surface area).
- Drug adsorption onto some membrane types.
- Duration of therapy, e.g. haemodialysis provides efficient clearance but is only an intermittent treatment. Peritoneal dialysis clears drugs much less efficiently than either haemodialysis or haemofiltration but is a continuous technique.
- Dialysate and blood flow rates (determine concentration gradient).
- For peritoneal dialysis:
 - Peritoneal membrane status, e.g. clearance increases during the inflammation caused by peritonitis.
 - Volume and frequency of exchanges.
- Drugs that are cleared by haemodialysis are usually administered after a treatment session.

Sepsis and antimicrobials

►► Sepsis is a relatively common cause and complication of renal failure.

Presentations may be atypical and non-specific. Samples for culture and sensitivity (including blood, urine, sputum, wound swabs, drain fluids, and any other relevant locations) should be obtained (preferably before antibiotic administration) wherever possible. See Table 12.1 on choice of antimicrobial treatment and Table 12.2 for antibacterial, antiviral, and antifungal dosing

Antimicrobials

Choice of antibiotic

- History and examination may identify the most likely source of infection and guide initial antibiotic selection. However, prompt empirical treatment to cover all likely pathogens may be necessary in deteriorating patients.
- ► Local antibiotic policies, developed with microbiology and pharmacy input, should be adhered to in all, but exceptional, circumstances.
- Prudent antibiotic prescribing can reduce hospital-related infections, such as MRSA and *C. difficile*, and help to prevent antibiotic resistance.
- Always record indication and intended antibiotic duration or review date.
- IV antibiotics should be switched to oral equivalents after 48h if T <38°C for 48h, patient is clinically improving, a suitable oral agent is available, and there is no evidence of malabsorption, gastric stasis, or vomiting. There are exceptions (e.g. PD peritonitis, endocarditis, meningitis)—your microbiology team will advise.
- Numerous antimicrobials depend on renal clearance. However, most have a wide therapeutic index, and dose reductions are only necessary once GFR is <20mL/min (Δ aminoglycosides and vancomycin are important exceptions).
- High doses of β-lactam antibiotics can accumulate and cause neurological sequelae, including confusion, agitation, and seizures in advanced CKD, including dialysis patients.
- Cephalosporins and quinolones require dose reductions in more severe renal impairment (see Table 12.2).
- Vancomycin is extensively used for staphylococcal infections (including dialysis line sepsis and PD-related peritonitis). Monitoring of drug levels is essential (📖 p. 882).
- Aminoglycosides can be used with care (📖 p. 880).

Haemodialysis patients

Central vascular dialysis catheter infection or PTFE access graft sepsis should always be considered (📖 p. 297). Even if a PTFE graft has previously been surgically removed, residual material may remain *in situ*.

► Always consider immediate removal of any foreign body (particularly dialysis lines). Do not wait for culture results. Empirical therapy often involves vancomycin and gentamicin, which are dosed according to trough drug levels (📖 p. 882). Unlike gentamicin (📖 p. 881), vancomycin

is not effectively removed by standard HD, so speed of clearance will largely depend on residual renal function (if any). In practice, doses may be days apart.

⚠ Beware the complacency this can induce—it is crucial to proactively measure and respond to drug levels if periods of inadequate antibiotic activity are to be avoided.

In addition to aminoglycosides, penicillins (e.g. benzylpenicillin, amoxicillin, and co-amoxiclav), meropenem, cefotaxime, ceftazidime, ciprofloxacin, metronidazole, clarithromycin, and trimethoprim are removed by HD and should be given post-treatment. ▶▶ Severe sepsis is an exception—administer immediately.

Peritoneal dialysis patients (📖 p. 322)

In suspected PD peritonitis, perform an exchange, and send fluid for M,C+S. Peritonitis in overnight APD patients may be less easily diagnosed, as the patient may not witness a cloudy bag. Also consider (and examine for) exit site or tunnel infections related to Tenckhoff catheters. ⚠ Remember: other causes of peritonitis or an acute abdomen can, and do, occur in peritoneal dialysis patients. All renal units will have a detailed antibiotic policy for the treatment of PD-related peritonitis and exit site infections. International guidance can be found at 🌐 <http://www.ispd.org>.

Post-transplantation (📖 p. 426)

Patients are susceptible to a wide variety of infectious pathogens at different stages post-transplantation. Atypical infections must always enter the differential. Initial broad-spectrum antimicrobial treatment is often necessary until investigations are completed and culture results available. Also review the degree of immunosuppression, and consider a reduction. If overwhelming sepsis, stop all immunosuppression, and replace with IV steroid (e.g. hydrocortisone IV 50mg qds) until condition allows phased reintroduction. ▶ Discuss with transplant team ASAP.

Antivirals

Many antivirals, including aciclovir, ganciclovir, valganciclovir, famciclovir, and lamivudine, are dependent on renal clearance and will begin to accumulate, even in relatively mild renal insufficiency (GFR <50mL/min). Dose-related (and usually reversible) neurological toxicity is typical (→ dizziness, tremor, confusion, ataxia, hallucinations, drowsiness, encephalopathy, seizures). Bone marrow suppression is also possible. Ribavirin and its metabolites rely on renal clearance, and their accumulation can cause severe anaemia. The neuraminidase inhibitor oseltamivir undergoes hepatic breakdown to active metabolites, requiring subsequent renal clearance. An increased dose interval is ∴ recommended once GFR <30mL/min. Many antivirals are removed freely by dialysis.

Antifungals

Unlike many other azole antifungals (e.g. ketoconazole, itraconazole), fluconazole is renally excreted, so maintenance dosing requires adjustment in moderate to severe CKD. It should also be administered after dialysis. Fluconazole's urinary excretion means that it is useful in the treatment of fungal infections of the urinary tract.

Aminoglycosides

- **⚠** Aminoglycosides must always be used with caution in renal impairment, as they undergo renal clearance, have a narrow therapeutic window, and are nephrotoxic. A vicious cycle of rising drug levels and worsening renal function can (and often does) result.
- Aminoglycosides are freely filtered by the glomerulus (so dose is adjusted according to GFR) and then partially taken up by tubular cells. This can cause tubular cell injury (→ ATN).
- **▶** Several factors increase risk of both nephrotoxicity (and ototoxicity): prolonged treatment, dehydration, concomitant diuretic use, obstructive jaundice, hypokalaemia, and hypomagnesaemia.
- Dose adjustments aim to achieve peak plasma levels that are bactericidal whilst permitting low trough levels that avoid toxicity.

⚠️ Gentamicin dosing

- Gentamicin does not enter fat, so obese patients should be dosed, according to ideal body weight (IBW), calculated as follows:
 - Adult ♂: $IBW \text{ (in kg)} = 50 + (2.3 \times \text{height in inches over 5 feet})$.
 - Adult ♀: $IBW \text{ (in kg)} = 45.5 + (2.3 \times \text{height in inches over 5 feet})$.
- ► Protocols will vary, so consult local policies, and discuss with microbiology.
- GFR >20mL/min: usual first dose for empirical treatment is 5mg/kg (according to ideal body weight), with a maximum dose of 450mg.
- GFR <20mL/min in those who are *not* on dialysis treatment: usual recommended dose is 3mg/kg, according to ideal body weight, with a maximum of 280mg.
- Patients on HD or PD: usual recommended first dose is 2mg/kg, with a maximum dose of 180mg.
- Seek advice regarding subsequent doses.
- Serum levels are maintained in the therapeutic range for longer in patients with ↓ GFR, and the dosing interval may be every 2–5 days.
- A trough serum level, taken 20h post-dose, should be <1mg/L (unless the patient is on HD) before repeat administration. Peak level measurement is unnecessary in once daily dosing regimens.
- If the level is not <1mg/L, then repeat every 24h, and redose when <1mg/L (and if there remains a clear indication for the drug).
- In HD patients, redose when pre-dialysis levels are <2mg/L. Dialysis removes a significant proportion of gentamicin—waiting for pre-dialysis trough levels to fall to <1mg/L risks sub-therapeutic periods.
- Gentamicin is generally administered at the end of HD and by intraperitoneal administration in PD patients.
- Amikacin, netilmicin, and tobramycin have similar pharmacokinetics and require similar management. Consult local policies.
- In HD and PD, the effect of aminoglycosides on residual ‘native’ renal function remains unpredictable, but the risk of sepsis outweighs the risk of a fall in residual urine output. It is ∴ the risk of ototoxicity and developing an irreversible balance disorder that is the paramount concern in this situation.

Table 12.1 Antimicrobial treatment in common renal scenarios (local policies will vary)

Condition	First-line	Penicillin allergy	Comments
UTI	Co-amoxiclav 375–625mg tds PO for 3 days in ♀ and 7 days in ♂. Give 7 days in renal transplant patients. Catheter-related bacteriuria does not require treatment if no clinical evidence of a UTI.	Ciprofloxacin PO for 3 days in ♀ and 7 days in ♂. 7 days in renal transplant patients. Dose reduction required in renal impairment.	Modify treatment, according to culture results.
Pyelonephritis (native or transplant kidney)	Co-amoxiclav IV for 10–14 days (+ gentamicin IV stat if renal transplant or severe sepsis).	Gentamicin IV stat, and discuss with microbiology. Dose reduction if renal impairment (see ☞ p. 881).	Modify, according to culture results.
PD peritonitis	See ☞ p. 322.		
Haemodialysis catheter exit site infection	Flucloxacillin 500mg qds PO for 5 days.	Clarithromycin 250mg bd PO for 5 days.	If MRSA-colonized, seek microbiological advice.
Haemodialysis catheter tunnel infection	Flucloxacillin 500mg qds PO for 5 days or 1g qds IV for 5–10 days if severe. Consider line removal.	Clarithromycin 250mg bd PO/IV for 5–10 days. Consider line removal.	If MRSA-colonized, give vancomycin IV stat, and seek microbiological advice.
Haemodialysis catheter (or PTFE graft)-related bloodstream infection	Vancomycin 1g (500mg if <50kg) IV stat (check trough level at 20h, and redose if <15mg/L) + gentamicin 2mg/kg (max 280mg) IV stat through dialysis catheter (check trough level at 20h, and redose if <2mg/L (see ☞ p. 297). ⚠ If rigors or unwell, take blood cultures, and administer immediately; do not wait until the end of dialysis.		Modify, according to culture results. Remove line if possible.
Empirical treatment of severe sepsis	Co-amoxiclav IV 1.2g + gentamicin IV 2–5mg/kg, depending on renal function (☞ p. 881).	Vancomycin 1g IV stat (regimen dependent on renal function, ☞ Table 12.2) + gentamicin 2–5mg/kg IV stat, depending on renal function (☞ p. 881).	Seek urgent advice. Use penicillin-allergic regimen if known to be MRSA-colonized.

Table 12.2 Antibacterial, antiviral, and antifungal dosing

Antimicrobial		Dose adjustment according to eGFR				Dose adjustment according to dialysis modality			Comments
		Normal	20–50mL/min	10–20mL/min	<10mL/min	HD	CAPD	CVVH	
Penicillins	Amoxicillin	250mg–1g every 8h	No change	No change	No change	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	No change	
	Benzylpenicillin	IV: 1.2–2.4g every 6h	No change	IV: 600mg–2.4g every 6h	IV: 600mg–1.2g every 6h	IV: 600mg–1.2g every 6h	IV: 600mg–1.2g every 6h	IV: 600mg–2.4g every 6h	
	Flucloxacillin	Oral: 250–500mg every 6h IV: 250mg–2g every 6h	No change	No change	Up to a total dose of 4g/24h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	No change	Neurotoxicity may still occur Watch for confusion/ drowsiness
	Piperacillin-tazobactam	4.5g every 8h	No change	4.5g every 12h	4.5g every 12h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	2.25–3.375g every 6h or 4.5g every 8h	
	Co-amoxiclav	Oral: 375–625mg every 8h IV: 1.2g every 8h	No change	Oral: 375–625mg every 8h IV: 1.2g every 12h	Oral: 375–625mg every 8h IV: 1.2g every 12h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 10–20mL/min	

(Continued)

Table 12.2 (Continued)

Antimicrobial		Dose adjustment according to eGFR				Dose adjustment according to dialysis modality			Comments
		Normal	20–50mL/min	10–20mL/min	<10mL/min	HD	CAPD	CVVH	
Cephalosporins	Cefuroxime	Oral:125–500mg every 12h IV: 750mg–1.5g every 6–8h	Oral:125–500mg every 12h IV: 750mg–1.5g every 8h	Oral:125–500mg every 12h IV: 750mg–1.5g every 8–12h	Oral: 125–500mg every 12h IV: 750mg–1.5g every 12–24h	Oral: no change IV: dose as in eGFR <10mL/min	Oral: no change IV: dose as in eGFR <10mL/min	Oral: no change IV: dose as in eGFR 10–20mL/min	Neurotoxicity may still occur
	Cefotaxime	1g every 6–8h	1g every 6–8h	1g every 6–8h	1g every 12h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	1–2g every 12 h	Watch for confusion/drowsiness
	Ceftazidime	500mg–2g every 8–12h	1–2g every 12h	1–2g every 24h	500mg–1g every 24h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	1–2g every 12h	
Quinolone	Ciprofloxacin	Oral: 250–750mg every 12h IV: 100–400mg every 12h	No change	Oral: 250mg every 12h IV: 200mg every 12h	Oral: 250mg every 12h IV: 200mg every 12h	Oral: 250mg every 12h IV: 200mg every 12h	Oral: 250mg every 12h IV: 200mg every 12h	Oral: 500–750mg every 12h IV: 200–400mg every 12h	Consider 24–48h before dose reduction in severe sepsis
Macrolides	Clarithromycin	Oral: 250–500mg every 12h IV: 500mg every 12h	No change	Oral: 250–500mg every 12h IV: 250–500mg every 12h	Oral: 250–500mg every 12h IV: 250–500mg every 12h	Oral/IV: dose as in eGFR <10mL/min	Oral/IV: dose as in eGFR <10mL/min	Oral/IV: dose as in eGFR 10–20mL/min	Potentially serious interaction with a number of other medication

	Erythromycin	Oral: 250–500mg every 6h IV: 25–50mg/kg/day, maximum dose 4g/day	Oral: 250–500mg every 6h IV: 25–50mg/kg/day, maximum dose 4g/day	Oral: 250–500mg every 6h IV: 25–50mg/kg/day, maximum dose 4g/day	Oral: 250–500mg every 6h IV: 50–75% of normal dose, maximum 2g/day	Oral/IV: dose as in eGFR <10mL/min	Oral/IV: dose as in eGFR <10mL/min	Oral/IV: dose as in normal renal function	Particularly of note increases the level of calcineurin inhibitors and warfarin
Nitroimidazoles	Metronidazole	Oral: 200–500mg every 8–12h IV: 500mg every 8h	Oral: 200–500mg every 8–12h IV: 500mg every 8h	Oral: 200–500mg every 8–12h IV: 500mg every 8h	Oral: 200–500mg every 8–12h IV: 500mg every 8h	Oral/IV: dose as in normal renal function	Oral/IV: dose as in normal renal function	Oral/IV: dose as in normal renal function	
Aminoglycosides	Gentamicin	5–7mg/kg once daily, adjust according to levels	3–5mg/kg once daily and adjust according to levels	2–3mg/kg once daily and adjust according to levels	2mg/kg every 48–72h and adjust according to levels	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 30–70mL/min	Please refer to Table 12.1 regarding aminoglycoside dosing and monitoring of levels
	Amikacin	15mg/kg/day in two divided doses, maximum of 1.5g/day	5–6mg/kg every 12h	3–4mg/kg every 24h	2mg/kg every 24–48h	5mg/kg after dialysis	Dose as in eGFR <10mL/min	7.5mg/kg every 24h	

(Continued)

Table 12.2 (Continued)

Antimicrobial	Dose adjustment according to eGFR				Dose adjustment according to dialysis modality			Comments
	Normal	20–50mL/min	10–20mL/min	<10mL/min	HD	CAPD	CVVH	
Glycopepti- des Vancomycin	Oral: 125–500mg every 6h IV: 1g every 12h (monitor levels)	Oral: no change IV: 0.5–1g every 12–24h (monitor levels)	Oral: no change IV: 0.5–1g every 24–48h (monitor levels)	Oral: no change IV: 0.5–1g every 48–72h (monitor levels)	Oral/IV: dose as in eGFR <10mL/min (monitor levels)	Oral/IV: dose as in eGFR <10mL/min	Oral: No change IV: 1g daily and monitor levels	Vancomycin can cause ‘red man syndrome’; this is not a true anaphylaxis and often relates to infusion rate
Teicoplanin	Loading dose: 400mg every 12h for three doses Maintenance dose: 200–400mg daily	Loading dose: 400mg every 12h for three doses Maintenance dose: 200–400mg daily	Loading dose: 400mg every 12h for three doses Maintenance dose: 200–400mg every 24–48h	Loading dose: 400mg every 12h for three doses Maintenance dose: 200–400mg daily every 48–72h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 10–20mL/min	
Lipopeptide Daptomycin	4–6mg/kg once daily	4–6mg/kg once daily	4mg/kg once daily	4mg/kg once daily	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	4–6mg/kg every 48h	Monitoring of CK is recommended with daptomycin use due to risk of myopathy
Oxazolidi- none Linezolid	600mg every 12h	600mg every 12h	600mg every 12h	600mg every 12h	No change	No change	No change	

Carbapenems (β-lactam)	Ertapenem	1g daily	1g daily	50–100% of dose in normal renal function	50% of dose in normal renal function, or 1g three times a week	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 10–20mL/min	Meropenem and ertapenem less likely to cause seizures than imipenem, but still need to monitor for neurotoxicity
	Meropenem	500mg–1g every 8h	500mg–2g every 12h	500mg–1g every 12h	500mg–1g every 24h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	1g every 12h	
Glycylcycline	Tigecycline	Loading dose of 100mg, then 50mg every 12h	No change	No change	No change	No change	No change	No change	
Others	Co-trimoxazole	Treatment: 120mg/kg/day in 2–4 divided doses Prophylaxis: 480mg daily or 960mg alternate days	No change	Treatment: 60mg/kg/day in two divided doses for 3 days, then 30mg/kg/day in two divided doses Prophylaxis: 50% of dose in normal renal function	Treatment: 60mg/kg/day in two divided doses for 3 days, then 30mg/kg/day in two divided doses Prophylaxis: 50% of dose in normal renal function	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 10–20mL/min	

(Continued)

Table 12.2 (Continued)

Antimicrobial	Dose adjustment according to eGFR				Dose adjustment according to dialysis modality			Comments
	Normal	20–50mL/min	10–20mL/min	<10mL/min	HD	CAPD	CVVH	
Nitrofurantoin	Treatment: 50–100mg every 6h Prophylaxis: 50–100mg at night	Use with caution	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated	When eGFR is <20mL/min, the drug is ineffective due to inadequate urine concentration; toxic plasma levels can occur, causing adverse effects, particularly neuropathy and blood dyscrasias
Trimethoprim	Treatment: 200mg every 12h Prophylaxis: 100mg daily	No change	No change	No change	No change	No change	No change	Serum creatinine may rise due to competition for renal secretion, and hyperkalaemia is common in CKD4/5

	Doxycycline	200mg on day 1, then 100mg daily	No change	No change	No change	No change	No change	No change	No change
	Clindamycin	No change	No change	No change	No change	No change	No change	No change	No change
Synthetic nucleoside analogues	Aciclovir (IV)	5–10mg/kg every 8h	5–10mg/kg every 12h	5–10mg/kg every 24h	2.5–5mg/kg every 24h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 10–20mL/min	Neurotoxicity can occur with maximum
	Aciclovir (PO)	Simplex: 200–400mg x5/day Zoster: 800mg 5x day	200–400mg x5/day Zoster: 800mg 5x day	200mg 3–4x/day Zoster: 800mg 8–12h	200mg every 12h Zoster: 400–800mg 8–12 h	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 10–20mL/min	recommended dose, so monitor carefully for confusion/drowsiness
	Ganciclovir (IV)	5mg/kg every 12h for 2–3 weeks	2.5mg/kg every 12h for 2–3 weeks	2.5mg/kg every 24h for 2–3 weeks	1.25mg/kg every 24h for 2–3 weeks	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	2.5mg/kg every 24h	Increased risk of myelosuppression in combination with other myelosuppressive drugs
	Valganciclovir (PO)	Treatment: 900mg every 12h for 3 weeks Prophylaxis: 900mg every 24h	Treatment: 450mg every 24h for 3 weeks Prophylaxis: 450mg every 48h	Treatment: 450mg every 48h for 3 weeks Prophylaxis: 450mg twice weekly	Treatment: 450mg 2–3x/week for 3 weeks Prophylaxis: 450mg 1–2x/week	Dose as in eGFR <10mL/min	Dose as in eGFR <10mL/min	Dose as in eGFR 10–20mL/min	

(Continued)

Polyenes	Amphotericin	250 micrograms– 1.5mg/kg/ day	No change	No change	No change	No change	No change	No change	Amphotericin is highly nephrotoxic and can cause distal tubular acidosis, polyuria, hypovolaemia, hypokalaemia, and metabolic acidosis; liposomal amphotericin is preferred for patients with renal disease
	AmBisome® (liposomal Amphotericin)	1–3mg/kg/day, maximum 5mg/ kg/day	No change	No change	No change	No change	No change	No change	
Echino- candins	Anidulofungin	200mg loading dose, then 100mg daily	No change	No change	No change	No change	No change	No change	
	Caspofungin	70mg loading dose, then 50mg daily thereafter, unless >70kg, then use 70mg daily	No change	No change	No change	No change	No change	No change	
Fluorinated pyrimidine analogue	Flucytosine	100–200mg/kg per day in four divided doses	50mg/kg every 12h	50mg/kg every 24h	50mg/kg, then redose according to levels	Dose as in eGFR <10mL/min	50mg/kg every 24h in four divided doses	Dose as in eGFR 10–20mL/min	Bone marrow suppression is more common in patient with renal disease

Cardiovascular drugs

Introduction

△ Cardiovascular disease is a significant cause of morbidity and mortality in patients with kidney disease (📖 p. 198). However, most of the large practice-changing cardiology trials have specifically excluded patients with renal impairment. This means that the robust evidence base developed for many CV drugs in the general population is not necessarily transferable to individuals with renal disease. 🧠 In fact, in certain situations, there may be a risk of more harm than good.

▶ Hypertension in dialysis patients is often driven by salt and water overload, with volume expansion. Discuss changes in an antihypertensive regimen with the patient's renal team to avoid hypotensive episodes during dialysis treatment.

Specific drug groups

Beta-blockers Atenolol is excreted by the kidneys and is removed by HD (but not PD). It is still used widely in advanced CKD, but the dose is best titrated to avoid the effects of accumulation (e.g. bradycardia). Similarly, metoprolol, bisoprolol, and carvedilol should be titrated cautiously, according to clinical circumstances. The latter three are not removed by dialysis.

Calcium channel blockers, α -blockers, and nitrates Do not require dose reduction, although caution around the precipitation of postural hypotension should be exercised.

Aspirin Is prescribed in standard doses in CKD for primary and secondary CV risk modification, although bleeding risk is likely to increase as renal dysfunction progresses. Use with caution when combined with other antiplatelet agents. Consider gastric protection.

Clopidogrel Indications, benefits, and ideal dose in more advanced CKD are unknown. Most clinicians use as for non-renal patients, but caution is required, as the risk of bleeding is likely to be increased.

Heparin LMWHs undergo renal clearance and accumulate in advanced CKD (particularly GFR <30mL/min). △ While the doses used for prophylaxis against venous thromboembolism are generally well tolerated, larger 'treatment' doses have been associated with significant, and serious, bleeding complications. Monitoring of activated factor Xa levels has been advocated but may not always be practical. While suggestions for dose modification are available for some LMWHs, unfractionated heparin may be preferred in many situations. ▶ It is vital that a local guideline is developed and adhered to. At present, many patients with CKD do not receive, or receive inappropriate doses of, anticoagulants in emergency situations, such as acute coronary syndrome—even though CKD places them in a high-risk group.

Unfractionated heparin is usually commenced in standard dosage and adjusted, according to APTT.

Fondaparinux is a factor Xa inhibitor that can be used at a reduced dose in mild to moderate renal impairment but is best avoided in more advanced CKD (GFR <30mL/min).

Oral anticoagulants Risk/benefit assessment must be carefully undertaken for many indications (such as prevention of dialysis access thrombosis or prevention of thromboembolism in AF), particularly as CKD progresses. Δ Individuals with CKD often require lower doses of warfarin, have poorer control of anticoagulation, and are at increased risk of bleeding complications. Anticoagulants may \therefore need lower dosage at initiation and closer monitoring. The risks (as well as uncertainties regarding benefit) increase in CKD stage 5 and 5D. There is much more experience with warfarin than other oral anticoagulants, such as phenindione. However, there is increasing recognition that warfarin therapy in CKD 5D may significantly contribute to ectopic vascular calcification.

Experience with the direct thrombin inhibitor dabigatran is limited in CKD. Patients with a CrCl $<30\text{mL/min}$ were excluded from the RE-LY study that defined its utility in AF. While dose reductions have been suggested, it is best avoided if GFR $<30\text{mL/min}$ and certainly if $<15\text{mL/min}$. Its anticoagulant effect is more difficult to reverse. It undergoes renal clearance and is also removed by dialysis (which has been proposed as a potential means of reversal in emergency situations).

Thrombolytics No dose reduction recommended, although the potential for bleeding complications rises as CKD advances.

ACE inhibitors (and ARBs) Widely prescribed in CKD (📖 p. 203). Clinical trials show a good safety profile, even in higher CKD stages. Check eGFR and K^+ before and 3–5 days after. Expect (and allow) a rise in SCr or \downarrow eGFR of up to 20%, but recheck within 2–4 weeks. Δ A precipitous fall in GFR may be seen in situations where renal perfusion is dependent on RAS activation (\rightarrow CCF, bilateral renal artery stenosis, stenosis to a solitary kidney). \blacktriangleright Rapid \downarrow GFR and AKI are always made more likely by volume depletion (diuretics, GI upset, etc.). It is sensible to advise patients to temporarily stop these medications in the event of intercurrent illness, particularly if dehydration is a factor.

Digoxin Is less tissue-bound in the presence of impaired renal function and \therefore has a reduced volume of distribution. Dose reductions are necessary from relatively early CKD, and monitoring of levels can guide maintenance treatment. Loading doses are also reduced at ESRD (e.g. 750 micrograms—1mg in three divided doses). Digoxin is not removed by dialysis or filtration. Digitoxin, an alternative cardiac glycoside, undergoes liver metabolism and does not require such substantial dose adjustments.


Amiodarone Does not require dose modification, but beware multiple drug interactions.

Statins Evidence of benefit for lipid-lowering therapy in CKD is limited (📖 p. 205), but statins can be used at standard doses. Myopathy is more common, so high doses should be used with caution. There is an important interaction with ciclosporin in transplant recipients (\rightarrow \uparrow myopathy risk). Δ *Fibrates* require dose reduction in moderate renal impairment (GFR $<40\text{mL/min}$) and should be avoided in advanced CKD. They are also associated with a reversible increase in SCr (thought to be mediated by peroxisome proliferator-activated receptor α). *Ezetimibe* is considered safe for use with no dose modification.

Prescribing in specific situations

Diabetic CKD

Close working between renal and diabetic teams is highly desirable. Collaboration can ensure a patient's treatment remains appropriate as CKD progresses. Medications must be adjusted for optimal control of glycaemia, reduction of proteinuria, modification of cardiovascular risk, and prevention of CKD progression. Diabetic patients may also require intervention for CKD-related complications, including anaemia, at a higher eGFR, and these can be more symptomatic in the presence of other diabetes-related comorbidities.

Insulin Δ Metabolized, rather than excreted, by the kidneys. Careful prospective review of an individual's insulin regimen is necessary, as GFR falls, if hypoglycaemia is to be avoided. Educate the patient that insulin requirements may decrease, independent of changes in diet or activity. Insulin also has a role in the management of hyperkalaemia ( p. 130). Insulin is not removed by dialysis.

Metformin 90–100% renal excretion and \therefore contraindicated in advanced CKD. Consider switching to alternatives (often insulin) once eGFR $<40\text{mL}/\text{min}$ and certainly once $<30\text{mL}/\text{min}$. \blacktriangleright Accumulation in renal insufficiency can rarely cause profound lactic acidosis, particularly during episodes of acute-on-chronic kidney injury (Δ contrast) or during intercurrent illnesses involving hypoxaemia (e.g. sepsis, MI).

Sulfonylureas Gliclazide and glipizide undergo minimal renal clearance and require no dose adjustment. However, since they increase insulin secretion, which itself may have a prolonged action in CKD, they should be titrated with caution. Δ The metabolites of glibenclamide and glimepiride may accumulate and cause unpredictable hypoglycaemia, so these agents are best avoided.

Acarbose Avoid if eGFR $<25\text{mL}/\text{min}$, as metabolites accumulate.

Metglitinides Repaglinide and nateglinide can be used without a dose adjustment.

Thiazolidinediones Undergo biliary excretion and do not require dose adjustment. However, they have been associated with problematic fluid retention and oedema in patients with NYHA class III or IV heart failure. Given the incidence of cardiac disease and volume overload in CKD, they should be avoided or used with extreme caution.

Gliptins predominantly undergo renal excretion (except linagliptin-bile and GI tract). Sitagliptin requires dose reduction; e.g. 50mg daily for GFR 30–50mL/min and 25mg for GFR $<30\text{mL}/\text{min}$. Sitagliptin is not dialysed and can be used in HD and CAPD patients (generally 25mg daily). Linagliptin's route of elimination means that it does not require dose adjustment. There is less experience with other gliptins.

Thyroid disease

Thyroid hormone Replacement does not require dose adjustment. However, co-administration with phosphate binders or oral iron impairs absorption. T3 and T4 are both highly protein-bound. In profound

hypoalbuminaemia, such as in the nephrotic syndrome, changes in the unbound fraction of T3 and T4 may cause temporary toxicity.

In addition, TFTs should be interpreted with caution in advanced CKD, as uraemia is associated with ↓ peripheral enzymatic conversion of T4 → T3, as well as ↓ protein binding. Practically, this means titrating dose changes more slowly against clinical, not just biochemical, response.

Hyperuricaemia and gout

Fractional excretion of uric acid falls as GFR declines, and this may be aggravated by drugs that reduce urate clearance (e.g. diuretics, ciclosporin, NSAIDs). Gout is, therefore, highly prevalent in CKD.

Colchicine Accumulates in renal impairment, so lower doses are recommended to avoid GI and haematological side effects. e.g. 500mcg bd.

Allopurinol Is metabolized to oxypurinol, an active metabolite that accumulates in renal impairment. This means it should be introduced at lower dosage (e.g. 100mg daily) and titrated. Side effects include cutaneous reactions and bone marrow suppression. ⚠ There is an important drug interaction between azathioprine and allopurinol (→ profound bone marrow suppression). Concomitant administration should be avoided.

There is limited experience with *febuxostat*, a newer xanthine oxidase inhibitor once GFR <30mL/min. Concomitant use with azathioprine should be avoided.

NSAIDs Are best avoided, where possible, but may be useful for brief administration under close supervision. **Corticosteroids** may be helpful in severe or refractory cases, with no dose adjustments.

Rasburicase Is an intravenously administered urate oxidase inhibitor that potently reduces uric acid levels in the prophylaxis and treatment of acute hyperuricaemia during chemotherapy. No dose adjustment is required.

Bone metabolism

Bisphosphonates Are extensively excreted in the urine. They are assimilated into bone and promote osteoclast apoptosis. The normal bone remodelling cycle (the coupling of osteoclastic resorption with osteoblastic formation) lasts ~200 days but may exceed 1,000 days, following bisphosphonate administration. Impaired clearance in renal insufficiency increases the amount incorporated in the skeleton where it may cause or exacerbate low bone turnover and ∴ adynamic bone disorder. Safety in CKD 4–5 is unproven, and bisphosphonates should be avoided in this context (📖 p. 234). Rapid administration of IV bisphosphonates (e.g. pamidronate) without adequate hydration has also been associated with acute nephrotoxicity and AKI.

Nausea

Dopamine antagonists Such as domperidone, metoclopramide, and prochlorperazine, are not renally excreted and can be used in renal insufficiency. However, extrapyramidal side effects are more common, so titrate doses carefully. Domperidone does not cross the blood–brain barrier and may be preferred.

5-HT₃ antagonists Such as ondansetron and granisetron, do not require dose modification.

Dyspepsia

Dyspeptic symptoms are common in advanced CKD. Uraemia may affect autonomic and enteric nervous system function. CAPD may delay gastric emptying and promote reflux. In addition, gastric irritants, such as aspirin, are widely prescribed in this population.

Antacids Are safe, although aluminium or magnesium can accumulate if taken in excess.

Proton pump inhibitors Can be safely prescribed in standard doses. PPIs have been implicated in the development of interstitial nephritis. Although this is a rare side effect, the number of individuals taking them means that they are now the most important cause of acute interstitial nephritis in many countries.

H₂ receptor antagonists Are renally excreted but generally prescribed safely, with no dose modification. Cimetidine is best avoided: it interacts with cytochrome P450 enzymes, causing drug interactions, and falsely elevates SCr through the inhibition of active urinary creatinine secretion.

Constipation

GI motility is affected by renal failure: uraemia disturbs colonic innervation; diet is often suboptimal, and polypharmacy is common. Both HD and CAPD patients should avoid constipation—the former because of increased enteric K⁺ absorption, and the latter as it impairs inflow and outflow of dialysis and ∴ dialysis efficiency.

Dietary intervention Can be effective. Dose modifications of *bulking agents* (e.g. ispaghula), *stimulating agents* (e.g. senna, bisacodyl), and *osmotic agents* (e.g. lactulose) are generally not required.

Bowel cleansing solutions Should be used with caution in advanced CKD and AKI due to the potential risk of hypovolaemia as well as their high phosphate or magnesium content.


Psychotropic drugs

Mostly lipid-soluble and liver-metabolized. However, caution is prudent, as side effects may be more common in advanced CKD. Slow dose titration is advisable. Often non-dialysed.

Serotonin-specific reuptake inhibitors (SSRIs) Are widely prescribed at normal doses, with cautious titration (e.g. citalopram, paroxetine, sertraline).

Tricyclic antidepressants Are predominantly hepatically metabolized and may be used with careful titration. However, patients with advanced CKD may be more prone to anticholinergic side effects, such as postural hypertension.

Benzodiazepines Are liver-metabolized, but heightened CNS toxicity, particularly sedation, is a concern. Short-acting agents are ∴ preferred. Protein binding of midazolam is reduced, so it should be used with caution in advanced CKD.

Antipsychotics Such as clozapine, olanzapine, and quetiapine, are generally well tolerated. Risperidone and its active metabolites are renally excreted, so initiation and titration are cautious. Lithium is discussed on  p. 904.

Haloperidol Is often used in acute agitation as well as an antiemetic. Smaller initial doses should be used in advanced CKD because of increased CNS sensitivity.

Anticonvulsants

Carbamazepine Is dosed as normal. However, it is a potent enzyme inducer with multiple interactions, so particular care must be taken post-transplantation.

⚠ **Gabapentin and pregabalin** require *significant* dose reduction, according to GFR, as well as clinical vigilance for evidence of toxicity (confusion, dizziness, ataxia, drowsiness). Both are dialysable (useful in overdose).

The pharmacokinetic behaviour of **phenytoin** is significantly altered in renal insufficiency (→ variable absorption, ↓ protein binding, and ↑ V_d). Modest dose changes may ∴ result in disproportionate side effects. Therapeutic drug monitoring is also more complicated. Many laboratories measure total drug (i.e. protein-bound and unbound). However, the proportion of free drug may be higher, so total levels are often misleading. Cautious dose titration and clinical correlation are required. Measurement of free drug levels may be available. ⚠ Phenytoin is also a potent enzyme inducer, with several important drug interactions.

Valproate is not significantly renally excreted and has fewer interactions. However, changes to the protein binding may cause increased sensitivity.

Levetiracetam, topiramate and vigabatrin undergo significant renal excretion, and dose modification is required. **Lamotrigine** has metabolites that are renally excreted and should be used with caution.

Opioid analgesics (▶▶ see also 📖 p. 271)

- Opioid analgesics have metabolites with variable activity and dependence on renal excretion.
- Cautious titration is necessary. ▶ However, this should be an excuse for the habitual undertreatment of pain in patients with CKD.
- Metabolite accumulation → prolonged action and potential CNS toxicity (⚠ confusion, sedation, respiratory depression, hallucinations, seizures).
 - Morphine metabolism → active and renally cleared metabolites (morphine-3-glucuronide and morphine-6-glucuronide), accumulation of which can be problematic, so morphine is best avoided.
 - Hydromorphone → hydromorphone-3-glucuronide, which does not accumulate significantly.
 - Buprenorphine → relatively inactive biliary excreted metabolites.
 - Codeine → morphine-6-glucuronide accumulation with the inherent problems above.
 - Alfentanil, fentanyl, and oxycodone are relatively safe choices, as they do not have active metabolites.
 - Tramadol → O-desmethyltramadol, which can accumulate in CKD.
- ▶ Naloxone is used for opiate reversal in standard doses. Dialysis may also be helpful in overdose situations.

Drug-related nephrotoxicity

Introduction

The kidneys' role in the excretion of many drugs means that they are particularly vulnerable to drug-related toxicity. High renal blood flow and \therefore high renal drug delivery intensify this. The concentration of a drug in tubular fluid and the medullary interstitium may be many times higher than that in plasma or other tissues.

A variety of renal presentations and syndromes may result from drug toxicity (📖 see Chapter 1, p. 7). This means that the drug history is an absolutely fundamental component of renal medicine.

Antifungals

Amphotericin Is associated with frequent and severe toxicity (>50%). Risk factors: cumulative dose, infusion rate (continuous infusion appears less toxic), pre-existing renal disease, older age, concomitant diuretic use, electrolyte disturbances. Usually causes reversible AKI during treatment. Mechanisms: afferent vasoconstriction and increased tubular permeability. Prevention: adequate hydration, continuous infusion, correct electrolyte imbalances. Liposomal formulations appear less nephrotoxic (if significantly more expensive). Distal renal tubular acidosis and urinary Mg^{2+} and K^+ wasting may also occur. $\downarrow K^+$ is common and often significant, requiring replacement. Note: beware the difference in doses across the different formulations.

Antiviral therapy

Aciclovir, valaciclovir, famciclovir, ganciclovir and valganciclovir May crystallize in renal tubules, causing reversible AKI, particularly in the setting of volume depletion and after IV bolus administration. Urine microscopy reveals birefringent crystals under polarized light (and haematuria). \triangle All require significant dose reduction in renal impairment and are freely dialysed (📖 Table 12.2).

Cidofovir Causes reversible dose-dependent toxicity through the induction of proximal tubular apoptosis (\rightarrow proteinuria, \downarrow GFR, interstitial nephritis, Fanconi syndrome, nephrogenic DI). Administer with hydration. Co-administration of probenecid has been used to slow renal tubular excretion and ameliorate toxicity.

Foscarnet Frequently causes AKI, especially if given to volume-depleted patients. Pre-hydrate.

Indinavir Is only poorly soluble at urine pH 5.5–7.0. Precipitation causes crystalluria and tubular obstruction (\rightarrow dysuria, haematuria, renal colic, flank pain, and significant renal impairment). Stones (radiolucent) may form. Pre-hydrate.

Ritonavir Can cause reversible AKI, particularly in patients with pre-existing renal insufficiency.

Tenofovir A reverse transcriptase inhibitor, has been associated with a proximal tubulopathy.

Chemotherapeutic drugs

Anti-cancer drugs are often given at high dose and have a relatively narrow therapeutic index. Toxic effects include AKI, CKD, tubular dysfunction, and thrombotic microangiopathy.

Methotrexate Is primarily renally excreted and requires a dose reduction, according to GFR. Renal toxicity is rare with chronic low-dose administration (e.g. rheumatoid arthritis) but more common with high-dose regimens (e.g. cancer treatment). Best avoided if GFR <30mL/min. Removed by HD (Δ but not CAPD). Intrarenal drug precipitation causes tubular obstruction (→ ATN and AKI). The administration of the recombinant bacterial enzyme carboxypeptidase (glucarpidase) can reduce toxic serum levels when renal impairment compromises clearance.

Cisplatin Toxicity can restrict its clinical utility. Multiple mechanisms are involved (→ vasoconstriction, ↑ proinflammatory cytokines, tubular cell necrosis and apoptosis). Renal impairment may persist and progress despite cessation of therapy. Usually avoided if pre-existing renal disease. Other presentations: ↓ Mg²⁺, ↓ Ca²⁺, tubular proteinuria, and (rarely) TTP. Prevention: hydration; maintain good urine output; use modified daily dosing regimens, and restrict cumulative dose. Carboplatin is considered less nephrotoxic and may be preferred in many situations.

Cyclophosphamide and ifosfamide May cause haemorrhagic cystitis (prevention: hydration and concomitant Mesna administration). Also: irreversible tubular toxicity (including Fanconi syndrome).

Mitomycin and gemcitabine Have been associated with severe thrombotic microangiopathy.

Immunomodulation therapy

Intravenous immunoglobulin (IVIg) Is generally well tolerated, but AKI can result from toxic tubular effects of carbohydrates in many formulations (→ cell vacuolization and swelling → progressive luminal obstruction). Diabetes and pre-existing renal disease appear to be risk factors. Prevention: avoid sucrose-containing products, slow infusion rate, adequate hydration.

Interferon alfa Causes proteinuria (~25%) and ↑ SCr (~10%). A variety of glomerular lesions, including minimal change disease and crescentic GN, have been described. TTP also reported. Δ In addition, interferons can upregulate the expression of class II histocompatibility antigens, provoking rejection of transplanted organs.

Calcineurin inhibitors (CNIs)

Ciclosporin and tacrolimus are widely used in transplantation, glomerular disease, and inflammatory disorders. Both are associated with important nephrotoxicity.

Acute toxicity

- Haemodynamically mediated and reversible.
- Often no structural damage.
- Responds to dose adjustment or drug withdrawal.
- Presents as an asymptomatic ↑ SCr (even where serum level is in the desired therapeutic range). This can mimic rejection in transplant recipients, triggering further investigation, e.g. a transplant biopsy (📖 p. 416).
- Histology may be normal or reveal indicative tubular changes, such as vacuolization, tubular microcalcification, or giant mitochondria.
- AKI is relatively common in post-heart, lung, and bone marrow transplantation (although is not exclusively 2° to CNIs in this situation).
- CNI-induced thrombotic microangiopathy is an uncommon, but important, syndrome post-transplantation (📖 p. 412).

Chronic toxicity

- Characterized by irreversible and progressive tubulointerstitial fibrosis.
- Fibrosis typically a 'striped' pattern from the medulla to the cortical medullary rays. Degenerative afferent arteriolar changes may be present.
- In non-renal transplantation, CNIs are linked to the development of CKD, e.g. ESRD occurs in ~1–8% of cardiac transplant recipients.
- Nephrotoxicity may increase with concurrent use of mTOR inhibitors, e.g. sirolimus, everolimus.
- Prevention:
 - Therapeutic drug monitoring. Tacrolimus trough concentrations (C_0) correlate well with overall drug exposure (AUC) and are used to monitor therapy.
 - 🗨️ Debate remains surrounding the optimal way of monitoring ciclosporin levels. C_0 , C_2 (2 hours post-dose), and AUC_{0-4} (multipoint testing from 0–4 hours) are all in clinical use.
 - Avoid concomitant nephrotoxins.
 - Be cautious with drugs that inhibit cytochrome P450 liver microsomal enzymes and ↑ CNI levels (e.g. ketoconazole, fluconazole, erythromycin, clarithromycin, verapamil, diltiazem).
 - Drugs that induce cytochrome P450 and ↓ CNI levels include carbamazepine and rifampicin.

Herbal medicines

Herbal medicines, often dispensed in an unregulated manner, are a ubiquitous part of healthcare provision in many developing countries, and their use in the developed world has expanded considerably (see Table 12.3). The kidney is the primary route of excretion for many such compounds, and their potential for nephrotoxicity is increasingly recognized. The true global incidence of CKD related to the ingestion of herbal remedies is currently unknown but could be very significant. When suspected, reporting is desirable.

Causes of toxicity

- Consumption of herbs known to have toxic potential.
- Consumption of herbs with unknown, or underappreciated, toxicity.
- Incorrect identification → inadvertent ingestion of a toxic herb.
- Deliberate or accidental contamination of herbal products, e.g. NSAIDs or heavy metals (such as cadmium).
- Interaction with prescribed drugs.

Table 12.3 Clinical syndromes and associated herbal medicines

Clinical syndrome	Example
AKI	<i>Securida longe pedunculata</i> , <i>Euphoria matabelensis</i> , <i>Callilepis laureola</i> (African medicines) <i>Taxus celebica</i> (yew tree) Tung Sheuh pills (containing mefenamic acid)
CKD	<i>Aristolochia</i> spp. (p. 583), <i>Fucus vesiculosus</i> (bladder wrack), <i>Larrea tridentate</i> (chapparal)
Tubular dysfunction	<i>Aristolochia</i> spp. (p. 583), cadmium contamination
Electrolyte disturbances	↓ K ⁺ : <i>Glycyrrhiza glabra</i> (liquorice) ↑ K ⁺ : <i>Medicago sativa</i> (alfalfa), <i>Taraxacum officinale</i> (dandelion)
Hypertension	<i>Glycyrrhiza glabra</i> (liquorice)
Renal stone disease	<i>Ephedra sinica</i> (ma-huang) <i>Vaccinium macrocarpon</i> (cranberry → oxalate)
Papillary necrosis	<i>Salix daphnoides</i> (willow bark → salicylate)
Urothelial cancer	<i>Aristolochia</i> spp. (p. 583)

NSAIDs and the kidney

Mechanism of action

NSAIDs inhibit the cyclo-oxygenases (COX), an enzyme family critical for prostaglandin synthesis. There are at least two COX isoforms: most NSAIDs inhibit both, but COX-2 inhibitors (the ‘-coxib’ family) are selective for COX-2 (☞ and ∴ possibly cause fewer GI side effects).

Side effects

Potent anti-inflammatory and analgesic properties make these drugs amongst the most ubiquitous in the world. Adverse effects include:

- Renal toxicity (☞ see below).
- GI side effects: dyspepsia, ulceration, and small and large bowel toxicity.
- Cardiovascular: ↑ risk of CV disease and ↑ BP (☞ COX-2 > non-selective NSAIDs).
- Bronchospasm.
- Liver toxicity: abnormal LFTs (although serious liver failure is rare).
- Antiplatelet effects (↓ thromboxane A₂ production). Beneficial when aspirin is given to modify CV risk but a potential adverse effect in other situations.

Renal toxicity

- ► NSAIDs should generally be avoided in the presence of either AKI or CKD, except in very select and carefully monitored situations.
- ⚠ NSAIDs are a very significant cause of hospital-based AKI.
- NSAIDs and renal haemodynamics:
 - NSAIDs have only a marginal effect on renal haemodynamics when kidney function is normal.
 - However, when renal blood flow is impaired, they abolish prostacyclin- and prostaglandin E₂-mediated compensatory afferent arteriolar vasodilation, causing reduced glomerular perfusion.
 - Clinically relevant situations include: pre-existing CKD, CCF, sepsis, nephrotic syndrome, hypovolaemia, concomitant ACE-I/ARB use, concomitant gentamicin or other nephrotoxin use, increasing age.
- NSAIDs also ameliorate the antagonistic effect of prostaglandins on ADH action. This antidiuretic effect can cause salt and water retention, ↑ BP, and blunt the action of diuretics.
- Many of the renal effects of NSAIDs are mediated by COX-2, so COX-2 inhibitors appear equally nephrotoxic.
- ⚠ In general, always beware claims of more ‘renal friendly’ NSAIDs, as there is limited supporting evidence.
- Other NSAID-induced renal lesions:
 - Important cause of acute interstitial nephritis (☞ p. 580).
 - Chronic interstitial nephritis (and ∴ CKD) with long-term use.
 - Analgesic nephropathy (☞ p. 584).
 - Nephrotic syndrome: particularly minimal change disease and membranous GN (☞ p. 564).
 - Papillary necrosis (☞ p. 585).
 - Electrolyte disorders ↓ Na⁺, ↑ K⁺, acidosis.

Sulfasalazines

- Sulfasalazine is 5-aminosalicylic acid (5-ASA) coupled to a carrier sulfapyridine molecule that assists GI absorption.
- 5-ASA shares structural similarities with aspirin.
- Second-generation sulfasalazines (e.g. mesalazine) were designed to minimize troublesome haematological side effects.
- Such agents are effective and important treatments for inflammatory bowel disease (IBD).
- There has been significant historical concern regarding an association with acute interstitial nephritis.
- However, available data suggest this is actually relatively uncommon. Case control data from a UK primary care database suggested an adjusted odds ratio for renal disease of 0.86 for current 5-ASA users and 2.48 for recent users. Mesalazine and sulfasalazine appeared to carry comparable risks. Causality was unclear in the majority of cases.
- What is more important is to keep in mind that patients with IBD are at increased risk of renal disease, in general. In addition to 5-ASA toxicity, the differential of renal impairment in patients with IBD includes:
 - Glomerulonephritis (e.g. membranous GN).
 - Amyloidosis.
 - Oxalate stone disease.
- If suspected, acute interstitial nephritis usually requires a diagnostic renal biopsy for confirmation.

In summary, all patients with active IBD are at higher risk of renal dysfunction and should have their renal function and urinalysis checked intermittently. This is particularly true of those treated with 5-ASA derivatives, who should have their renal function monitored every ~3–6-monthly.

Lithium and the kidney

Introduction

- Lithium is a very effective treatment for uni- and bipolar affective disorders, allowing many patients to stabilize their symptoms and enjoy an excellent quality of life.
- Lithium clearance mirrors that of Na^+ : it is freely filtered at the glomerulus and predominantly reabsorbed in the proximal tubule. ~20% is excreted unchanged in the urine.
- Accumulation can occur in principal cells of the collecting duct, particularly if GFR falls (\rightarrow hypovolaemia, concomitant diuretics, NSAIDs, or ACE-I).
- Long-term exposure can cause tubular atrophy, tubular cyst formation, progressive interstitial fibrosis, and, eventually, glomerulosclerosis.
- Lithium has a narrow therapeutic window, and therapeutic drug monitoring is mandatory. The goal should be the lowest serum concentration that maintains adequate control of affective symptoms (e.g. 0.4–0.8mmol/L). Once-daily dosing regimens appear to have less potential to cause toxicity.
- Renal damage is related to both the average serum lithium concentration and cumulative dose.
- Any patient receiving lithium should have their renal function measured 6–12-monthly.

Toxic effects

Renal

- Nephrogenic diabetes insipidus (📖 p. 789).
 - Lithium causes ADH resistance (\downarrow aquaporin-2 expression).
 - ~50% of patients have impaired urinary concentrating ability and ~25% develop polyuria and polydipsia (although these do not generally require cessation of treatment).
 - Amiloride can be used to \downarrow urine volumes in this situation, as it blocks lithium uptake through the collecting duct epithelial Na^+ channel (ENaC).
 - Δ Thiazides may \uparrow toxicity through both volume contraction and \uparrow Na^+ and lithium reabsorption in the proximal tubule.
- Lithium use is a rare cause of hypercalcaemia (and mild hypermagnesaemia), which may further perpetuate renal damage.
- Chronic interstitial damage:
 - Leads to progressive CKD.
 - Uncommon, although the true incidence is difficult to ascertain, as patients may have non-lithium-related causes of CKD. Kidney biopsies are often not undertaken—or reveal non-specific, non-diagnostic change only.
 - Histological clues: microcytic change in distal tubules, with only limited interstitial inflammation or vascular change.
 - The mechanism of renal damage is unclear, but tubular cell uptake with impairment of cell proliferation appears important.

- Once established, drug withdrawal may not stabilize renal function.
- Diagnosis does not necessarily mandate lithium withdrawal. Many patients will prefer to remain on lithium, rather than risk destabilization of their symptoms, particularly if their GFR is declining slowly. Careful individual assessment and explanation are necessary.

Other

- GI disturbance.
- Goitre and thyroid dysfunction.
- Neurological including tremor and cognitive impairment.

Treatment of acute lithium intoxication

- Complications:
 - Common: tremor, thirst, polyuria, diarrhoea, and vomiting.
 - More severe: ↓ GCS, hypertonia, seizures, focal neurological signs, cardiac arrhythmias, ↓ BP.
- Investigations:
 - Serum lithium concentration.
 - U&E, SCr.
- Management:
 - Protect airway and monitor cardiac rhythm.
 - Consider gastric lavage if early presentation post-ingestion (1h).
 - No role for activated charcoal.
 - Fluid-resuscitate: correct hypovolaemia using 0.9% NaCl ± 0.45% NaCl (if hypernatraemic).
- Haemodialysis (📖 p. 906):
 - Effectively removes lithium.
 - Use high pump speed and large membrane for 4–6h.
 - Indications for haemodialysis:
 - Lithium level >3.5mmol/L.
 - Lithium level >2mmol/L with severe symptoms ± ↓ GFR.
- Rebound is common, as lithium moves from the intracellular to extracellular space.
- Recheck lithium concentration after 6h, and repeat dialysis treatment, as necessary.

Dialysis treatment of poisoning

Introduction

Although rarely necessary (0.05% of all cases), dialysis can be an effective way to treat drug overdoses and toxicity. Standard supportive measures for poisoning must still always be undertaken.

Indications

- The poison (or its toxic metabolites) is removed by dialysis. Favourable characteristics:
 - Low MW (<500Da).
 - Relatively low protein binding.
 - Small volume of distribution (i.e. confined to plasma volume).
 - Water-soluble.
- Severe toxicity.
- Elimination is quicker via dialysis, or native clearance is impaired (e.g. renal or hepatic impairment is present).

Examples

Methanol and ethylene glycol (📖 pp. 910–912), lithium (📖 p. 904), aspirin (salicylic acid) (📖 p. 908), theophylline, barbiturates, antibacterials, antivirals, star fruit poisoning (*Averrhoa carambola*).

Techniques

Haemodialysis

- The goal is to remove as much of the drug/toxin as possible.
 - Use a high efficiency dialyser with a large surface area (>1.5m²).
 - High pump speeds; blood flow >300mL/min.
 - Long treatment (4–8 hours).
- Complications:
 - The patient often does not have renal impairment, so 'overcorrection' of electrolyte imbalances may occur.
 - ↓ PO₄ may occur and require correction (phosphate is not present in standard dialysate solutions).
 - ↓ K⁺.
 - Metabolic alkalosis.

Haemofiltration

- Haemofiltration is less effective than HD for drug and toxin elimination but is often the only technique immediately available. Haemodiafiltration improves clearance and is the preferred continuous technique.

Peritoneal dialysis

- PD is less efficient and rarely used in this context.

Haemoperfusion

- Involves circulation of blood through an extracorporeal circuit, containing an adsorbent (activated charcoal, carbon, or a polystyrene resin).
- Requires a similar circuit to HD, but without dialysate, and generally with the adsorbent contained within a cartridge. The circuit requires anticoagulation with heparin.
- Haemoperfusion can eliminate protein-bound and lipophilic drugs and toxins (e.g. phenytoin, digoxin, and paraquat).
- Complications: hypocalcaemia, hypoglycaemia, leucopenia, thrombocytopenia.
- Less widely available than dialysis or filtration.

Salicylate poisoning

Introduction

Salicylate poisoning remains relatively common. In addition to aspirin (acetylsalicylic acid), methyl salicylate is present (in large amounts) in oil of wintergreen preparations used topically for musculoskeletal ailments.

After absorption, salicylate is rapidly converted to salicylic acid. In overdose, absorption may be delayed >4–6h as a consequence of pylorospasm, delayed gastric emptying, tablet clumping, or the ingestion of extended-release formulations.

Salicylate handling

Under normal circumstances it is highly protein-bound (>90%) and undergoes hepatic metabolism to salicylic acid, which is both less toxic and more rapidly excreted by the kidney than salicylate. Only a small amount is excreted unchanged by the kidneys. However, in overdose, protein binding falls; liver conjugation pathways are saturated, and renal excretion (via the anion secretory pathway in the proximal tubule) becomes more important. Drug $t_{1/2}$ increases from ~2–4h to >20h.

Salicylate actions

- Medullary trigger zone stimulation → nausea and vomiting.
- Medullary respiratory centre stimulation → hyperventilation.
- Cyclo-oxygenase inhibition → ↓ prostaglandin, ↓ prostacyclin, and ↓ thromboxane synthesis (→ platelet dysfunction and gastric injury).
- Cellular injury → disturbed metabolism (including oxidative phosphorylation) → metabolic acidosis.

Acid–base considerations

- An assortment of acid–base disturbances are possible, following salicylate overdose:
 - Direct salicylates stimulation of the respiratory centre → hyperventilation → initial ↓ $p\text{CO}_2$ → respiratory alkalosis.
 - Accumulation of organic acids (including lactic acid and keto-acids) → ↑ anion gap → metabolic acidosis.
 - Salicylate itself has an insignificant effect on pH, as serum concentrations are relatively low.
 - A 1° respiratory acidosis is unusual and indicates severe poisoning (Δ or the co-ingestion of a respiratory depressant).
 - Most patients present with either a 1° respiratory alkalosis or mixed 1° respiratory alkalosis and 1° metabolic acidosis.

Symptoms and signs

- May correlate poorly with serum levels (esp. in the elderly):
 - Nausea, vomiting, diarrhoea, epigastric pain.
 - ↑ RR.
 - Tinnitus, vertigo, blurred vision,

- Agitation, swearing, tremor, confusion, seizures, respiratory depression, coma, hyperthermia, cerebral oedema (esp. if severe acidosis → salicylate crosses the blood–brain barrier more easily if non-ionized).
- Non-cardiogenic pulmonary oedema (↑ vascular permeability), arrhythmias.

▶▶ Treatment of salicylate poisoning

- Monitor in HDU setting.
- O₂ as required.
- Investigations: U&E (↑ or ↓ K⁺, ↓ HCO₃⁻), ABG (2–4-hourly), lactate, glucose (hypoglycaemia common), LFT, FBC (GI bleeding is rare), ↑ INR, ECG, and CXR (pulmonary oedema).
- Salicylate level every 2h until falling:
 - Therapeutic level are <300mg/L (<2.2mmol/L).
 - Moderate toxicity 500–750mg/L (3.6–5.4mmol/L).
 - Severe overdose >750mg/L (>5.4mmol/L).
- Exclude other drug ingestions (Δ paracetamol and respiratory depressants, such as benzodiazepines).
- Gastric lavage if presenting within 1h of ingestion. Later if delayed gastric emptying suspected.
- Activated charcoal (50g × 3 at 4-hourly intervals) may be effective.
- Optimize fluid status:
 - Aim for urine output >100mL/h.
 - Alkalinize the urine (salicylate is more soluble at ↑ pH). Give NaHCO₃ 1.26% IVI (e.g. 1L over 4h, repeated, as necessary, with regular clinical assessment of fluid status) until urine pH >7.5–8.5.
 - Metabolic alkalosis is not a contraindication to bicarbonate administration.
 - IV glucose (e.g. 20% glucose) if any neurological signs, including confusion, even if blood glucose is normal (salicylates → neuroglycopenia).
- Recheck K⁺ 2–4-hourly. Correct hypokalaemia, if present (allows more effective urinary alkalinization).
- Dialysis:
 - Effectively removes salicylate.
 - Indications: renal impairment, poor urine output, pulmonary oedema (non-cardiogenic or volume overload), deteriorating neurological signs, cerebral oedema, progressive acidosis despite adequate medical management, salicylate level >700mg/L (>5.1mmol/L).
 - Use high pump speeds and a large dialyser for 4–6h.
 - Continue to monitor salicylate level after dialysis (e.g. at 2h).
 - Repeat dialysis treatment may be required if levels rebound (2° to delayed salicylate absorption).

Ethylene glycol poisoning

Introduction

- Ingestion of ethylene glycol (EG) is usually 'accidental' when imbibed as an ethanol substitute. It is widely used in antifreeze and solvents.
- EG is rapidly absorbed and metabolized in the liver (by alcohol dehydrogenase) to glycolaldehyde, then to various acids (including glycolic, glyoxylic, and oxalic). Ingestion of just 50–100 mL can be lethal.
- These acids are responsible for EG toxic effects.
 - Glycolic acid is cleared by the kidney and is the dominant cause of the anion gap acidosis, characteristic of severe cases.
 - Tissue calcium oxalate monohydrate crystals are the cause of cerebral oedema and renal failure.
- Concomitant ethanol ingestion will be protective by blocking the metabolism of glycol to toxic metabolites.

Symptoms and signs

⚠ Patients may not admit to ingestion and can present in any of the following stages.

- **Stage 1 (30min–12h):** inebriation, although often no alcoholic feter, nausea and vomiting, convulsions (may be focal), nystagmus, ataxia, visual disturbance, ophthalmoplegia, papilloedema, hypotonia, hyporeflexia, myoclonic jerks, cranial nerve palsies, altered conscious level, coma. Metabolic acidosis (with ↑ AG).
- **Stage 2 (12–24h):** ↑ RR, tachycardia, ↑ BP, pulmonary oedema.
- **Stage 3 (24–72h):** flank pain, renal tenderness, AKI, ↓ Ca²⁺, crystalluria (calcium oxalate), ↑ K⁺, ↓ Mg²⁺.

Investigations

- **ABG:** ↑ AG metabolic acidosis with respiratory compensation (mainly glycolic acid, but lactate may contribute). Lactate may also be spuriously high, as many analysers report an elevated glycolate as lactate. ► The degree of acidosis correlates with tissue injury and outcome.
- **Ethylene glycol level:** may be normal if ingestion >12h prior to measurement. >500mg/L (8mmol/L) indicates severe toxicity. Check ethanol, methanol, and isopropyl alcohol levels if suspected co-ingestion.
- **Other:** U&E, Ca²⁺, FBC (↑↑ WCC). LFTs, paracetamol, and salicylate levels (⚠ beware co-ingestion), urine microscopy for crystals (needle-shaped calcium oxalate monohydrate). If undertaken, a renal biopsy would show widespread tubular crystal deposition with ATN.
- **Osmolality and anion gap:** measured serum osmolality is raised, but calculated osmolality ($[2 \times \text{Na}^+] + \text{urea} + \text{glucose}$) is often normal. The difference between the two is termed the osmolar gap (often >10mOsmol/kg). This develops as patients absorb glycol over the first few hours post-ingestion. Subsequently, as glycol is metabolized to acids, the osmolar gap falls—while the anion gap increases and systemic acidosis worsens. ⚠ Other toxic alcohols also raise the osmolar gap.

Management

- Gastric lavage if <1h since ingestion.
- If within 12h of ingestion, administer *fomepizole* (4-methylpyrazole).
 - Competes with EG for alcohol dehydrogenase, preventing rapid accumulation of toxic metabolites (8,000× greater affinity than ethanol). It is relatively easy to use.
 - Loading: 15mg/kg IVI in 100mL normal saline over 30min.
Maintenance: 12-hourly doses of 10mg/kg (increase frequency 4h if dialysis is required—fomepizole is dialysable). The dose is increased to 15mg/kg 12h after 48h treatment.
 - Continue until acidosis has resolved and EG level <200mg/L (<3.2mmol/L), or preferably undetectable.
- If fomepizole is not available, then administer *ethanol*.
 - Ethanol is much more difficult to use: ⚠ intoxication and respiratory depression.
 - Give IVI as a 10% solution in 5% glucose, e.g. remove 50mL from a 500mL bag of glucose, and replace with 50mL absolute ethanol.
 - Loading dose: 7.5mL/kg of 10% solution.
 - Maintenance: 1mL/kg/h for non-drinkers (2mL/kg/h for drinkers).
 - Titrate to a plasma ethanol level of ~1g/L (22mmol/L).
- *Haemodialysis* effectively removes EG and metabolites. Discuss in all cases, and refer without delay if:
 - Renal failure, oliguria, severe acidosis.
 - End-organ dysfunction, e.g. neurological signs.
 - Plasma level >500mg/L (8mmol/L).
- Adjunct therapies include:
 - NaHCO₃ 1.26% IVI infusion to correct acidosis.
 - Maintain high urine flow rate to minimize risk of crystal deposition.
 - Thiamine, pyridoxine, and other co-factors (e.g. as Pabrinex® IV).

Methanol

Present in methylated spirits, contaminated alcoholic drinks, and many varnishes. Metabolized by alcohol dehydrogenase (\rightarrow formaldehyde \rightarrow formic acid).

Symptoms and signs Presentation may be delayed until 24h after initial intoxication resolves. Nausea, vomiting, confusion, headache, abdominal pain (pancreatitis), seizures (► check blood sugar), ↓ GCS and visual disturbance (retinal oedema and optic nerve demyelination \rightarrow ↓ acuity, photophobia, 'snow storm' vision). Late: white matter haemorrhage (\rightarrow parkinsonism).

Investigations U&E, SCr, CK (Δ rhabdomyolysis), amylase (\uparrow in ~60%), glucose (hypoglycaemia common), serum osmolality, ABG. Peak methanol level $>0.2\text{g/L}$ (6.25mmol/L) represents significant ingestion, and $>0.5\text{g/dL}$ (15.6mmol/L) indicates severe intoxication.

Management Supportive care, administer fomepizole or ethanol if level $>0.2\text{g/dL}$ (6.25mmol/L), high osmolar gap ($>10\text{mOsm/kg}$), or metabolic acidosis ($\text{pH} < 7.3$).

Haemodialysis Refer if renal failure, visual impairment, metabolic acidosis, or methanol level $>0.5\text{g/L}$ ($>15.6\text{mmol/L}$).

Renal physiology

Renal structure and function 914

The glomerulus 916

Regulation of GFR 920

Tubular function: overview 922

The proximal convoluted tubule 924

The loop of Henle 926

The loop of Henle: the countercurrent system 928

The distal nephron 930

Renal structure and function

Kidney structure

- The functional unit of the kidney is the nephron (see Fig. 13.1).
- Each kidney contains ~1 million nephrons.
- There are five parts to the nephron (see Fig. 13.1):
 - The glomerulus, which acts as the blood–kidney interface. Plasma is filtered from capillaries into Bowman’s capsule before heading off down the nephron.
 - The proximal convoluted tubule where most of the filtered load is reabsorbed (~60%).
 - The loop of Henle, which is able to concentrate urine because of the high osmolality of the surrounding medullary interstitium. This high concentration of solutes is maintained by the countercurrent multiplier system.
 - The distal convoluted tubule, which ‘fine-tunes’ solute and water reabsorption.
 - The collecting system is formed by the convergence of several nephrons to create a collecting duct. These progressively amalgamate, as they cross the medulla, until opening into papillary ducts in the renal pelvis.
- There are two types of nephrons, those localized to the cortex and those extending into the medulla, the latter characterized by longer loops of Henle and additional metabolic activity.
- Renal blood supply:
 - Renal artery → renal sinus → interlobar arteries (occupy the space between the renal pelvis and adjacent cortical tissue) → divide at the corticomedullary junction → branching arcuate arteries → interlobular arteries (traverse the cortex).
 - No arteries penetrate the medulla.
 - The kidneys are unique for possessing two capillary beds in series. The glomerular capillaries are maintained at the high pressure required for filtration. Peritubular capillaries are low pressure. This arrangement allows for large volumes of fluid to be filtered and reabsorbed.

Functions of the kidney

- Glomerular filtration rate (📖 p. 30):
 - This refers to the filtrate of plasma crossing the glomerular barrier into the urinary space per unit time across all functioning nephrons (usually expressed in mL/min).
- Tubular function:
 - The renal tubules reabsorb ~99% of the glomerular filtrate, enabling them to regulate electrolyte excretion and to concentrate or dilute urine, according to physiological circumstances.

Production of urine

- The production of urine is the result of three processes within the kidney:
 - Glomerular filtration.
 - Selective and passive reabsorption within the renal tubules.
 - Excretion from the distal nephron into the urinary tract.
- Acid–base regulation (📖 p. 818).
 - The kidneys and lungs work together to maintain an arterial pH of 7.35–7.45. The lungs excrete CO_2 . The kidneys: (i) prevent HCO_3^- loss; (ii) excrete H^+ ; and (iii) buffer urinary H^+ .
- Endocrine functions:
 - Renin: produced by specialized cells within the juxtaglomerular apparatus (📖 p. 456).
 - Erythropoietin: produced by the peritubular interstitial fibroblasts in the outer medulla and deep cortex (📖 p. 218).
 - The kidneys are also an important site of action of several hormones, e.g. aldosterone (promotes Na^+ reabsorption), ANP (promotes Na^+ loss), and ADH (increases distal tubular permeability, allowing urinary concentration).
- Autocrine function:
 - Production of NO, endothelins, prostaglandins, natriuretic peptides.
- Protein and polypeptide metabolism, e.g. metabolism of insulin.

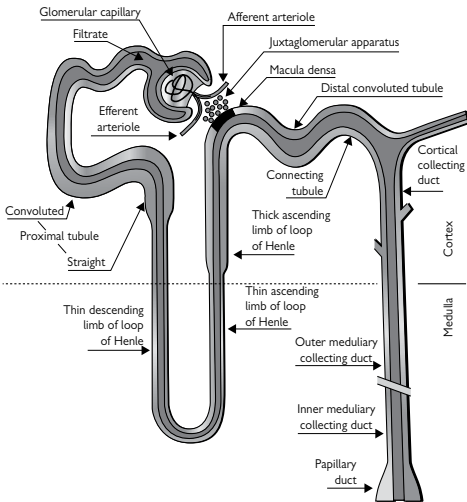


Fig. 13.1 The geography of the nephron. Reproduced from O'Callaghan, C (2009). *The Renal System at a Glance*, 3rd edn. With permission from Wiley-Blackwell.

The glomerulus

Introduction

The glomerulus is at the start of the nephron and provides the first step in filtering the blood to form urine. The glomerulus comprises a tuft of specialized capillaries attached to the mesangium, both of which are enclosed in a pouch-like extension of the tubule called Bowman's capsule. Bowman's capsule is a pocket of epithelial cells in continuity with the epithelial cells of the proximal convoluted tubule (PCT). Blood is filtered through the capillaries of the glomerulus into Bowman's capsule, and it can then start its journey down the remainder of the nephron (see Fig. 13.2).

Bowman's capsule contains:

Capillaries

A knot of capillaries lined by endothelial cells. Blood flows in via the afferent arteriole and out via the efferent arteriole (for a capillary bed to have arterioles on both ends is unique in the circulation). Changes in afferent and efferent arteriolar tone are powerful ways of regulating blood flow and pressure within the glomerulus (p. 920). The capillary endothelium contains large fenestrae. This renders it considerably more permeable (~100×) than most capillary beds. A strong ionic glycocalyx helps with charge selection.

The glomerular basement membrane (GBM)

The GBM is a non-cellular layer, consisting mainly of glycoproteins (esp. type IV collagen), sialoglycoproteins (e.g. laminin, fibronectin), proteoglycans (e.g. heparin sulfate). It is manufactured mainly by podocytes and is the principal filtration barrier. On electron microscopy, it consists of three layers: the lamina interna, lamina densa, and lamina externa.

Epithelial cells (podocytes)

Podocytes are specialized epithelial cells that produce the components of the GBM (under cytokine control). They have specially adapted foot processes (hence the name 'podocyte') that possess a contractile apparatus. Interdigitating podocytes are separated from each other on the GBM by 'slit diaphragms', which constitute the key mechanical and signalling barrier to filtration. Podocytes produce podocalyxin (a sialoglycoprotein) to form a highly anionic coating that allows charge selectivity. Abnormal podocyte function is considered central to proteinuric nephropathies.

Mesangial cells

Mesangium is the remaining structural component of the glomerulus. Mesangial cells have an important regulatory function. Two main types have been identified; most are derived from a smooth muscle lineage (and respond to similar stimuli). These are situated adjacent to the endothelium (within the GBM) and are active in signalling, recruitment of non-resident cells, and maintenance of vascular tone. Other mesangial cells are derived from macrophages and monocytes and possess phagocytic properties. Mesangial cells are embedded in an extracellular matrix containing collagen IV and V, fibronectin, laminin, and proteoglycans. Mesangial cell activation and proliferation occur in response to immune-mediated glomerular injury.

The glomerular filter

See Figs 13.3 and 13.4.

The glomerular filter is composed of four layers:

- Charged endothelial glycocalyx.
- Endothelial fenestrations.
- The glomerular basement membrane.
- The inter-podocyte slit diaphragm.

The inter-podocyte slit diaphragm offers a mesh of interlocking proteins and lipids, including nephrin, podocin, CD2AP, and podocalyxin.

Podocyte dysfunction (at the heart of many proteinuric nephropathies) impairs both the slit diaphragm and foot process adhesion.

Filtration is principally determined by molecular size and, to a much lesser extent, by charge.

The glomerular barrier is very permeable to water. Substances with a MW <5,000Da are freely filtered (unless albumin-bound in plasma).

Larger molecules are partially filtered, with filtration fraction depending on both size and charge. Negatively charged molecules have a lower filtration fraction than similarly sized cationic molecules.

Albumin (MW 61kDa) is polyanionic and scarcely filtered under normal circumstances. Approximately 70,000g passes through the glomerulus every 24h, of which just 7g (0.01%) appears in the filtrate (and this is usually reabsorbed further down the nephron).

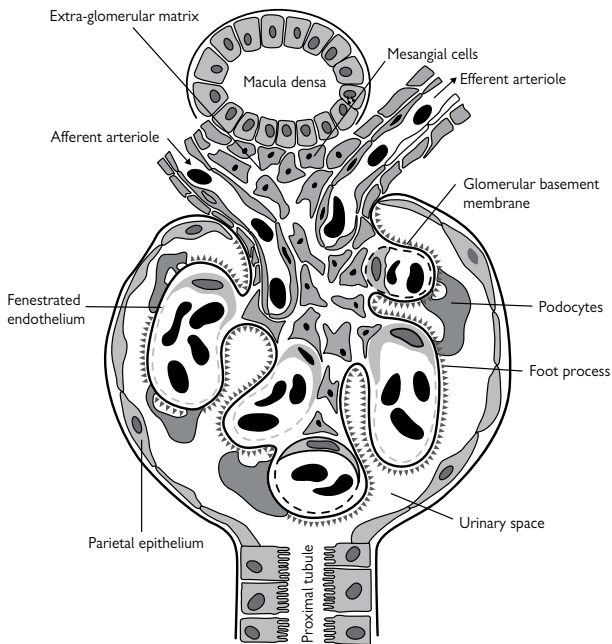


Fig. 13.2 Glomerular structure. Blood enters via the afferent arteriole and leaves via the efferent arteriole. The capillaries have a fenestrated endothelium. The visceral epithelium of Bowman's capsule consists of podocytes, the foot processes of which (with the GBM) cover the capillaries and the mesangium. At the vascular pole, the visceral epithelium reflects into the parietal epithelium, which itself becomes the proximal tubule at the urinary pole. US, urinary space. Reproduced from Fogo, A, Kashgarian, M (2011). *Diagnostic Atlas of Renal Pathology*, 2nd edn. With permission from Elsevier.

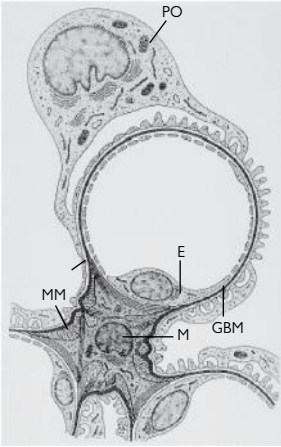


Fig. 13.3 Schematic demonstrating the filtration barrier. The glomerular capillary has a fenestrated endothelium (E). The capillary is surrounded by the GBM, which deviates to cover the mesangial cells (M). The interdigitating foot processes of the podocyte (PO), separated by the slit diaphragm, cover the GBM and form the final barrier to filtration. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P *et al* (eds) (2005). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford, Oxford University Press.

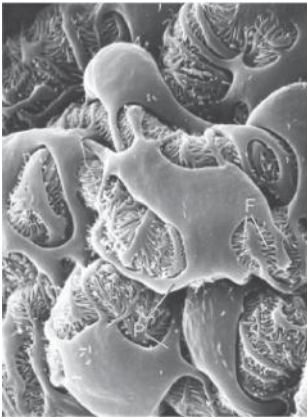


Fig. 13.4 Scanning EM of rat glomerular capillaries. The capillary is covered by branching podocytes. The primary (P) and secondary (F) processes interdigitate, separated by slit diaphragms, and cover the entire surface of the GBM. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P *et al* (eds) (2005). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford, Oxford University Press.

Regulation of GFR

Introduction

GFR is dependent on the net hydrostatic and colloid osmotic pressure gradients between glomerular plasma and the fluid in Bowman's space. This will be determined by:

- Renal blood flow (RBF):
 - Renal blood flow represents 20–25% of cardiac output (1.25L/min). Two to three million nephrons produce an ultrafiltrate of plasma (125mL/min or ~170L/day). Most water and solutes are all reabsorbed into the tubular epithelium.
- Glomerular structure (filtration surface area and permeability).
- Transglomerular capillary pressure (afferent–efferent tone).
- Plasma oncotic pressure.

Physiological regulation

Autoregulation

Preserves renal blood flow and GFR despite variations in systolic BP. Predominantly effected by the afferent arteriole: local stretch receptors quickly adjust afferent arteriolar tone via a 'myogenic reflex'.

Afferent and arteriolar tone

Controls intra-glomerular pressure and flow:

- Increased afferent arteriolar tone (vasoconstriction) leads to *reduced* flow and *reduced* pressure within the glomerulus.
- Increased efferent arteriolar tone (vasoconstriction) leads to *reduced* flow and *increased* pressure within the glomerulus.

Tubuloglomerular feedback

TGF allows tubular flow sensing to change GFR: Cl^- delivery to the juxtaglomerular apparatus is sensed at the macula densa (📖 p. 921). \uparrow distal Cl^- delivery \rightarrow afferent arteriolar vasoconstriction \rightarrow \downarrow GFR (mediators include adenosine, adenosine triphosphate, thromboxane, NO, and A2). The importance (and beauty) of this mechanism can be appreciated if large quantities of Cl^- (and thus Na^+) are pathologically delivered to the distal tubule (e.g. non-oliguric ATN). Through TGF, \downarrow renal blood flow leads to \downarrow GFR, safeguarding against profound diuresis and volume depletion. In other words, TGF basically aims to avoid volume depletion/overload if GFR \uparrow or \downarrow .


Systemic factors

- The sympathetic nervous system (noradrenaline/norepinephrine) is a key mediator of vasoconstriction of the afferent arteriole. Thus, in systemic hypotension (\rightarrow \uparrow sympathetic activity), renal blood flow is reduced (allowing blood to be diverted to the brain and heart). Noradrenaline also stimulates production of renin and A2.
- A2, with its potent vasoconstrictive effects at the efferent arteriole (with much weaker vasoconstrictor effects at the afferent arteriole), will assist in the maintenance of GFR (Δ this is why ACE-I drop

transglomerular capillary pressures). Renin also increases with sodium depletion $\rightarrow \uparrow$ A2.

- Vasodilator prostaglandins (PGE_1 , PGE_2 , and prostacyclin) are also important (Δ hence the need to avoid NSAIDs when renal blood flow is compromised).
- Other factors: endothelins (esp. ET_1) are vasoconstrictors (efferent $>$ afferent). ANP and BNP cause afferent dilatation. NO relaxes both the afferent and efferent arteriole and increases renal blood flow.


The juxtaglomerular apparatus

- The juxtaglomerular apparatus has a regulatory role. It consists of a specialized area of cells that are intimately related to the distal nephron and to the adjacent afferent and efferent arterioles and glomerulus.
- It comprises the macula densa, extra-glomerular mesangium, and arterioles (the last part of the afferent and the first part of the efferent). The macula densa is situated toward the end of the thick ascending limb of the loop of Henle (i.e. in the distal nephron) (see Fig. 13.1).
- The cells of the macula densa are closely packed with large nuclei and attached to a basement membrane that is intimately related to the extra-glomerular mesangium. They contain large amounts of NO and cyclo-oxygenase.
- Modified smooth muscle cells, called granular cells, surround the afferent arteriole. 'Granular' refers to conspicuous cytoplasmic granules containing renin that is ready for exocytosis into the surrounding interstitium. Granular cells have dense sympathetic innervation.
- Tubular Cl^- is sensed in the macula densa as part of tubuloglomerular feedback ( p. 920). This instigates changes in glomerular blood flow and GFR via arteriolar haemodynamics. Renin release is also controlled by this system, although the exact mechanisms are unclear.

Tubular function: overview

Introduction

The tubular epithelium is a single cell layer. The cells have a distinct polarity (determined by their cytoskeleton). Their luminal (apical or tubular) surface is exposed to filtrate and their basolateral surface to interstitial fluid (and capillary beds). Specific transporters are located in the membranes at each of these surfaces. There is a tight junction between cells near the luminal side. Solute and water movement may be passive via paracellular routes (regulated via the tight junction) or active via transcellular routes (regulated via the membrane transporters). This movement may be from tubular fluid to blood (reabsorption) (see Table 13.1) or from blood to tubular fluid (secretion).

The four sections of the renal tubule are described on  p. 914.

Basic concepts

- The tubules:
 - Reabsorb the majority of the filtrate (mainly the proximal convoluted tubule (PCT)). Given that ~180L of plasma is filtered each day, an enormous amount of reabsorption is required.
 - Regulate solute and water balance (PCT, loop of Henle (LH), distal tubule (DT), and collecting ducts (CD)).
 - Regulate acid–base balance (DT and CD).

Table 13.1 Sites of reabsorption of the major ions in the nephron (%)

	Na ⁺	K ⁺	HCO ₃ ⁻	Ca ²⁺
PCT	65	65	80	70
Loop	25	30	10–15	20
DT and CD	0–10	0–5	0–5	10

- Passive transport occurs via:
 - Simple diffusion down a concentration or charge gradient.
 - Carrier-mediated diffusion where a specific membrane carrier assists transport across the cell membrane.
 - A specific membrane channel.
- Active transport refers to an ion being moved against a concentration, or charge, gradient. It requires energy (from enzymatic hydrolysis of ATP). The most important active transporter is the sodium pump (Na⁺ K⁺-ATPase).
- Another example of an active transporter in the tubule is the H⁺ ATPase (excretes H⁺ in the distal nephron).

The sodium pump ($\text{Na}^+ \text{K}^+ \text{-ATPase}$)

- Transfers three Na^+ from inside a cell in exchange for two K^+ (this imbalance means it moves a net positive charge).
- In the kidney, it is found exclusively at the basolateral (capillary) surface of the tubule and plays a prime role in tubular reabsorption.
- It keeps intracellular Na^+ concentration very low (10–30mmol/L) and K^+ concentration very high (~150mmol/L).
- Na^+ will then want to move back into the cell down the electrochemical gradient that has been created—this occurs either through specific sodium channels or via carrier proteins.
- These carrier proteins provide an opportunity for co-transport of other ions into the cell (e.g. K^+ and Cl^-) or countertransport out of the cell (e.g. H^+ and Ca^{2+}) against concentration, or charge, gradients, i.e. to take advantage of the movement of Na^+ .

Glomerulo-tubular balance

The process whereby a change (\uparrow or \downarrow) in GFR is compensated for by a corresponding change in absorption by the rest of the nephron. This prevents changes in the filtered load having major consequences for solute excretion. For example, the amount of sodium reabsorbed in each nephron segment is, in general, proportional to the amount of sodium delivered to that segment. The mechanisms underlying this are poorly understood.

The proximal convoluted tubule

Introduction

- The PCT reabsorbs the bulk of sodium, chloride, bicarbonate, glucose, amino acids, urate, water (~60%), and low molecular weight proteins (e.g. β 2 microglobulin). Appreciable amounts of Ca^{2+} and PO_4 are also reabsorbed here (see Table 13.1).
- It is not homogenous—it consists of two parts, a convoluted (cortical) section and a straight (medullary section).
- The 'average' PCT is ~14mm long and offers a large surface area (due to the villous-like arrangement at the apical surface of epithelial cells). The normal kidney contains around 1,000,000 glomeruli; this equates to a potential surface area for reabsorption of $>50\text{m}^2$.
- The PCT is rich in mitochondria.
- The PCT is able to reabsorb up to 65% of the 24,000mmol of Na^+ and 180L of water filtered per day.

Sodium and chloride

- In the early part of the PCT, most sodium is reabsorbed via specific transporters (see Fig. 13.5), coupled with absorption of glucose and organic molecules.
- A further transporter exchanges Na^+ with H^+ ions.
- The energy for these processes comes from the sodium gradient into the cell, itself generated by the $\text{Na}^+ \text{K}^+$ -ATPase (p. 923).
- The gap junctions between epithelial cells are slightly leaky, so the PCT is highly permeable to water.
- In the early PCT, chloride (an excess is generated when sodium is absorbed with other anions or molecules) is reabsorbed via the paracellular route.
- Further along the PCT, Na^+ and H^+ are exchanged, while Cl^- is exchanged for another base (e.g. formate, bicarbonate, oxalate) (see Fig. 13.6). The base and H^+ are then reabsorbed, so the net result is reabsorption of NaCl .
- Cl^- leaves the cell in exchange for K^+ or via specific chloride pumps.

Potassium

In this area of the nephron, K^+ is mostly reabsorbed down a concentration gradient via the paracellular space.

Bicarbonate (see also p. 818)

The PCT reabsorbs 90% of filtered HCO_3^- but does not acidify the urine. HCO_3^- reabsorption is accomplished by means of H^+ secretion. Dissociation of carbonic acid (H_2CO_3) within epithelial cells yields an H^+ ion that enters the filtrate via the Na^+/H^+ exchanger in the luminal membrane (see Fig. 13.5). The H^+ combines with HCO_3^- in the filtrate to form carbonic acid, which is rapidly converted to CO_2 and H_2O by carbonic anhydrase. This recycling of H^+ means there is no net acid excretion at this point. CO_2 enters the cell by simple diffusion and is converted back to carbonic acid to start the cycle again. Within the cell, the HCO_3^- generated from carbonic acid dissociation leaves via the basolateral surface in exchange for Cl^- or in association with Na^+ .

Calcium

Mainly paracellular reabsorption across the tight junction down a concentration (and charge) gradient.

Phosphate

Co-transported into the cell along with Na^+ . ► Inhibited by PTH—meaning that PTH is phosphaturic.

Glucose, amino acids

Both are co-transported into the cell along with Na^+ . The sodium-glucose co-transporter 2 (SGLT2) has become a novel therapeutic target in diabetes (inhibition \rightarrow ↓ glucose reabsorption \rightarrow glucose excretion). The SGLT2 inhibitor dapagliflozin (SE: weight loss, dehydration) is approved for use in T2DM.

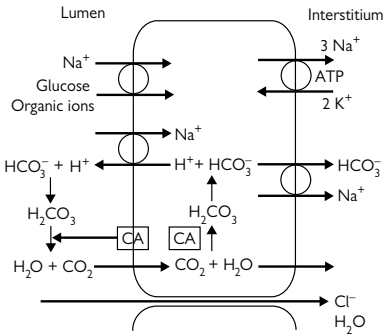


Fig. 13.5 Major pathways of solute reabsorption in the early part of the PCT. CA, carbonic anhydrase. Adapted with permission from Greger R (1999) New insights into the molecular mechanism of the action of diuretics. *Nephrol Dial Transplant* 14: 536–40.

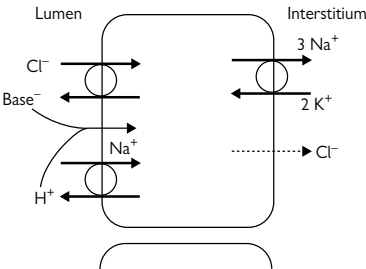


Fig. 13.6 Major pathways of solute reabsorption in the late part of the PCT. Adapted with permission from Greger R (1999) New insights into the molecular mechanism of the action of diuretics. *Nephrol Dial Transplant* 14: 536–40.

The loop of Henle

Introduction

The prime function of the loop of Henle is to establish a gradient of osmolality in the renal interstitium and \therefore the tubular fluid. This allows the concentration of urine to be varied widely.

Structure

- The loop dives deep into the renal medulla and then back out into the cortex.
- It consists of a thin descending limb, a thin ascending limb (in some nephrons), and a thick ascending limb. There are important solute and water permeability differences along the loop.
- The macula densa (📖 p. 921) is found close to the thick ascending limb.
- Capillaries serving the loop accompany it on its journey. These vasa recta have a bespoke 'hairpin' arrangement, as a 'standard' capillary network would simply allow the medullary osmotic gradient to dissipate through equilibration with capillary blood.
- This U-shaped organization allows water loss and solute entry in the descending limb to be offset by water entry and solute loss in the ascending.
- This passive exchange of water and solutes perpetuates the hypertonic extracellular environment of the medulla that is crucial for water homeostasis. It is referred to as 'countercurrent exchange'.
- The thick ascending limb contains cells rich in mitochondria, enabling the active transport of electrolytes. The reabsorption of Na^+ , K^+ , Cl^- , Ca^{2+} continues in this section of the nephron, and the majority of Mg^{2+} is recovered here.

Solute transport

(See Fig. 13.7)

- The descending limb is impermeable to Na^+ , but water moves into the interstitium down the osmotic gradient. The result is a high luminal Na^+ and Cl^- concentration.
- Na^+ reabsorption is passive in the thin ascending limb (Na^+ and Cl^- move into the interstitium down a concentration gradient) and active in the thick ascending limb. The active process is again driven by the basolateral $\text{Na}^+ \text{K}^+$ -ATPase (the low intracellular Na^+ concentration it generates allows Na^+ entry from the lumen).
- This Na^+ enters principally through the Na^+ , K^+ , Cl^- , Cl^- (NKCC) co-transporter, which is unique to this section of the nephron (and the target of loop diuretics) (📖 p. 792).
- Na^+ then exits the cell on the basolateral side through the $\text{Na}^+ \text{K}^+$ -ATPase, while Cl^- and K^+ exit through a co-transporter. In addition, K^+ re-enters the lumen through a luminal K^+ channel (ROMK channel)—a recycling process that is necessary to prevent K^+ availability from becoming a limiting factor for the operation of NKCC.
- This movement of K^+ back to the lumen also keeps it electrically net positive, which facilitates the passive paracellular reabsorption of Na^+ (as well as K^+ , Ca^{2+} , NH_4^+ , and Mg^{2+}).

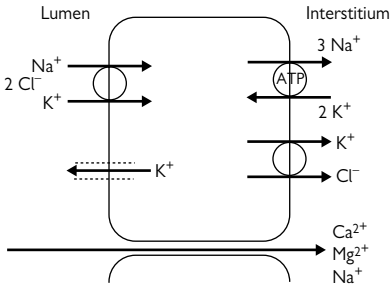


Fig. 13.7 Transport mechanisms in the thick ascending limb of the loop of Henle. The NKCC co-transporter is the key. Potassium can 'leak' back into the lumen via the ROMK channel, rendering the lumen positively charged. This charge gradient facilitates passive reabsorption of Ca^{2+} , Mg^{2+} , and more Na^+ via the paracellular route.

The loop of Henle: the countercurrent system

- Allows the concentration of urine to be varied, according to physiological circumstances.
- The U shape of the loop and its capillary network, the differences in permeability (to Na^+ and water) between the descending and ascending limbs, and the active reabsorption of Na^+ in the thick ascending limb all underpin the countercurrent system (see Fig. 13.8).
- The system maintains an interstitial osmotic gradient that increases from the renal cortex ($\sim 290\text{mOsmol/kg}$) to the tip of the medulla ($\sim 1,200\text{mOsmol/kg}$).
- The thin and thick ascending limbs are both *impermeable* to water.
- Despite this water impermeability, Na^+ is reabsorbed in this segment. This reabsorption of Na^+ (and Cl^-), but not water, leaves the tubular fluid dilute and hypotonic (\rightarrow this region is often called the diluting segment).
- So:
 - Isotonic fluid ($\sim 290\text{mOsmol/kg}$) enters the loop from the PCT.
 - As it progresses down the descending limb, it encounters medullary interstitial fluid of increasing tonicity (the interstitium is hypertonic because of Na^+ reabsorption without water in the thick ascending limb).
 - The descending limb is *permeable* to water (but not Na^+), so water flows out, down an osmotic gradient, into the concentrated milieu of the interstitium.
 - As this occurs, the tubular fluid progressively equilibrates osmotically with its surroundings and becomes more and more hypertonic as the loop descends into the medulla.
 - The effect is to concentrate the luminal fluid so that, at the deepest part of the loop, both the luminal and interstitial osmolality reach up to $1,200\text{mOsmol/kg}$.
 - In the ascending limb, Na^+ (and Cl^-) are absorbed (via the NKCC transporter) without water, generating an osmotic gradient of $\sim 200\text{mOsmol/kg}$ between lumen and interstitium at any given level.
- By the time the luminal fluid reaches the distal tubule, it is dilute and hypotonic.
- It would remain dilute as it passes through the distal nephron and collecting duct, were it not for the action of vasopressin (ADH) (📖 p. 933).
 - *High plasma osmolality* \rightarrow ADH release \rightarrow \uparrow permeability of collecting duct to water \rightarrow \uparrow urine osmolality (up to $\sim 1,200\text{mOsmol/kg}$).
 - *Low plasma osmolality* \rightarrow ADH release suppressed \rightarrow \downarrow permeability of collecting duct to water \rightarrow \downarrow urine osmolality (down to $\sim 200\text{mOsmol/kg}$).

Box 13.1 Role of urea

- Urea also makes an important contribution to the maintenance of a hypertonic medullary interstitium.
- The tubules are relatively impermeable to urea, meaning that a significant amount is delivered to the collecting duct. Then, vasopressin-dependent water reabsorption increases luminal urea concentration further.
- However, the vasopressin-sensitive transporters UT-A1 and UT-A3 allow urea to escape into the medullary interstitium.
- Although some re-enters the luminal fluid or equilibrates with the capillary network, the net result is an increase in interstitial tonicity.

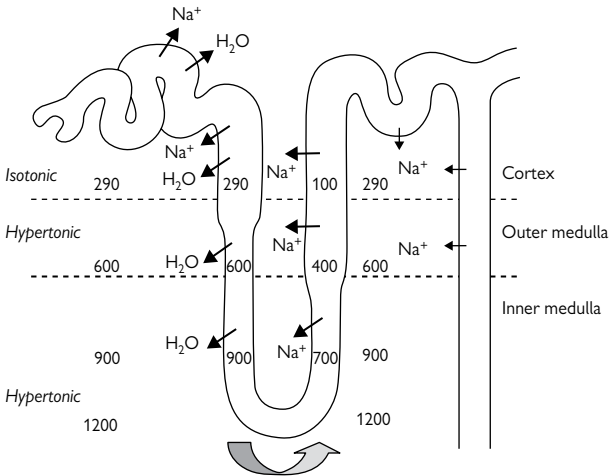


Fig. 13.8 Countercurrent multiplication by the loop of Henle (all units are mOsmol/kg). The thin descending limb is water-permeable. The tubular fluid becomes hypertonic (the interstitium is hypertonic). In the ascending limb, NaCl is absorbed (via the NKCC transporter) without water, generating an osmotic gradient of ~200mOsmol/kg at any given level. Countercurrent flow in the two limbs of the loop multiplies this gradient longitudinally. The result is a hypertonic interstitium in the inner medulla (urea also contributes to this hypertonicity—see Box 13.1). Thus, fluid entering the distal tubule is hypotonic. Further Na⁺ reabsorption in the distal tubule can make the fluid still more hypotonic. If ADH is not present, the collecting duct is impermeable to water, and dilute urine is passed. If ADH is present, the collecting duct becomes permeable to water, and the urine becomes hypertonic as it passes through the medulla. Reproduced with permission from Davison AMA, Cameron JS, Grunfeld J-P et al. (eds) (2005). *Oxford Textbook of Clinical Nephrology*, 3rd edn. Oxford: Oxford University Press.

The distal nephron

Introduction

The fine-tuning of solute and water reabsorption occurs in the distal nephron.

The distal convoluted tubule

The distal convoluted tubule (DCT) is impermeable to the passive movement of Na^+ and Cl^- and water (vasopressin does not affect water absorption here). This allows large concentration gradients to develop when necessary (see Fig. 13.9).

Sodium ~5% of the filtered Na^+ is reabsorbed in the DCT. The thiazide-sensitive Na^+Cl^- co-transporter (NCCT) is the major route. Further Na^+ is absorbed by Na^+/H^+ exchange, and additional Cl^- by $\text{Cl}^-/\text{HCO}_3^-$ exchange. H^+ and HCO_3^- then combine in the lumen to form CO_2 and H_2O (the CO_2 can be reabsorbed and recycled). The energy for the action of the NCCT co-transporter is again derived from Na^+K^+ -ATPase, as the resulting electrochemical gradient permits Na^+ reabsorption into the cell.

Calcium Absorbed via a specific epithelial Ca^{2+} channel under the influence of PTH and calcitriol.

Thiazide diuretics block the NCCT co-transporter. They also enhance Ca^{2+} absorption (exact mechanisms unknown), reducing calcium excretion in the urine. Hypokalaemia occurs, as there will be an increase in Na^+ delivery to the collecting ducts and \therefore additional uptake via ENaCs (p. 931). This will increase activity of the basolateral Na^+K^+ -ATPase, and the resulting intracellular K^+ will then move into the lumen and be lost in the urine.

Defects in the NCCT co-transporter also underlie Gitelman's syndrome (p. 800).

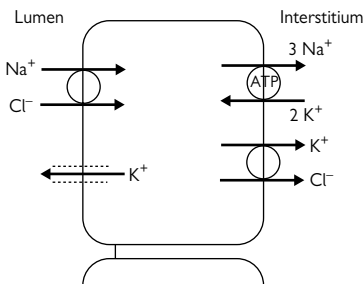


Fig. 13.9 Distal tubular sodium and chloride reabsorption occur predominantly via the NCCT co-transporter.

The collecting duct

- Two cell types are found in the collecting duct. *Principal* cells are responsible for Na^+ (and water) reabsorption and K^+ excretion. *Intercalated* cells secrete H^+ (α -intercalated cells) or HCO_3^- (β -intercalated cells).
- Changes in permeability of the collecting duct allow concentration of urine under the control of vasopressin (ADH).

Principal cells (~65% of cells) (See Fig. 13.10)

Sodium Reabsorption from the lumen occurs via a specific Na^+ transporter, the epithelial sodium channel (ENaC), and it then leaves the cell on the basolateral side via the Na^+K^+ -ATPase. (see Fig. 13.10). Although only ~5% of filtered Na^+ is reabsorbed here, this is the main site of body Na^+ regulation (see Box 13.2). In contrast to Na^+ reabsorption higher in the nephron, it is predominantly the electrical, rather than concentration, gradient that drives Na^+ from the lumen into the cell (as the luminal Na^+ concentration may be as low as 5mmol/L by this stage of the nephron). Na^+K^+ -ATPase generates a net negative charge within the cell, and Na^+ moves down this charge gradient via ENaC into the cell. As the tubular fluid becomes more negatively charged, it favours K^+ movement into the lumen.

Potassium Enters principal cells on the basolateral side via the Na^+K^+ -ATPase and then move into the lumen (along the favourable charge gradient discussed previously) via specific aldosterone-sensitive K^+ channels (aldosterone promotes K^+ excretion). High urinary flow rates help to maintain low intraluminal K^+ concentrations, allowing the gradient to persist and the channel to operate. Hence, hypovolaemia can → hyperkalaemia.

Box 13.2 Control of Na^+ excretion

- **Aldosterone**, after binding its mineralocorticoid receptor, increases the number of open ENaC channels, regulating Na^+ absorption (and excretion). It also increases the number and activity of the Na^+K^+ -ATPase (it can double the surface area of the basolateral membrane).
 - **Atrial natriuretic peptide (ANP)** also acts on ENaC, with \uparrow ANP → inactivation of ENaC.
 - **Na^+ delivery:** \downarrow delivery → \uparrow ENaC activity, thereby reducing Na^+ loss in the urine (and preventing volume depletion).
 - **Vasopressin (ADH)** may also be important through an increase in ENaC numbers and activity.
 - Locally produced PGE_2 decreases ENaC activity.
- ▶ **Amiloride** and **triamterene** block ENaC, thus reducing both Na^+ reabsorption and K^+ excretion. **Spironolactone** inhibits the effect of aldosterone on its receptor, with similar effects on Na^+ and K^+ .

Intercalated cells

These cells are essential to acid–base homeostasis. There are two functional and morphological types. α -intercalated cells are tall, columnar epithelial cells, containing a luminal H^+ ATPase that enables them to secrete protons. β -intercalated cells are flatter cells that contain a basolateral H^+ ATPase and a luminal $Cl^- HCO_3^-$ exchanger (called pendrin) that enables them to excrete base,

The α -intercalated cells transport H^+ ions out of the cell into the tubular fluid. This is aldosterone-sensitive (aldosterone $\rightarrow \uparrow H^+$ excretion). H^+ is generated (along with HCO_3^-) from the dissociation of carbonic acid via carbonic anhydrase. HCO_3^- is then returned to the circulation in exchange for Cl^- ions via a different basolateral $Cl^- HCO_3^-$ co-transporter (called AE1 protein) (see Fig. 13.11).

Metabolic acidosis converts the collecting tubule from a state of HCO_3^- secretion to HCO_3^- absorption (and $\therefore H^+$ secretion) that involves a phenotypic shift of β -intercalated cells to α -intercalated cells. The role of the kidney in acid–base regulation is further discussed on p. 818.

In circumstances of severe acidosis or $\downarrow K^+$, intercalated cells also express an H^+/K^+ ATPase, similar to that responsible for gastric acid secretion. This allows additional H^+ secretion in exchange for K^+ .

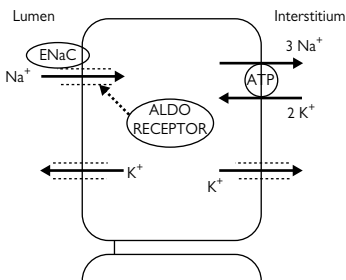


Fig. 13.10 The principal cell in the collecting tubule.

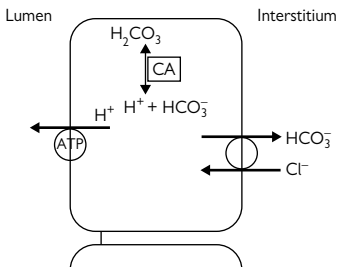


Fig. 13.11 Acid secretion in the α -intercalated cell in the collecting tubule. H^+/K^+ ATPase is an alternative route for secretion of H^+ into the lumen. CA, carbonic anhydrase.

Vasopressin (ADH)

Vasopressin, or antidiuretic hormone (ADH), is synthesized in the hypothalamus and released by the posterior pituitary in response to rising plasma osmolality (sensed by hypothalamic osmoreceptors) and/or significant hypovolaemia (sensed by arterial baroreceptors and atrial stretch receptors).

Vasopressin acts via V_1 receptors to stimulate thirst and systemic vasoconstriction. In the kidney:

- Vasopressin binds V_2 receptors located on the basolateral membrane of principal cells in the collecting duct.
- It acts to reabsorb water in the collecting duct and \therefore to concentrate the urine.
 - The duct becomes more permeable to water by the translocation of specific water channels (aquaporin-2) to the luminal membrane.
 - Aquaporin-2 is stored in intracellular vesicles ready for membrane insertion (the basolateral membrane is already water-permeable by virtue of aquaporin-3 and -4).
 - The high interstitial osmolality, maintained by the countercurrent system, facilitates easy movement of water (📖 p. 928).
- Vasopressin also increases the permeability of the collecting duct to urea (📖 p. 929).
- Defects in aquaporin-2 structure and function underlie X-linked nephrogenic diabetes insipidus (📖 p. 789).
- Increased intraluminal Ca^{2+} concentration interferes with aquaporin-2 membrane insertion. This explains the observation that hypercalcaemia causes defective urinary concentrating ability, polyuria, and dehydration.

High plasma osmolality → ADH release → binds V_2 receptors → aquaporin-2 translocation → ↑ permeability of collecting duct to water → ↑ urine osmolality up to that of the inner renal medulla (up to ~1,200mOsmol/kg) → production of a concentrated urine.

Low plasma osmolality → ADH release suppressed → no aquaporin-2 translocation → collecting duct impermeable to water → ↓ urine osmolality as low as that of tubular fluid entering the cortical collecting duct (down to ~200mOsmol/kg) → production of a weak urine.

Appendices

Insertion of temporary haemodialysis catheters [936](#)

Preparing renal patients for theatre [942](#)

Acute coronary syndrome (ACS) in CKD [946](#)

Plasma exchange [950](#)

Useful resources [954](#)

Insertion of temporary haemodialysis catheters

Indications

Temporary haemodialysis catheters should be temporary—ideally no line should remain *in situ* for longer than a few days. The risk of infection increases significantly if in place for longer—consider switching to a tunneled line if continuing access is required (📖 p. 296).

Routes of insertion

- The right internal jugular vein is the preferred route. It is superficial, technically easy to cannulate (in a ‘virgin’ neck), and joins the SVC in a straight line. The left internal jugular is an alternative, but the guidewire and line have to curve in order to reach the SVC. The risk of malposition and malfunction (and perforation of the vein) is ∴ greater.
- The femoral veins are suitable for short-term use and may be the safest and quickest option in an emergency (see 📖 p. 180).
- The subclavian route should be avoided: there is a higher risk of subsequent central venous stenoses, potentially rendering the ipsilateral arm unsuitable for permanent access in the form of an AVF.

Pre-insertion

- Is the line really needed? Check that dialysis is required and whether the patient is suitable for a tunneled line (📖 p. 296) or a PD catheter insertion.
- Check FBC and clotting.
- The operator should obtain consent from the patient (verbal and/or a family member if too unwell). Warn about potential complications:
 - Failure to cannulate vein.
 - Haematoma ± arterial puncture.
 - Pneumothorax, haemothorax (and potential need for a chest drain).
 - Air embolus.
 - Catheter malfunction.
 - Infection and its complications.
- Equipment: every renal unit should have a dedicated room for line insertion. It should be a sterile environment, containing a 2D ultrasound probe to facilitate vein cannulation. You will need:
 - An assistant.
 - Sterile gown, gloves, drapes, and towels. Iodine or chlorhexidine to clean the skin.
 - An ultrasound device to guide line insertion.
 - Dressing pack, with a supply of syringes, swabs, and needles.
 - Sterile saline for injection.
 - Lidocaine (1 or 2%): 10mL.
 - Line pack (if pre-packed, will contain introducer needle, guidewire, and the line itself). Choose a shorter line (e.g. 15cm) for the RIJ route, longer line (e.g. 20cm) for the left side or the larger patient.
 - Tri-sodium citrate lock (Citralock®) (46.7%) or Duralock® have largely replaced heparin (5,000 units/mL) to ‘lock’ the line once it is *in situ*.

- Wash and dry hands, as for a surgical procedure; wear sterile gown, mask, and sterile gloves.
- Position the patient slightly head down (for right-sided insertion).
- Clean a wide area of skin around the insertion site. Lay out sterile drapes on all sides. Prime both lumens of the line with sterile normal saline solution.

Tips for problematic line insertions

- Stop insertion if the patient is in *pain*. Seek senior assistance. Pain probably indicates that the guidewire or line is in the wrong location.
- Venous blood looks darker than arterial blood and does not fill a syringe with its own pressure: if in doubt, put a 5mL syringe on either hub, and see if it fills in a pulsatile fashion. If still in doubt, perform an ABG. ⚠ Do not take the line out yet (see later in this list).
- Inadvertent arterial puncture with an 18-gauge needle can usually be controlled by pressure for 5–15min. If the larger introducer needle punctures the artery, it is often safest to abandon the procedure. Do not attempt the other side of the neck after significant arterial puncture and haematoma (risk of airway obstruction, if bilateral).
- ⚠ If an artery is accidentally cannulated (i.e. the line is inserted), or if the vein is traversed such that the line tip is found to lie outside the vein, then *leave the line in situ and seek expert help*.
 - Check FBC, clotting, and cross-match blood.
 - Confirm your concern by aspirating blood (if possible) for ABG from both lumens. If unable to aspirate, you are in the *wrong* place.
 - Perform a CXR.
 - If there is a rapid deterioration in the patient's condition, a haemothorax or pneumothorax is likely, and an urgent chest drain may be required prior to CXR.
 - Monitor closely: pulse BP, and O₂ saturation.
 - Find out where the line is: either a CT or a contrast examination through the line to determine its location.
 - The line must be removed under controlled conditions, with vascular/thoracic surgical input.

Insertion technique

- Establish anatomical landmarks and the planned point of cannulation (see Figs 14.1 to 14.3).
- Ultrasound-guided insertion is now the technique of choice.
- Insert local anaesthetic under the skin. Always attempt to aspirate before injecting lidocaine to avoid inadvertent IV injection.
- Once the needle is in the vein, use a Seldinger technique. Pass the guidewire through the needle (*there should be no resistance*—if resistance is felt, do not force it, but remove the guidewire, and check the needle position. Do not advance the guidewire beyond the line length, i.e. 15/20cm, to avoid arrhythmias. Remove the needle, leaving the guidewire *in situ*).

- Use a scalpel blade to make a small nick in the skin. Pass the dilator over the guidewire until it is in the vein. Remove the dilator, keeping the guidewire in position. Without delay, pass the line over the guidewire until it is in position. Remove the guidewire.

Vein localization

Ultrasound-guided cannulation

Most probes have a sterile disposable cover. Follow the manufacturer's instructions. After infiltration of local anaesthetic, identify the vein with the probe. The introducer needle can be inserted with real-time guidance.

Blind insertion (no longer recommended)

The approach can be medial to SCM muscle, between the two heads, or lateral to the muscle. Local practice and expertise will dictate the optimal route.

- Palpate the carotid artery with one hand (the left for a right-sided insertion).
- Insert the needle just lateral to the carotid pulse, aiming at 45° to the skin, in the direction of the ipsilateral nipple. Aspirate gently on the syringe, as you go, until the vein is reached.
- If unsuccessful, withdraw the needle slowly (continuing with attempted aspiration—you may have traversed the vein). Reinsert, varying the angle of insertion slightly to the medial side. If still unsuccessful, invite a colleague or senior to have a go before you (and the patient) lose confidence.
- Once the vein is identified with a green needle, pass the introducer needle down the same track, in the same manner, into the vein, palpating the carotid pulse at the same time.
- Check the flows in both lumens. A 20mL syringe should fill easily with minimal aspiration (general rule of thumb: 20mL should aspirate in <5s (= 240mL/min). Flush both lumens with saline (which should also be easy), and then lock with Citralock®, Duralock®, or heparin. The priming volume should be written on the line (typically 1.3–2.0mL/lumen). Put caps on the lumens, and suture the line in position.
- Arrange a CXR and review it yourself: look for line position (tip should be in SVC), and double-check there is no pneumothorax.

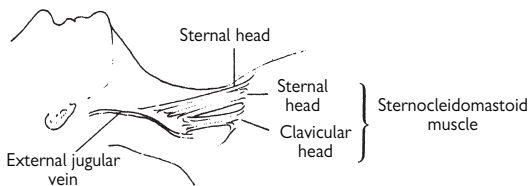


Fig. 14.1 Anatomical landmarks for internal jugular vein cannulation. Surface anatomy of external and internal jugular veins. Reproduced with permission from Ramrakha, P, and Hill, J, *Oxford Handbook of Acute Medicine 2e* (2004), with permission from Oxford University Press.

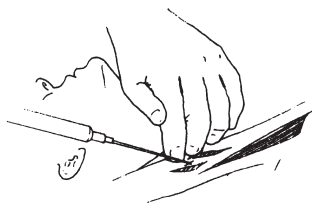


Fig. 14.2 Anatomical landmarks for internal jugular vein cannulation. Anterior approach: the chin is in the midline and the skin puncture is over the sternal head of the sternocleidomastoid muscle. Reproduced with permission from Ramrakha, P, and Hill, J, *Oxford Handbook of Acute Medicine 2e* (2004), with permission from Oxford University Press.

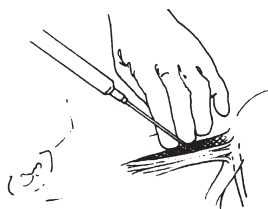


Fig. 14.3 Anatomical landmarks for internal jugular vein cannulation. Central approach: the chin is turned away and the skin puncture is between the two heads of sternocleidomastoid. Reproduced with permission from Ramrakha, P, and Hill, J, *Oxford Handbook of Acute Medicine 2e* (2004), with permission from Oxford University Press.

Femoral line insertion

Advantages over neck line

- Superficial vein, usually relatively easy to cannulate.
- Relatively safe (haematoma can be controlled by pressure, no risk of airway obstruction or pneumothorax).
- No CXR required post-procedure (saves time in an emergency).

Disadvantages over neck line

- Femoral line function can be highly positional, particularly in obese patients. Patients are also relatively immobilized.
- ⚠ *High risk of infection*—lines should only be left in for 2–3 days max.

Insertion technique

- The technique is identical as that for neck line insertion. Ultrasound guidance should be used.
- Position the patient horizontally or with feet slightly down. The hips should be partially abducted. Do not shave insertion site; if necessary, hair should be removed by clipping.
- Wear gown and gloves, prepare the skin, and use sterile drapes.
- For the right femoral vein, the fingers of the left hand should be used to palpate the femoral pulse. Take care to remain below the inguinal ligament so that a haematoma can be controlled with pressure. The vein runs just medial to this. Infiltrate local anaesthetic, and try to identify the vein with a green needle. Use the track of the 18-gauge needle to insert the introducer needle into the vein. Angle the introducer needle towards the head to facilitate the passing of the guidewire.
- The remainder of the procedure is as for the internal jugular line.

Tunnelled dialysis catheters

- The dual lumen line is inserted into the internal jugular vein (usually), with a subcutaneous tunnel that acts as a barrier to infection.
- Tunnelled catheters may be used as semi-permanent access whilst awaiting maturation of an AV fistula, or as permanent access for the patient unsuitable for an AVF or PTFE graft.
- Long-term complications include poor flows (and thus inadequate dialysis), infection, and venous stenosis.
- A trained operator should insert tunnelled lines; ideally, under X-ray screening to ensure the tip of the line lies in the SVC.
- The complications of insertion are similar to the insertion of any central line.

Preparing renal patients for theatre

Any patient with renal failure is a high-risk patient for surgery. Extreme care should be taken when preparing for theatre.

Pre-admission

- Full history. Focus on cardiac and respiratory history, dialysis regimen (if appropriate), and details about previous anaesthesia. Full drug history.
- Can the procedure be done under local or regional anaesthesia (this may be the case for an AV fistula)?
- Examination. Listen for murmurs and bruits (carotids); examine peripheral pulses; check lung fields are clear; assess volume status; measure BP, including postural BP (and check BP charts, if available). The anaesthetist will prefer a BP of <150/95mmHg.
- Investigations. FBC (? anaemia which could be corrected pre-op, if possible), SCr, U&E ($\uparrow K^+$), LFT, Ca^{2+} , ECG (any patient with advanced CKD), CXR if breathless or abnormal cardiorespiratory examination. Echocardiogram if any new murmur or suggestion of poor LV function.
- Liaise with anaesthetist if any doubt about fitness for anaesthesia or if further investigations are necessary.
- Liaise with the patient's dialysis unit, if relevant. Plan dialysis around the surgery (often the day before and the day after the procedure).

On admission

- Repeat full physical examination, including BP and assessment of volume status.
- If for creation of vascular access, avoid phlebotomy and cannulas in the limb targeted for surgery.
- Send bloods pre-op and after last dialysis session. U&E, FBC, clotting, G&S (and cross-match, according to nature of surgery). The anaesthetist will prefer a $K^+ < 5.5\text{mmol/L}$.
- Write up drugs to be given pre-op or at induction (e.g. antibiotics).

Post-operative care

- Avoid nephrotoxic drugs (e.g. NSAIDs, gentamicin), *even in dialysis patients if they still pass urine*.
- Ensure adequate analgesia is given, but be aware of risks of opioid toxicity (📖 pp. 271 and 897).
- Check volume status and BP. If IV fluids are required, prescribe 0.5–1L, and then reassess the patient.
- ▶▶ Measure SCr and U&E post-op in any patient with significant renal impairment (depolarizing anaesthetic agents lead to muscle K^+ release and may precipitate dangerous $\uparrow K^+$).
- If an AVF or PTFE graft have been formed, check for a thrill over the fistula, and avoid any compression (Δ BP) or blood tests in that limb.
- Consider \downarrow or no heparin anticoagulation during next HD treatment (discuss with the surgeon).

Bowel preparation

See Tables 14.1 and 14.2. A UK consensus guideline is available at http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/endoscopy/obca_12.pdf

Table 14.1 Types of bowel preparation

Group	Brand	Caution
Sodium picosulfate with magnesium citrate	Picolax® CitraFleet®	In all patients, there is a risk of hyponatraemia with excess water ingestion. In patients with CKD, there is a risk of hypermagnesaemia.
Polyethylene glycol (PEG)	Klean-Prep® Moviprep®	
Oral sodium phosphate (OSP)	Fleet®	Acute phosphate nephropathy; should not be used for patients with eGFR <60mL/min.
Magnesium carbonate with citric acid	Citramag®	In all patients, there is a risk of hyponatraemia with excess water ingestion. In patients with CKD, there is a risk of hypermagnesaemia.

Table 14.2 Bowel preparation preference, according to renal modality

Stage/modality	Optimal	Acceptable	Avoid	Notes
CKD 3	Klean-Prep® Moviprep® Picolax® CitraFleet® Citramag®		Fleet®	
CKD 4	Klean-Prep® Moviprep®	Picolax® CitraFleet® Citramag®	Fleet®	Klean-Prep® is made up into 4L. Moviprep® is made up into 3L. Choose according to fluid status.
CKD 5	Klean-Prep® Moviprep®		Fleet® Picolax® CitraFleet® Citramag®	Klean-Prep® is made up into 4L. Moviprep® is made up into 3L. Choose according to fluid status.
Haemodialysis	Picolax® CitraFleet®			Despite contraindication in CKD 4/5 pre-dialysis, these agents can be used safely once on dialysis.
Peritoneal dialysis	Picolax® CitraFleet®		Fleet®	Caution to avoid hypovolaemia, as may be detrimental to CAPD patients who often rely on residual urine output.
Renal transplant	According to eGFR	According to eGFR	Fleet®	Avoid OSP, regardless of eGFR.

Acute coronary syndrome (ACS) in CKD

Introduction

ACS is classically divided into ST elevation MI (STEMI), non-ST elevation MI (NSTEMI), and unstable angina, depending on the combination of cardiac chest pains, ECG findings, and cardiac enzyme elevations.

The underlying pathology is atherosclerosis, unstable plaque, and *in situ* thrombosis formation. The CKD population has a high burden of traditional risk factors (e.g. ↑ BP, DM, ↑ lipids, smoking, advanced age). In addition, the pathology may differ in advanced CKD with diffuse, calcific coronary arteries and microvascular disease. Vessels may be stiff and unable to compensate for changes in haemodynamics (e.g. ↓ BP, tachycardia), leaving the myocardium more vulnerable to ischaemic injury (even in the absence of thrombosis).

► CKD predicts mortality in ACS (and vice versa), but the secure diagnosis of ACS, especially in CKD 5, can be challenging due to a number of factors.

- Atypical presentation—atypical chest pain, ‘silent MI’, and hypotension/collapse are more common.
- Atypical ECG—typical ischaemic changes, including ST elevation, are less likely. LVH (and strain) may complicate interpretation. New regional wall motion abnormalities on echo may be required to confirm diagnosis.
- Interpretation of cardiac enzymes (see Box 14.2).

Joint management between a nephrologist and a cardiologist, experienced with renal patients, is ideal.

Management

Broadly speaking, the treatment of suspected ACS is the same, but it is important to remember that patients with advanced CKD are often excluded from large cardiology trials and have an inherently increased bleeding risk (uraemic platelet dysfunction), and that the underlying pathology may be fundamentally different.

- Give O₂ to maintain normal saturations.
- Treat pain with opiate analgesia. If repeated dosing is required, consider fentanyl or oxycodone to reduce accumulation (📖 p. 271).
- Nitrates (sublingual or IV), titrated to pain and BP.
- Aspirin and clopidogrel are administered at standard doses. Glycoprotein IIa/IIIb inhibitors require dose reduction. One meta-analysis suggests that clopidogrel and glycoprotein IIa/IIIb inhibitors may increase bleeding risk without improving mortality in CKD,¹ but the current consensus is to administer them for standard indications.

- LMWHs are renally excreted. 50% dose reduction is required if GFR <30mL/min (e.g. enoxaparin 1mg/kg od) or use unfractionated heparin instead (📖 p. 892).
- Beta-blockers (may require dose reduction—📖 p. 892) should be titrated to pulse and BP.
- ACE-I/ARBs should be carefully introduced once haemodynamically stable and no further angiography/surgery is planned.
- Statins (📖 p. 893) have not been prospectively evaluated post-ACS in CKD. Standard practice is to prescribe them.
- Anaemia is a predictor of poor outcome in ACS. There is no strong evidence that transfusing patients improves outcomes, and the potential benefits need to be weighed against the risks of volume loading and hyperkalaemia (dialysis may be required). However, it is standard practice to target an Hb 10–11g/dL.
- ACS commonly causes a deterioration in SCr in CKD. Temporary RRT may be required. Both acute and chronic HD patients may be better on CVVHF or SLED initially (📖 p. 174).
- STEMI: the standard of care is emergency PCI (see Box 14.1). If unavailable, thrombolysis can be performed. Common renal contraindications include recent renal biopsy, recent line insertion (esp. if arterial puncture occurred), uncontrolled BP >200/100mmHg, uraemic pericarditis.

Box 14.1 Angiography and PCI

Commonly performed. Standard contrast nephropathy precautions apply, including for dialysis patients with residual function (📖 p. 148).

It is vital to monitor renal function for 72 hours post-procedure. Dialysis dependence may be precipitated.

Calcific disease is less amenable to stenting, and rates of restenosis are higher. This may be reduced by drug-eluting stents, but prolonged dual antiplatelet therapy is required, which may complicate subsequent access procedures or transplant listing.

Reference

1. Palmer SC, Di Micco L, Razavian M, et al. (2012). Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Annals of Internal Medicine*, **156**, 445–59.

Box 14.2 Cardiac biomarkers in CKD***Troponin***

Cardiac troponin T (cTnT) and I (cTnI) are proteins present in cardiac myocytes that may be detectable in serum when released following myocardial injury.

Elevated serum troponin (esp. cTnT) is commonly found, even in asymptomatic patients, and does not necessarily indicate acute ischaemia. Contributing factors include LVH, the uraemic milieu itself, endothelial dysfunction, and reduced renal excretion. cTnI is more specific for ischaemia. Elevated troponins are not an inevitable consequence of renal impairment and are a poor prognostic marker, even in the absence of ACS.

If ACS is suspected, it is best to measure serum troponin as soon as possible and again 12 hours post-event, as dynamic changes are generally more helpful than absolute values.

Creatine kinase (CK)

CK is frequently elevated in advanced CKD. Causes include myopathy, vitamin D or carnitine deficiency, and reduced renal clearance. Neither total CK, nor the more specific CK-MB, are reliable for the diagnosis of ACS.

Brain natriuretic peptide (BNP)

BNP is released from the cardiac ventricles in response to volume loading and promotes salt and water excretion. BNP and its physiologically inert by-product NT-proBNP have been used in the diagnosis, prognosis, and monitoring of heart failure.

BNP and NT-proBNP are commonly elevated in renal failure for a number of reasons, e.g. salt and water handling is impaired, leading to volume overload and ventricular stretch, chronic ↑ BP and LVH, reduced renal excretion (esp. of NT-proBNP). As such, their utility in CKD is very limited.

Plasma exchange

Introduction

A technique in which plasma is separated from the rest of the blood so that it can be removed and replaced. There are two main methods (see Fig. 14.4):

- Centrifugation: removing plasma by centrifuging the blood.
- Filtration: uses highly permeable membranes through which blood is pumped at ~100–150mL/min. Plasma readily passes through the membrane pores (MW cut-off ~2,000kDa), but cells do not. In general, all immunoglobulins will pass through the membrane.

A third technique involves two pumps and membranes and selectively removes large molecules, including antibodies ('double filtration'). This may be used when there is no doubt about the molecule that needs removing, such as anti-HLA antibodies in transplantation. However, in other diseases, such as ANCA-associated vasculitis, this is not so clear, and one of the non-selective methods is recommended.

Anticoagulation of the extracorporeal circuit with heparin (e.g. 30–60IU/kg loading dose, followed by 1,000IU/h) or citrate (📖 p. 186) is required.

Indications

- Diseases in which plasma exchange is used include:
 - Anti-GBM disease.
 - ANCA-associated vasculitis.
 - HUS/TTP.
 - Cryoglobulinaemia.
 - Hyperviscosity syndrome.
 - Recurrent FSGS post-transplant.
 - Treatment of highly sensitized transplant recipients.
 - Treatment of antibody-mediated transplant rejection.
 - Non-renal conditions, including Guillain–Barré syndrome and myasthenic crises.

Replacement fluid and coagulation monitoring

Approximately 60mL/kg, up to a maximum of 4L, of plasma is usually removed during an exchange. The major replacement fluid in most cases is 5% human albumin solution. A single exchange will lower plasma macromolecules by ~60% (~90% after five exchanges). In some conditions, such as HUS/TTP, the replacement fluid is fresh frozen plasma (FFP) or Octaplas[®], as this provides part of the therapeutic effect. ⚠ If albumin is the major replacement fluid, then 1–2L FFP or Octaplas[®] may be needed at the end of the exchange if there has been a recent biopsy or pulmonary haemorrhage.

In all cases, coagulation should be monitored (clotting factors are removed) and FFP or Octaplas[®] given, as indicated. Cryoprecipitate or fibrinogen should be administered if fibrinogen levels are low. Liaise with your haematology team.

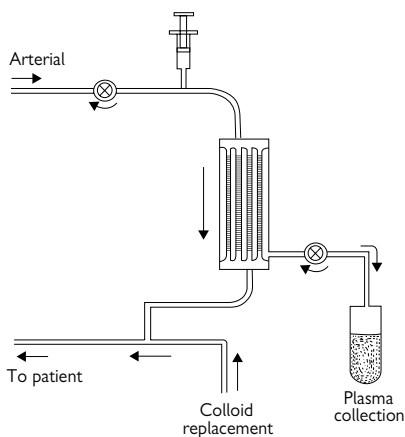
Potential complications

- Hypotension (usually related to volume depletion).
- Hypocalcaemia: related to the use of citrate as an anticoagulant (and FFP contains citrate). Can be prevented or treated by calcium administration during the exchange, e.g. 2–4mL 10% calcium gluconate added to 500mL 5% human albumin.
- Clotting abnormalities and bleeding (see ‘Replacement fluid and coagulation monitoring’).
- Complications of central venous catheter insertion and use: pneumothorax, haemothorax, infection (📖 p. 936).
- Anaphylactic reactions to FFP (~2%), infection from plasma products.
- Alkalosis from the metabolism of citrate.
- Dilutional \downarrow K^+ .

Immunoabsorption

A technique that selectively removes immunoglobulin. This may be useful in particular circumstances, e.g. removal of anti-HLA antibody pre-transplantation. Replacement fluids are not required, and there is no depletion of clotting factors. Uses protein A columns that bind IgG (mostly) via the Fc domain. Plasma is first filtered, prior to being run through columns containing immunosorbent-coated beads. Antihuman IgG antibody-coated columns are highly specific for human Ig but are very expensive. Protein A columns can be reused.

(a) Membrane plasma filtration



(b) Centrifugal cell separation

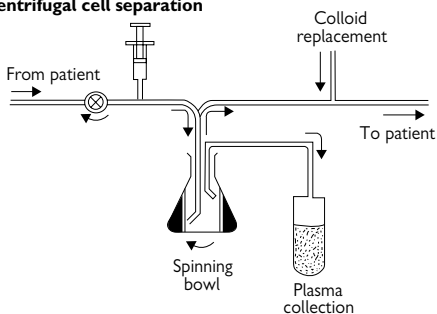


Fig. 14.4 Techniques of plasmapheresis. (a) Membrane plasma filtration: blood flow 100–150 mL/min. Highly permeable membrane (MW cut-off 2,000 kDa)—most Igs are removed, but some larger immune complexes and cryoglobulins may not be well cleared. Cells, along with fluid replacement, are returned to the patient. (b) Centrifugation: plasma is removed by centrifugation, using a spinning bowl. Blood is (synchronously or intermittently) returned to the patient, along with replacement fluid. No upper limit to the size of protein which can be removed. Can be performed via an antecubital vein. Reproduced with permission from Levy J, Morgan J, Brown E (2004) *Oxford Handbook of Dialysis*, 2nd edn. Oxford: Oxford University Press.

Useful resources

The number of organizations, educational resources, patient groups, and blogs in the field of nephrology is increasing exponentially. A selection of high-quality resources and respective websites is provided here.

The Renal Association (RA)

This is the professional body for UK renal physicians and scientists. It promotes research, disease prevention, and welfare. It sets standards for all aspects of renal care against which data are collected and analysed by the renal registry.

🔗 <http://www.renal.org/Clinical/GuidelinesSection/Guidelines.aspx>

The Renal Registry

The UK Renal Registry was established by the Renal Association as a resource for the development of patient care in renal disease. UK units submit data on disease categories and against audit standards applicable to dialysis and transplantation. It produces annual reports and enables comparisons between units. Its website provides a huge quantity of information and now has the facility for visitors to generate customized data.

🔗 <http://www.renalreg.com/index.html>

🔗 http://www.renalreg.com/n_portal/pages/main/registryportal.php

The British Renal Society (BRS)

This is a multidisciplinary society, with members across all professions, providing care to renal patients. Its aims are the promotion and delivery of effective, patient-centred care. Its website contains educational resources for both professionals and patients.

🔗 <http://www.britishrenal.org/Home.aspx>

The British Transplant Society

This is the professional body for UK transplant physicians, surgeons, and scientists. It promotes clinical standards, research, and access to transplantation.

🔗 <http://www.bts.org>

NHS blood and transplant organ donation (formerly UK transplant)

Provides a 24-hour service for the matching and allocation of donated organs throughout the UK. It also maintains the NHS organ donor register. The website includes detailed information on the matching scheme and points allocation, success rates, waiting times, and FAQs for patients.

🔗 <http://www.organdonation.nhs.uk/>

The kidney patient guide

This website is a collaboration of healthcare professions, IT experts, and renal patients and their carers. It provides a broad range of information, encompassing the physical, social, financial, and emotional aspects of kidney disease, and is aimed at patients and those close to them. It also has an interactive forum.

🔗 <http://www.kidneypatientguide.org.uk/contents.php>

The American Association of Kidney Patients

'The independent voice of kidney patients since 1969', whose aims are to provide education, advocacy, and community to kidney patients and their carers. They have wide range of educational resources, divided into transplantation, CKD, and dialysis.

🔗 <http://www.aakp.org/>

British Kidney Patient Association

This charity aims to improve the lives of kidney patients through information, advice, and active financial support. They give grants to individual patients as well as to renal units to improve their services.

🔗 <http://www.britishkidney-pa.co.uk>

National Institute for Health and Care Excellence (NICE)

NICE produces evidence-based guidance to help to resolve uncertainty about which medicines, treatments, procedures, and devices represent the best quality care and offer the best value for money for the NHS. Guidelines relevant to nephrology include those for CKD and hypertension management.

🔗 <http://www.nice.org.uk/>

The International Society of Nephrology (ISN)

The ISN is dedicated to advancing the diagnosis, treatment, and prevention of kidney diseases in the developing and developed world. As well as supporting research and producing the journal *Kidney International*, it coordinates global charitable work in nephrology, including the Renal Disaster Relief Task Force.

🔗 <http://www.theisn.org>

National Kidney Foundation (NKF) and KDOQI

This large, American voluntary organization is dedicated to preventing kidney and urinary tract diseases, improving the health and well-being of individuals and families affected by kidney disease, and increasing the availability of all organs for transplantation. A major focus is producing clinical guidelines for the management of kidney patients. It has been producing them via KDOQI—Kidney Disease Outcomes Quality Initiative, since 1997. It produces the *American Journal of Kidney Diseases*.

🔗 <http://www.kidney.org/index.cfm>

🔗 http://www.kidney.org/professionals/KDOQI/guidelines_commentaries.cfm

Kidney Disease: Improving Global Outcomes (KDIGO)

Initially developed by the NKF, this is a multinational committee to develop international evidence-based guidelines for the management of renal disease. These guidelines are becoming the international benchmark in many renal diseases.

🔗 <http://www.kdigo.org>

The American Society of Nephrology (ASN)

The ASN aims to educate health professionals, share new knowledge, advance research, and advocate the highest quality care for kidney patients. The ASN kidney week is the largest annual nephrology conference in the world. It produces the *Journal of the American Society of Nephrology (JASN)* and the *Clinical Journal of the American Society of Nephrology (CJASN)*.

🔗 <http://www.asn-online.org/>

Peritoneal dialysis academy

Sponsored by Baxter, this free educational resource was authored by two internationally recognized experts in PD. Its online modules cover all aspects of PD, and a certificate is awarded for completion of all sections.

🔗 <http://www.pdacademy.org.uk/>

Reference

1. Palmer SC, Di Micco L, Razavian M, et al. (2012). Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Annals of Internal Medicine*, **156**, 445–59.

Index

A

- AA amyloidosis 630–1
 AASK trial 494–5
 abdominal compartment syndrome 162–3
 ABO incompatibility in transplantation 444–5
 acarbose 894
 ACE inhibitors 486, 508–9, 523, 893
 CKD 203
 diabetic nephropathy 614
 acebutolol 503
 N-acetyl- β -D-glucosaminidase 95
 N-acetylcysteine 145, 150
 aciclovir 889
 nephrotoxicity 898
 acid-base balance 814–16
 buffering 814, 818
 excretion 818–19
 mixed disturbances 834–5
 models of 815, 816
 nomogram 835
 see also acidosis; alkalosis
 acidosis
 CKD 205, 215
 lactic 828–9
 metabolic 137–40, 834
 renal tubular 76–8, 826
 respiratory 822, 834
 acromegaly 475
 acute coronary syndrome 946–8
 acute fatty liver of pregnancy 845
 acute interstitial nephritis 694
 acute kidney disease (AKD) 90
 acute kidney injury (AKI) 87–92
 abdominal compartment syndrome 162–3
 biomarkers 94–5
 causes 96–7, 97, 164–5
 infective 164–5
 non-infective 165
 in cirrhosis see hepatorenal syndrome
 classification 96–7
 clinical assessment 114–15
 blood tests 118–19
 histology 121
 imaging 120
 urinalysis 116–17
 complications 129
 contrast-induced 148–51, 618
 definition 88–9, 90
 AKIN classification 88
 KDIGO AKI 88, 89
 RIFLE criteria 88
 developing world 164–5
 drug-induced 7, 898
 gadolinium 51
 metformin 52
 epidemiology 92–3
 haemoglobinuric 155
 intrinsic renal 105
 clinical assessment 114–15
 management 147
 anaemia 138
 bleeding 138
 checklist 122–3
 electrolytes and acidosis 136–7
 hyperkalaemia 130–3
 infection 139
 myths 144–5
 nutrition 140–1, 142–3
 pulmonary oedema 134–5
 volume replacement 124–5, 126–9
 mortality 93
 organ cross-talk 109
 perioperative risk reduction 99
 phases of 146
 pre-renal 102–3
 causes 104
 clinical assessment 114
 pregnancy 844–5
 prevention 98–101, 154
 STOP AKI checklist 100–1
 priorities 112–13
 prognosis 92–3
 recognition of 110–1
 renal biopsy 82
 renal replacement therapy 172–4
 anticoagulation 182–4, 186–7
 modalities 174–5, 176–7
 peritoneal dialysis 188–9
 prescription 178–181
 rhabdomyolysis 152–3, 154–5
 sepsis 166–7, 168–70
 tubular necrosis see acute tubular necrosis
 tumour lysis syndrome 160–1
 acute tubular injury see acute tubular necrosis
 acute tubular necrosis 106–7
 infective endocarditis 694
 pathophysiology 108–9
 ADAMTS13 576
 ADPKD see autosomal dominant polycystic kidney disease
 adrenal function, CKD 262
 adrenal hyperplasia, congenital 478
 adynamic bone disease 234, 235, 240
 management 249
 AKI see acute kidney injury
 AL amyloid 628–9
 alcohol, and hypertension 472–3
 aldosterone 457, 931
 aldosterone antagonists, and hyperkalaemia 797
 alemtuzumab 383–4
 alkalosis 830–2
 chloride-losing 830
 hypokalaemic 830
 metabolic 830, 834
 respiratory 831, 834
 allergic peritonitis 321
 ALLHAT study 494–5, 505
 allopurinol 895
 allrecognition 346–7, 348
 α -blockers 486, 504–5, 523, 892
 benign prostatic hyperplasia 761
 bladder outflow symptoms 505
 Alport syndrome 420, 568, 570
 kidney transplant 569
 aluminium toxicity 247, 308
 aluminium-based phosphate binders 248
 ambulatory blood pressure monitoring 458–9, 460
 amikacin 395
 dose 885
 amiloride 792, 931

- amino acid reabsorption 925
- aminoaciduria 76, 77
- aminoglycosides 880
- amiodarone 893
- ammonium 819
- amoxicillin 883
- amphotericin B 395
dose 891
- amyloid/amyloidosis see renal amyloid
- anaemia
AKI 138
CKD 205, 216–17
differential diagnosis 217
prevalence 216
- analgesia
live donors 379
patient-controlled 380
post-operative 395–6
- analgesic nephropathy 584, 584–5
- ANCA 119, 642
and pathogenesis 643
- ANCA-associated vasculitis 640–2
Birmingham vasculitis activity score (BVAS) 641
investigations 642–3
relapse 646–7, 648
renal biopsy 647
treatment 644, 644–5
- angiography 947
- angiotensin II 453, 456
- angiotensin II receptor blockers 486, 510–11
CKD 203
diabetic nephropathy 614
- angiotensin receptor blockers with neutral endopeptidase inhibition (ARNi) 513
- anidulofungin 891
- anion gap 820
- antacids 896
- antegrade ureteropyelography 57
- anti-glomerular basement membrane antibody 119, 656
- anti-glomerular basement membrane disease see Goodpasture's syndrome
- anti-HLA antibodies 361–2, 363
HLA antibody testing 363
screening for 362
tissue typing 360–1
- anti-neutrophil cytoplasmic antibodies see ANCA
- anti-nuclear antibodies 119
- anti-streptolysin O titres 119
- anti-thymocyte globulin 383, 384
- anti-tumour necrosis factor agents 668
- antibiotics see antimicrobials
- antibodies
ANCA 119
anti-glomerular basement membrane 119
anti-HLA 361–2, 363
anti-nuclear 119
antiphospholipid 119
depleting 383–5
donor-specific 361
non-depleting 382
non-HLA 362
panel reactive 362
- antibody-mediated rejection 409–10
- anticholinergic agents, benign prostatic hyperplasia 762
- anticoagulants 357
pre-transplantation management 394
- anticoagulation
renal replacement therapy 182–3, 184
citrate regional 186–7
haemodialysis 182–3
- anticonvulsants 854, 897
- antidiuretic hormone see vasopressin
- antiemetics 379
- antifungals 879–80, 890–1
nephrotoxicity 898
- antigens 22
- antihypertensive therapy 484–6, 489
ACE inhibitors 486, 508–9, 523
 α -blockers 486, 504–5, 523
- angiotensin receptor blockers 486, 510–11
- β -blockers 486, 502–3, 523
- calcium channel blockers 486, 506–7, 523
- CKD 204
- clinical trials 492–3, 494–7
- diuretics 498–9, 500–1, 523
- guidelines 488–9
- mineralocorticoid antagonists 501
- pre-transplantation management 394
- special situations 490–1
see also *individual drugs*
- antimicrobials 878–9
dose 883–9
peritonitis 322–3
in pregnancy 843
prescribing 882
prophylactic 395
see also *individual drugs*
- antiphospholipid antibodies 119, 665
- antiphospholipid syndrome 664–5
- antiplatelet drugs 357
pre-transplantation management 394
- antipsychotics 896
- antivirals 885
nephrotoxicity 898
- anuria 74
- aortic coarctation 475, 483
- apolipoprotein AI 632
- Aranesp® see darbepoetin A
- argatroban 291
- arterial blood gases 118
- arterial stiffness 455
- arteriovenous fistula 292
- ASCOT study 494–5
- 'asparagus urine' 15
- aspirin 485, 892
in pregnancy 858, 866, 867
- ASTRAL trial 172
- asymptomatic bacteriuria 706, 710
pregnancy 843
- atenolol 503, 523
- atherosclerotic renal artery stenosis 586
- atrial natriuretic peptides 145, 931
- autoregulation 920
- autosomal dominant polycystic kidney disease 553, 592–593
complications 594–5, 596
CKD 594
cyst haemorrhage 594
cyst infection 594
extrarenal cysts 595
hypertension 594
intracranial aneurysms 594
nephrolithiasis 594
management 595
pregnancy 857
Ravine criteria 593
- autosomal recessive polycystic kidney disease 598
- avosentan 617
- azathioprine 380, 390, 866
nephritic syndrome 543
- azotaemia 70

B

B cells 347
 bacteraemia,
 catheter-related
 297, 298
 bacterial prostatitis 711
 bacteriuria 24
 asymptomatic 706, 710
 Balkan endemic
 nephropathy 582
 Bardet-Biedl syndrome 601
 bardoxolone methyl
 209, 617
 baroreceptor activation
 therapy (BAT) 515
 Bartter's syndrome 480,
 800
 basal cell carcinoma, and
 transplantation 358
 basiliximab 382
 belatacept 391
 belimumab, in lupus
 nephritis 660
 benign prostatic hyperplasia
 758–9
 investigations 760
 management 761–3, 764
 physical examination 760
 benzodiazepines 896
 benzylpenicillin 883
 β -blockers 486, 502–3,
 523, 892
 see also *individual drugs*
 β_2 -agonists, in
 hyperkalaemia 132
 bicarbonate
 crystalloid solutions 125
 in dialysate 283
 normal range 834
 preventing loss 818
 reabsorption 922, 924
 supplements 823
 bilirubin, urinary 18
 Birmingham vasculitis activ-
 ity score (BVAS) 641
 bisoprolol 503
 bisphosphonates 895
 BK virus nephropathy
 436–7
 treatment 437
 bladder
 irritability 75
 neurogenic 618
 outflow obstruction 78,
 78–9
 post-transplant
 dysfunction 403
 stones 718
 suprapubic pain 75
 bladder carcinoma, and
 transplantation 358

bladder neck
 obstruction 727
 bladder tumours 750–1
 clinical features 751
 genetics 750
 investigations 751
 management 753–4
 pathology 752
 risk factors 750
 staging and prognosis
 752–752, 753–753
 bleeding
 AKI 138
 post-transplant 402
 bleeding tendency,
 pre-transplant
 assessment 357
 blood groups
 donor-recipient
 matching 360
 transplantation
 across 444
 blood pressure
 CKD 203, 204
 diabetic nephropathy
 612–13
 high see hypertension
 kidney in regulation of
 452, 452–3
 measurement 458–60
 ambulatory monitoring
 458–9, 460
 clinic readings 458
 home 460
 in pregnant women 846
 and salt intake 453
 systolic 451
 targets 466
 variability 460
 Blood Pressure Lowering
 Treatment Trialists
 Collaborative
 (BPLTTC) 493
 blood tests, AKI 118–19
 blood transfusion, AKI 133
 BMP-7 208
 bone metabolism 895
 post-transplant 425
 botulinum toxin,
 benign prostatic
 hyperplasia 764
 bowel preparation 943, 944
 Bowman's capsule 916
 brachytherapy 775
 brain death, organ donation
 after 365, 367
 brain natriuretic peptide 948
 branchio-oto-renal
 syndrome 602
 breast cancer, and
 transplantation 358
 buffering 814, 818

C

C1q nephropathy 572
 C3 nephritic factor 41
 caffeine, and
 hypertension 473
 calcific uraemic arteriolo-
 pathy 256–7
 calcimimetics 252–3
 calcineurin inhibitors 386–7
 drug interactions 388, 389
 nephritic syndrome 543
 nephrotoxicity 899–900
 side effects 388
 calciphylaxis 256–7
 dialysis-related 311
 calcium 802
 crystalloid solutions 125
 in dialysate 283
 hypercalcaemia 806–7
 hypercalciuria 77, 717
 in hyperkalaemia 131
 hypocalcaemia see
 hypocalcaemia
 reabsorption 922,
 925, 930
 calcium acetate 248
 calcium channel blockers
 486, 506–7, 523, 892
 calcium oxalate
 crystals 28, 29
 calcium oxalate stones
 716, 723
 calcium phosphate
 crystals 28, 29
 calcium-based phosphate
 binders 248
 calcium-sensing
 receptor 252
 cancer
 bladder tumours 750–1
 post-transplant 440–3
 pre-transplant assessment
 358, 358
 renal cell carcinoma see
 renal cell carcinoma
 renal medullary
 carcinoma 637
 renal pelvis tumours
 756–7
 renin-secreting
 tumours 479
 ureteric tumours 756–7
 carbamazepine 897
 carbohydrate intake in
 CKD 259
 cardiac biomarkers 948
 cardiac death, organ dona-
 tion after 366, 368
 cardiac failure,
 diuretics in 793
 cardiac MRI 355

- cardiac output
measurement 13
reduced 104
- cardiopulmonary exercise testing 355
- cardiorenal syndrome 209, 210
- cardiovascular disease
CKD 198, 198–9
as contraindication to live organ donation 377
dialysis-related 308
post-transplant 422, 422–3
pre-transplant 352–5, 357
revascularization 356
risk factors 199
- cardiovascular drugs 892–3
- cardiovascular risk factors 463
- carvedilol 503
- casprofungin 891
- cast nephropathy 622, 622–5
- casts, urinary 25, 26
- catheters
dialysis see dialysis catheters
and UTI 710
- cation exchange resins 132
- cefotaxime 884
- ceftazidime 884
- cefuroxime 395
dose 884
- celiprolol 503
- central lines 127
- central pontine myelinosis 786
- cephalosporins 884
- cerebral salt-wasting 783
- cervical carcinoma, and transplantation 358
- CHARGE syndrome 601, 714
- chemotherapeutic drugs, nephrotoxicity 899
- chest X-ray, AKI 120
- Chinese herb nephropathy 583
- chlorambucil 541
- chloride
crystalloid solutions 125
reabsorption 922, 924
- chloride-losing alkalosis 830
- CHOIR trial 226
- cholesterol emboli 590
urinary 28
- chronic kidney disease (CKD) 69–70
acidosis 205, 215
acute coronary syndrome 946–8
and ADPKD 594
advanced
complications 214–15
uraemic syndrome 212–13
anaemia 216–17
analgesia 271
cardiac biomarkers 948
and cardiovascular disease 198, 198–9
causes 193
classification 192, 195
definition 192, 192–3
diagnosis 196–7
dialysis 267
decision not to have 270
withdrawal of 270
diet and nutrition 258–9
endocrine problems 262–3
fluid overload 214
hepatitis B vaccination 685
hyperkalaemia 214–15
malnutrition 260
management 264–5
advanced care 266–7
oral bicarbonate supplements 823
pre-transplantation 395
referral 265
renal replacement therapy see renal replacement therapy
symptom control 268, 268–9
mineral and bone disorder see CKD-MBD
palliative care 270
pathogenesis 200, 201
patient education 266–7
prevalence 194, 194–5
progression 200, 202–3
factors affecting 202
prevention 202–3, 204–5, 208, 210
recognition of 111
renal biopsy 82–3
screening 197
- Churg-Strauss syndrome 654–5
- chyluria 14
- ciclosporin 380–1, 866
- cidofovir 898
- cinacalcet 253
- ciprofloxacin 882
dose 884
circulation 12–13
- cirrhosis
AKI see hepatorenal syndrome
diuretics 793
cisplatin 899
- citrate regional anticoagulation 186–7
- CKD see chronic kidney disease
- CKD-MBD 235
bone disease
adynamic 234, 235, 240, 249
hyperparathyroid 234, 235, 238, 240, 249
mixed uraemic osteodystrophy 234
osteomalacia 234, 235
osteoporosis 234
classification 233
clinical features 240–1
hyperphosphataemia 246–9
vascular calcification 242–3
see also bone disease above
definition 232
diagnosis 240–1
physiology 236–7, 238
treatment 244, 244–5
calcimimetics 252–3
KDIGO guidelines 245
parathyroidectomy 254–5
vitamin D 250–1
- clarithromycin 882
dose 884
- clearance 872
- clindamycin 889
- clinical history 2, 2–3
diet 8
drugs and treatments 6
family 6
sexual, gynaecological and obstetric 8
social 4–5
symptoms 4
systems review 5
- cloacal abnormality 715
- clonidine 512
- clopidogrel 892
- co-amoxiclav 882
dose 883
- co-trimoxazole 395
dose 887
- COACH syndrome 601
coarctation of aorta 475, 483
- Cockcroft-Gault formula 34
- colchicine 895
- cold ischaemic time 365
- collecting duct 931
- colloids, synthetic 125
- colorectal carcinoma, and transplantation 358

- compartment syndrome
 abdominal 162–3
 rhabdomyolysis 155
 complement 11, 41
 computed
 tomography see CT
 congenital abnormalities
 714, 714–15
 constipation 896
 continuous ambulatory peritoneal dialysis 314, 315
 continuous epoetin receptor activator see methoxy polyethylene glycol epoetin β
 continuous positive airways pressure (CPAP) 135
 contrast media 53
 contrast-induced AKI
 148–51, 618
 cortical necrosis 845
 corticosteroids 866
 ANCA-associated vasculitis 644
 Goodpasture's syndrome 657
 immunosuppression 391
 nephritic syndrome 540
 lupus nephritis 660
 countercurrent system
 928–9
 CREATE trial 226
 creatine kinase 948
 creatinine, serum levels 32
 creatinine clearance 32–3
 critical illness, invasive monitoring 13
 cross-matching 363–4
 positive, transplantation across 444–5
 crossed fusion ectopia 715
 cryoglobulinaemia 634–5
 cryoglobulins 119
 crystalloids 124
 balanced 124
 composition 125
 hypotonic 124
 crystalluria 28, 29
 drug-induced 28
 CT 48, 50
 obstruction 732–3
 CT coronary angiogram 355
 Cushing's syndrome
 475, 482
 CYCAZAREM study 648
 cyclizine 379
 cyclophosphamide 541, 542
 ANCA-associated vasculitis 644
 Churg-Strauss syndrome 655
 gonadal toxicity 542
 Goodpasture's syndrome 657
 lupus nephritis 660
 nephrotoxicity 899
 CYCLOPS study 648
 CycLowVas study 648
 CYP3A4, induction/inhibition 388
 cystatin C 36, 94
 cystic kidney disease 598, 598–602
 acquired 598
 autosomal dominant see autosomal dominant polycystic kidney disease
 autosomal recessive 598
 classification 598
 medullary 599
 syndromes associated with 601–2
 cystine crystals 28, 29
 cystine stones 719
 cystinosis 836
 cystinuria 719, 836, 837
 cystitis 707
 interstitial 711
 pregnancy 843
 cystography 56
 cystoscopy 708
 cystourethroscopy 57
 cysts 742, 743
 cytomegalovirus,
 post-transplant 430–4
 management 432–3
 pre-emptive treatment 432, 433
 risk 431
- D**
 daclizumab 382
 dapsone 395
 daptomycin 886
 darbepoietin A 220
 DASH eating plan 472
 Dent's disease 836
 dermatomyositis 669
 device-guided respiration in hypertension 514
 diabetes insipidus 789
 diabetes mellitus
 CKD 205
 medications,
 pre-transplantation management 394
 post-transplant 422, 424–5
 urinary tract disorders 618–19
 see also diabetic nephropathy
 diabetic nephropathy
 420–1
 diagnosis 610, 611
 management 612–14, 614, 616–17, 894
 mortality risk 607
 pathology 608–9
 pregnancy 857
 prevention 610
 progression 606, 606–7
 screening 610
 diagnostic imaging
 abnormal renal size 26
 CT 48, 50
 intravenous urography 52–3
 MRI 50–1
 normal appearance 46
 nuclear medicine 54–5
 plain X-ray 44–5
 renal angiography 56
 ultrasound 46
 uroradiology 56–7
 dialysate
 haemodialysis 179–80
 concentrates 283
 cooling 303
 ultrapure water 282
 peritoneal dialysis 316–17
 biocompatible solutions 316
 commercially available solutions 317
 glucose concentrations 317
 dialysers 284
 dialysis see haemodialysis; peritoneal dialysis
 dialysis catheters 296–9
 bacteraemia 297, 298
 long-term complications 299
 malfunction 296–7
 problematic insertion 937
 temporary 296–300
 blind insertion 938
 femoral line 940
 indications 936–7
 insertion technique 937–8
 vein localization 938, 939
 tunnelled/cuffed 296, 940
 dialysis disequilibrium 177
 diet 8
 CKD 258–9
 DASH eating plan 472
 low-sodium 472
 DiGeorge syndrome 601
 digoxin 893
 dilution acidosis 820
 disease associations 3

- distal convoluted tubule 930
 diuretics 132–3, 500–1, 523–4
 AKI 135, 144
 hypertension 498–9, 486, 500–1
 loop 500, 792
 mineralocorticoid antagonists 501, 792
 potassium-sparing 500–1
 thiazide-type 486, 498–9, 792
 dobutamine stress test 355
 domperidone 895
 donor-specific antibody 361
 dopamine 144, 144–5
 dopamine antagonists 895
 dose-response curve 873
 doxazosin 523
 doxycycline 889
 drug distribution 871
 drug history 6
 drug metabolism 871
 drug prescribing 869–72
 cardiovascular drugs 892–3
 dialysis patients 870–4, 874, 876–7
 clearance 872
 pharmacodynamics 870
 lithium 904–5
 nephrotoxic drugs 898–901
 NSAIDs 895, 901–3
 renal impairment, pharmacokinetics 870–1, 872–3
 specific situations 894–7
 see also *individual drugs and classes*
 duplication
 (developmental) 715
 dyslipidaemia
 CKD 205
 nephrotic syndrome 557
 post-transplant 422, 423–4
 dyspepsia 896
- E**
 Eagle-Barrett syndrome 715
 ECG
 hyperkalaemia 130
 resting 355
 echocardiography 13
 ectopic kidneys 714
 eculizumab 391
 effective arterial blood volume 778
 falling 779
 rising 779
- electrolytes, AKI 136–7
 embolic renal infarction 694
 emphysematous pyelonephritis 711
 encephalopathy, hyponatraemic 786–7
 end-stage renal disease 70
 diabetic patients 619
 hepatitis B 684–5
 hepatitis C 690
 HIV patients 679
 and microscopic haematuria 68
 myeloma 624–5
 tuberculosis patients 699
 endocarditis, infective 692–4, 695
 endothelial dysfunction 453
 endothelin antagonists 208, 513
 endothelins 453
 epithelial cells 916
 epoetin 220
 Epogen® see epoetin
 Eprex® see epoetin
 Epstein-Barr virus, and post-transplant lymphoproliferative disorder 441
 Epworth sleepiness score 483
 Erdheim-Chester disease 738
 ertapenem 887
 erythromycin 885
 erythropoiesis-stimulating agents 220, 220–1
 adjunctive therapy 224
 benefits 224
 clinical trials 226–7
 current targets 227
 prescription 222–3
 resistance 223
 side effects 227
 erythropoietin 218–19
 cytoprotective effect 219
 in pregnancy 863
 production 218, 219
 esmolol 524
 etanercept 668
 ethylene glycol poisoning 910–1
 excretion 818–19
 exercise, and hypertension 472
 exercise stress test 355
 extended criteria donors 368, 369
 extracorporeal shock wave lithotripsy 725
- F**
 Fabry's disease 672–3
 factor H 41
 deficiency 578
 famciclovir 898
 familial amyloid polyneuropathy 632
 familial Mediterranean fever 632
 family history 6
 Fanconi syndrome 76–7, 825
 see also renal tubular acidosis
 femoral line insertion 940
 fenoldopam 146
 fentanyl 379, 380
 Feraheme® see feromoxylol
 feromoxylol
 feromoxylol
 Ferinject® see ferric carboxymaltose
 feromoxylol 231
 ferric carboxymaltose 231
 ferritin 230
 Ferrlecit® see sodium ferric gluconate
 FGF-23 236
 fibrillary glomerulonephritis 627
 fibrinogen A α -chain 632
 fibromuscular dysplasia 590, 591
 flucloxacillin 882
 dose 883
 fluconazole 890
 fluid balance, post-operative 397
 fluid overload in CKD 214
 fluid restriction 258
 fluid resuscitation
 AKI
 choice of fluid 124–5
 how much 126–8, 129
 fucytosine 891
 focal segmental glomerulosclerosis 418–19, 560–3
 inherited 562
 management 563
 primary 560–1
 secondary 562
 foscarnet 890
 nephrotoxicity 898
 fresh frozen plasma 577
 furosemide (see also diuretics) 523
- G**
 gabapentin 897
 gadolinium, nephrogenic systemic fibrosis 51

- ganciclovir
 cytomegalovirus 433
 dose 889
 nephrotoxicity 898
 gemcitabine 899
 genitourinary tuberculosis
 696–7
 gentamicin 881, 882
 dose 885
 gestational hypertension
 847–8
 GFR see glomerular
 filtration rate
 Gitelman's syndrome 480,
 800, 801
 glomerular basement
 membrane 916
 glomerular filter 917, 919
 glomerular filtration
 rate 30–1
 estimated 34–5
 CKD 196–7
 CKD-EPI equation 35
 Cockcroft-Gault
 formula 34
 MDRD 34
 reciprocal of plasma
 creatinine 35
 isotopic 36, 36–7
 live donor transplantation
 374, 375
 older patients 38–9
 post-transplant 422
 regulation of 920–1
 glomerular vessels 531
 glomerulo-tubular
 balance 923
 glomerulonephritis
 bacterial 695
 fibrillary 627
 hepatitis C-related 686–7
 immunotactoid 627
 mesangiocapillary 419–20,
 552–3
 MRSA 693, 694
 post-infectious 548–9
 rapidly progressive 71
 virus-associated 691
 glomerulus 916, 918, 919
 glucocorticoid-remediable
 hyperaldosteronism 478
 glucose
 dialysate solutions 317
 in hyperkalaemia 131
 peritoneal exposure 319
 reabsorption 925
 glutathione
 S-transferase 95
 glycosuria 18, 76
 renal 77
 Goodpasture's
 syndrome 72–3
 Gordon's syndrome 797
 gout 895
 granisetron 895
 granulomatosis with
 polyangiitis 640
 granulomatous interstitial
 nephritis 671
 GRF see glomerular
 filtration rate
 growth retardation in
 CKD 263
 gynaecological history 8
- H**
- H₁ receptor antagonists 896
 HAART therapy, renal side
 effects 679
 haematuria 22–3, 62–3
 causes 33
 classification 62
 clinical assessment 64–5
 macroscopic 62, 65
 microscopic 62, 66,
 67, 530
 causes 33
 as contraindication
 to live organ
 donation 377
 malignancy risk 48
 renal biopsy 82
 screening 68
 pregnancy 860
 with proteinuria 530
 transient 62
 haemodiafiltration 175, 279
 haemodialysis 9–10
 access 292–5
 AV fistula 292
 complications 294
 fistula care 293
 lines 296–9
 PTFE graft 292
 surveillance 293
 see also dialysis
 catheters
 adequacy of 286, 286–8
 anticoagulation 182–3
 antimicrobial therapy
 878–9, 882
 diabetic patients 619
 dialysate 179–80
 concentrates 283
 cooling 303
 ultrapure water 282
 dialysers and
 membranes 284
 equipment 278–80,
 280, 281
 hepatitis B 684
 HIV patients 679
 in-hospital nocturnal 304
 intensive 304
 intermittent 174, 175,
 176
 prescription 178–9
 intradialytic hypotension
 302–3
 long-term complications
 308–9
 aluminium toxicity 308
 amyloidosis 308–9
 cardiovascular
 disease 308
 malnutrition 308
 vascular calcification
 308, 311
 nocturnal home 304
 pregnancy 863
 short daily 304
 sodium homeostasis 301
 sustained
 low-efficiency 179
 treatment of
 poisoning 906
 volume control 300
 dry weight 300
 withdrawal 311
 haemodynamic
 monitoring 13
 haemofiltration 174,
 175, 279
 treatment of
 poisoning 906
 see also haemodialysis
 haemoglobinuria 14
 AKI 155
 haemolytic uraemic syn-
 drome 420–1, 574
 pregnancy 845
 haemoperfusion 907
 haloperidol 897
 hantavirus 73
 heavy chain deposition
 disease 627
 HELLP syndrome 855
 Henoch-Schönlein purpura
 650–1
 and IgA nephropathy 651
 heparin 892–3
 low molecular weight
 182, 290
 and thrombocytopenia
 184
 unfractionated 182,
 184, 290
 heparin-induced thrombocy-
 topenia 184, 290
 hepatitis B 680–1
 associated renal disease
 682–3
 end-stage renal disease
 684–5
 vaccination 685

- hepatitis C-related renal disease 686–7
 end-stage 690
 management 688–9
 hepatocyte growth factor 208
 hepatorenal syndrome 156–7
 classification 156
 diagnostic criteria 157
 management 158–9
 renal replacement therapy 159
 risk factors 158
 hepcidin 229
 herbal medicines 901
 hereditary amyloidosis 632
 hereditary nephropathies 568–70
 Alport syndrome 420, 568, 569, 570
 nail-patella syndrome 570
 thin membrane disease 568, 570
 herpes simplex virus, post-transplant 434
 hirudin 291
 histocompatibility 346–7, 348
 HIV immune complex kidney disease (HIVICK) 674, 678
 HIV-associated nephropathy (HIVAN) 676, 674–7
 classification 677
 HIV-associated thrombotic microangiopathy 674, 678
 HLA antibody testing 363
 HLA incompatibility in transplantation 444–5
 holmium laser enucleation of prostate (HoLEP) 764
 HOPE study 494–5
 hormone replacement therapy, and antihypertensive therapy 491
 horseshoe kidneys 714
 HOT study 494–5
 5-HT₃ antagonists 895
 human albumin solutions 125
 human leukocyte antigen see HLA
 humoral rejection 409–10
 hydralazine 513, 849
 hydronephrosis 726
 hyperacute rejection 408
 hyperaldosteronism 475, 476–7
 causes 476
 diagnosis 476–7, 479
 primary 478
 congenital adrenal hyperplasia 478
 glucocorticoid-remediable 478
 secondary 478
 treatment 477
 hypercalcaemia 806–7
 hypercalciuria 77, 717
 hypercoagulability 556–7
 hyperglycaemia, and diabetic nephropathy 608–9
 hyperkalaemia 130–3, 796–7
 with aldosterone antagonism 797
 CKD 214–15
 ECG 130
 treatment 131–2
 hyperkalaemic periodic paralysis 797
 hyperkalaemic renal tubular acidosis 718–19
 hypermagnesaemia 810
 hypernatraemia 788–9
 treatment 790
 hyperoxaluria 717, 836, 837
 prevention 723
 hyperparathyroid bone disease 234, 235, 238, 240
 management 249
 hyperparathyroidism and hypertension 475
 pre-transplant 356
 vs. malignancy (in hypercalcaemia) 807
 hyperphosphataemia 136, 811
 CDK-MBD 246–9
 CKD 205
 hyperprolactinaemia, CKD 262
 hypertension 71–8
 accelerated 518
 in ADPKD 594
 black patients 490
 cardiovascular risk assessment 470–1
 cardiovascular risk factors 463
 classification 464–50, 465, 466
 clinical assessment 462–3
 definition 451
 epidemiology 450
 facts and figures 450
 malignant 518, 519
 management
 drugs see antihypertensive therapy
 lifestyle measures 472–3, 473
 non-pharmacological 514–15
 older patients 490
 pathogenesis 452–3
 arterial stiffness 455
 genetics 454
 renin-angiotensin system 456, 456–7
 sympathetic nervous system 455
 post-transplant 422, 422–3
 pregnancy 846–8
 treatment 849
 resistant 516, 517
 secondary 474–5
 apparent mineralocorticoid excess 480
 coarctation of aorta 475, 483
 Cushing's syndrome 475, 482
 hyperaldosteronism 475–6, 477–8, 479
 obstructive sleep apnoea 475, 483
 phaeochromocytoma 475, 482
 thyroid disease 475, 483
 specialist referral 469
 target organ damage 462, 520
 treatment thresholds 465, 466–467
 urgencies/emergencies 518–19
 assessment 520–1
 management 522–3, 524
 white coat 460
 see also blood pressure
 hypertensive retinopathy 521
 hyperuricaemia 895
 hyperuricosuria 717
 prevention 723
 hypervolaemia 12
 hypoalbuminaemia, nephrotic syndrome 791
 hypocalcaemia 136–7, 804–5
 post-parathyroidectomy 254
 rhabdomyolysis 155
 hypocitraturia 717
 hypokalaemia 76–8
 investigations 799
 hypokalaemic alkalosis 830
 hypomagnesaemia 137–8
 hyponatraemia 780–1
 assessment 782–3
 with encephalopathy 786–7
 euvolaemic 781, 784
 hypervolaemic 781, 784

hypovolaemic 780, 784
 management 784–5
 hypoperfusion 102
 physiological
 response to 102
 hypophosphataemia 812
 hypotension
 intradialytic 302–3
 orthostatic 526–7
 hypovolaemia 12, 104
 HYVET study 496–7

I

ibuprofen 379
 icodextrin 319
 ifosfamide 899
 IgA nephropathy
 419–20, 545
 and Henoch-Schönlein
 purpura 651
 hepatitis B-associated 682
 management 546–7
 IgM nephropathy 572
 ileal loopography 57
 immunoabsorption 951
 immunoglobulins 119, 620
 intravenous 899
 immunology of transplanta-
 tion 346–9
 B cells 347
 histocompatibility and
 allorecognition
 346–7, 348
 T cell activation 347, 348
 tolerance 349
 immunosuppressive therapy
 380–1
 and cardiovascular
 disease 422
 clinical applications
 IgA nephropathy 547
 membranous
 nephropathy 567
 mesangiocapillary glo-
 merulonephritis 553
 nephritic syndrome
 540–3
 immunological risk 381
 induction 382–5
 depleting antibodies
 383–4, 385
 non-depleting
 antibodies 382
 maintenance 386–91
 azathioprine 390
 calcineurin inhibitors
 386–7, 388, 389
 corticosteroids 391
 mycophenolic acid
 389–90
 sirolimus 390

nephrotoxicity 899
 in pregnancy 866
 prescription 395
 triple therapy 380
 immunotactoid
 glomerulonephritis 627
 IMPROVE study 648
 in-hospital nocturnal hae-
 modialysis 304
 indinavir 898
 infections
 AKI 139
 post-transplant 426–9
 BK virus nephropathy
 436–7
 cytomegalovirus 430–4
 fever 427
 Pneumocystis
 pneumonia 428
 UTI 438–9
 pre-transplant 357
 INSIGHT study 496–7
 insulin 894
 in hyperkalaemia 131
 intercalated cells 932, 932
 interferon α 899
 interleukin-18 95
 interstitial cystitis 711
 interstitial nephritis
 acute 694
 tuberculous 698–9
 intracranial aneurysms 594
 intradialytic hypotension
 302–3
 intravenous
 urography 52–3
 contrast media 53
 obstruction 733
 invasive monitoring 13
 iron 228–9
 adverse reactions 231
 deficiency
 absolute 228
 functional 228
 reticuloendothelial
 block 228
 monitoring 230
 status markers 228–9
 targets 230
 therapy 230–1
 intramuscular 230
 intravenous 231–2
 oral 230
 iron dextran 231
 iron III hydroxide sucrose
 complex 231
 ischaemic nephropathy 586
 islet cell transplantation
 446, 447
 isoniazid 395
 isosthenuria 16
 isotonic saline 95, 125

isotope studies
 AKI 121
 obstruction 733
 itraconazole 890

J

J curve phenomenon 468
 Jeune syndrome 601
 Joubert syndrome 599, 601
 Joint national committee
 guideline 468
 Juvenile nephronophthisis
 598–9
 juxtaglomerular
 apparatus 921

K

Kawasaki disease 638
 ketoconazole 890
 ketonuria 18
 kidneys
 in blood pressure control
 452, 452–3
 functions 914–15
 palpation 11
 structure 914
 kidney disease 529–32
 acute see acute
 kidney injury
 chronic see chronic kidney
 disease
 histology 531–535, 535
 see also *individual diseases*
 kidney injury molecule-1 95
 kidney stones see
 nephrolithiasis
 kidney transplantation
 335–8
 ABO/HLA-incompatible
 444–5
 ANCA-associated
 vasculitis 647
 antimicrobial therapy
 after 879
 benefits 336, 337
 challenges 337, 337–8, 339
 complications 402–3
 early 402–3
 late 403
 post-transplant malig-
 nancy 440–3
 see also post-transplant
 infections, below
 contraindications 350
 diabetic patients 619
 donor characteristics
 365–7, 369
 brain death 365, 367
 cardiac death 366, 368

- kidney transplantation
(*Cont'd*)
 contraindications
 to deceased donation 369
 extended criteria donors 368, 369
 opting in or out 369
 warm/cold ischaemic time 365
 donor-recipient matching 360–1
 anti-HLA antibodies 361–2, 363
 blood group 360
 cross-matching 363–4
 non-HLA antibodies 362
 tissue typing 360–1
 failure 417
 graft dysfunction 404, 404–406
 delayed 404–5
 early 405–6
 hepatitis B patients 684
 hepatitis C patients 690
 HIV patients 679
 immunology 346–9
 immunosuppression 380–1
 immunological risk 381
 induction 382–5
 maintenance 386–92
 prescription 395
 triple therapy 380
 live donor 372–9
 live donor exchange schemes 445
 long-term follow-up 422–5
 bone and mineral metabolism 425
 cardiovascular disease 422, 422–3
 dyslipidaemia 423–4
 hypertension 422–3
 new-onset diabetes 424–5
 operation 400–1
 dual transplants 401
 organ retrieval 400
 recipient operation 400–1
 outcomes 340, 340–4
 graft failure 341
 graft survival 341–2, 344, 367, 368
 patient survival 339, 341
 patient education 350
 patient selection 350
 perioperative care 392–9
 investigations 393
 medications 394–6
 peritoneal dialysis
 patients 393–4
 pre-dialysis patients 393
 post-operative care 396–7
 low urine output 397–9
 post-transplant biopsy 407
 post-transplant infections 426–9
 BK virus nephropathy 436–7
 cytomegalovirus 430–4
 fever 427
 Pneumocystis pneumonia 428
 UTI 438–9
 pre-transplant assessment 350–1, 352
 cardiovascular disease 352–5, 357
 goals of 351
 infection risk and history 357
 mental health 359
 native renal disease 359
 previous malignancy 358, 358
 thrombotic or bleeding tendency 357
 pregnancy after 864, 865
 graft rejection 865
 management 866–7
 outcome 865
 pre-pregnancy and antenatal care 866–7
 recipient characteristics 370–1
 recurrent disease 418, 418–20
 Alport syndrome 420
 diabetic nephropathy 420
 focal segmental glomerulosclerosis 418–19
 haemolytic uraemic syndrome 420
 IgA nephropathy 419
 membranous glomerulonephritis 419
 mesangiocapillary glomerulonephritis 419
 rejection
 acute 408, 408–12
 Banff classification 411
 chronic 414, 414–17
 humoral/antibody-mediated 409–11
 T cell-mediated 408–9
 thrombotic microangiopathy 412
 vaccinations 428
 kidney-liver transplantation 448
 kidney-pancreas transplantation 446–8
 benefits 446
 Klotho 236
- L**
 labetalol 504, 849
 lactate, crystalloid solutions 125
 lactic acidosis 828–9
 lamotrigine 897
 lanthanum carbonate 248
 Lawrence-Moon syndrome 602
 lead nephropathy 583
 leptospirosis 164
 leucocyte esterase 18
 leucocytes, urinary 24
 levetiracetam 897
 Liddle's syndrome 480, 801
 LIFE study 496–7
 light chain deposition disease 626
 linezolid 886
 lithium 904–5
 intoxication 905
 nephrotoxicity 904–5
 lithium dilution technique 13
 live donor exchange schemes 445
 live donor transplantation 372–9
 advantages 372
 concerns 377
 contraindications 375–6
 disadvantages 372
 donor assessment 372–3
 GFR 374, 375
 donor nephrectomy 378
 pain relief 379
 renal outcomes 374
 liver transplantation 159
 hepatorenal syndrome 159
 liver-kidney transplantation 448
 liver-type fatty acid-binding protein 95
 loin pain 75
 loop diuretics 500, 792
 loop of Henle 926, 927
 countercurrent system 928–9
 low molecular weight heparin 182, 290
 low-sodium diet 472
 lupus nephritis 658–9
 classification 659
 initial therapy 660–1

maintenance therapy
 662–3
 pregnancy 857, 859
 renal biopsy 661
 lymphocele,
 post-transplant 403
 lymphoma, and
 transplantation 358
 lymphoproliferative dis-
 order, post-transplant
 441–3
 classification 442

M

magnesium 802–3
 crystalloid solutions 125
 hypermagnesaemia 810
 hypomagnesaemia 137–8
 magnesium ammonium
 phosphate crystals 28, 29
 magnesium carbonate 248
 magnetic resonance imaging
 see MRI
 malaria 702–3
 malignancy see cancer
 malignant hypertension
 518, 519
 malnutrition
 CKD 260
 dialysis-related 308
 mannitol 144, 154
 mean arterial pressure
 (MAP) 168
 Meckel-Gruber
 syndrome 601
 medullary cystic kidney
 disease 599
 medullary sponge
 kidney 599
 megaureter 715
 melioidosis 165
 membranous
 glomerulonephritis 419
 hepatitis B-associated 682
 rheumatoid
 arthritis-associated 668
 membranous nephropathy
 564, 564–5
 secondary 565
 treatment 566–7
 menopause, early, in
 CKD 262
 mental health of transplant
 patients 359
 MEPEX study 648
 meropenem 887
 mesangial cells 916
 mesangiocapillary glomeru-
 lonephritis 419–20
 hepatitis B-associated 682
 kidney transplant 419

presentation and manage-
 ment 552–3
 mesangioproliferative
 glomerulonephritides 572
 metabolic acidosis
 137–40, 834
 metabolic alkalosis
 830, 834
 reversal 832
 metformin 894
 contrast-induced AKI 52
 metglitinides 894
 methanol poisoning 912
 methotrexate 668
 nephrotoxicity 899
 methoxy polyethylene gly-
 col epoetin β 220, 221
 methyl dopa 512, 849
 metoclopramide 895
 metoprolol 503
 metronidazole 885
 microalbuminuria 60, 61
 β_2 -microglobulin-related
 dialysis amyloid 632–3
 micturating cystourethro-
 graphy (MCUG) 56
 Mimpara[®] see cinacalcet
 mineral metabolism,
 post-transplant 425
 mineralocorticoid antago-
 nists 501, 792
 mineralocorticoid excess,
 apparent 475, 480
 minimal change disease 558–9
 minoxidil 512
 Mircera[®] see methoxy
 polyethylene glycol
 epoetin β
 mitomycin 899
 mixed connective tissue
 disorder 669
 mixed uraemic
 osteodystrophy 234
 monoclonal gam-
 mopathy of uncertain
 significance 624
 monoclonal Ig deposition
 disease 626–7
 morphine 380
 moxonidine 512
 MRI 50–1
 cardiac 355
 obstruction 733
 MRSA glomerulonephritis
 693, 694
 Muckle Wells
 syndrome 632
 multicystic dysplastic
 kidneys 715
Mycobacterium leprae 695
Mycobacterium tuberculosis
 695, 696

mycophenolate mofetil
 543, 866
 lupus nephritis 660
 mycophenolic acid 389–90
 MYCYC study 648
 myeloma kidney 620–1
 cast nephropathy 622,
 622–5
 myocardial perfusion
 scan 355
 myoglobin 152

N

nadolol 503
 nail-patella syndrome 571
 nateglinide 894
 nausea 895
 nebivolol 503
 Neora[®] see ciclosporin
 nephrectomy, live
 donor 378
 nephritic syndrome 71
 acute 536–7
 immune
 complex-mediated 537
 management 538–9
 immune suppression
 540–3
 mechanisms 536
 renal biopsy 82
 nephritis see nephritic
 syndrome
 nephroblastoma 749
 nephrocalcinosis 45
 nephrogenic sys-
 temic fibrosis,
 gadolinium-induced 51
 nephrolithiasis 716–19
 clinical presentation 720–1
 imaging 721
 management 722–3
 pregnancy 860
 prevention of recurrence
 722, 723
 renal colic 724–5
 risk factors 717
 screening for 721
 stone composition 716
 stone formation 716
 stone types 716–17
 surgical management 725
 nephron 915
 nephrotic syndrome 60–1
 diuretics 793
 hypoalbuminaemia 791
 management 556–7
 oedema 791
 proteinuria 60, 554
 nephrotoxic drugs 898–901
 see also poisoning
 nephrotoxins 7, 98

- neurofibromatosis 602
 neurogenic bladder 618
 nephrophil
 gelatinase-associated lipocalin 94
 nifedipine 523, 849
 nitrates 524, 892
 nitric oxide 453
 nitrites, urinary 18
 nitrofurantoin 888
 nocturnal home haemodialysis 304
 non-HLA antibodies 362
 non-steroidal anti-inflammatory drugs see NSAIDs
 Noonan syndrome 601
 NSAIDs 895, 902–3
 nephrotoxicity 902
 nuclear medicine 54–5
 radiopharmaceuticals 54
 see also isotope studies
 nutrition
 AKI 140–1, 142–3
 CKD 258–9
 nutritional status 258
 nystatin 395
- O**
- obesity
 as contraindication to live organ donation 377
 and hypertension 472
 obstetric history 8
 obstruction 715, 726–7
 causes 727
 clinical presentation 730–1
 epidemiology 726
 imaging 732–3
 investigations 731
 pathophysiology 728–9
 pelvi-ureteric 736–7
 post-obstruction diuresis 735
 pregnancy 860
 recovery of renal function 729
 treatment 734–5
 obstructive nephropathy 726
 obstructive sleep apnoea 475, 483
 obstructive uropathy 726
 oedema 791
 diuretics see diuretics
 oesophageal Doppler 13
 OKT3 385
 older patients
 hypertension 490
 renal function 38–9
 oliguria 74
- omeprazole 379
 ondansetron 379, 895
 ONTARGET study 496–7
 opioid analgesics 897
 oral anticoagulants 893
 oral contraceptives, and anti-hypertensive therapy 491
 orthostatic hypotension 526–7
 osmoreceptors 779
 osteodystrophy
 mixed uraemic 234
 and vascular calcification 242–3
 osteomalacia 234, 235
 osteoporosis 234
 overactive bladder 765
 oxalate, dietary 723
 oxidative stress 453
 oxprenolol 503
 oxycodone 380
- P**
- pancreas transplantation 446–7
 panel reactive antibodies 362
 papillary necrosis 585, 618
 paracetamol 379, 395
 parathyroid hormone assays 241
 CKD-MBD 236, 238
 parathyroidectomy 254–5
 patient-controlled analgesia 380
 pCO₂ 834
 pelvi-ureteric obstruction 736–7
 penicillamine 668
 penicillins 883
 pentamidine 395
 percutaneous coronary intervention 947
 peripheral vasodilatation 104
 peritoneal dialysis 9–10
 adequacy of 328–9, 330
 advantages 312
 AKI 188–9
 antimicrobial therapy 879
 catheter placement 188
 complications 324–6, 334
 drainage problems 325
 exit site infection 324
 leaks 325
 peritonitis 320–1, 322–3
 sclerosing encapsulating peritonitis 326
 ultrafiltration failure 332, 333
 contraindications 313
- diabetic patients 619
 dialysate 316–17
 biocompatible solutions 316
 commercially available solutions 317
 glucose concentrations 317
 peritoneal glucose exposure 319
 physiology 312
 pre-transplantation management 393–4
 pregnancy 863
 prescription 189–90
 social rehabilitation 334
 transporter status 318
 types of 314–15
 assisted 314
 automated 314, 323
 continuous ambulatory 314, 315
 tidal 314
 well patients 334
 peritoneal equilibration test 330
 peritonitis 320–1
 allergic 321
 bacteriology 320–1
 catheter removal 323
 complications 321
 management 322–3
 risk factors 320
 sclerosing encapsulating 326
 PEXIVAS study 648
 pH 834
 pheochromocytoma 475, 482
 pharmacodynamics 870
 pharmacokinetics 870–1
 first order 872–3
 phentolamine 524
 phosphate
 dietary restriction 246, 259
 hyperphosphataemia 136, 811
 hypophosphataemia 812
 reabsorption 925
 phosphate binders 246–7, 248
 phosphaturia 76, 77
 phosphodiesterase-5 inhibitors, benign prostatic hyperplasia 762
 phosphorus 803
 photoselective vaporization of prostate 764
 physical examination 10–11
 by area 10
 by system 11
 circulation 12–13

- phytotherapy, benign prostatic hyperplasia 762
- pindolol 503
- piperacillin-tazobactam 883
- pirfenidone 208, 617
- plasma cell dyscrasias 620–1
- plasma exchange 577, 950, 952
- Goodpasture's syndrome 657
- plasmacytoma 624
- plasmapheresis see plasma exchange
- pneumaturia 14
- Pneumocystis jiroveci* 428
- pO₂ 834
- podocytes 916
- poisoning
- dialysis treatment 906–7
- ethylene glycol 910–11
- methanol 912
- salicylate 908–9
- polyarthritis nodosa 652–3
- hepatitis B-associated 682
- polycystic kidney disease
- see autosomal dominant adult polycystic disease and cystic kidney disease
- polymyositis 669
- polyomaviruses 436–7
- polyuria 74, 75
- post-infectious glomerulonephritis 548–9
- posterior urethral valves 737
- postural tachycardia syndrome 527
- potassium 794
- crystalloid solutions 125
- in dialysate 283
- dietary restriction 259
- hyperkalaemia see hyperkalaemia
- hypokalaemia 76–8
- reabsorption 922, 924, 931
- prazosin 486, 504–5, 849
- pre-eclampsia 850–1, 859
- diagnosis 852
- fetal assessment 853
- follow-up and prognosis 855
- indications for delivery 853
- management 852–3, 855
- organs affected 851
- pathogenesis 850, 851
- and placenta 850
- renal impairment 856
- severe 854
- symptoms 852
- precutaneous nephrolithotomy 725
- prednisolone 391, 541
- pregabalin 897
- pregnancy
- acute fatty liver 845
- AKI 844–5
- dialysis 862–3
- HELLP syndrome 855
- hypertension 846–8
- definition 846
- gestational 847–8
- pre-existing 847
- treatment 849
- physiological changes 840–1
- post-transplant 864–5
- pre-eclampsia see pre-eclampsia
- pre-existing renal disease 856–6, 859
- renal function 840
- septic abortion 845
- tubular function 841
- urinary tract disorders 860
- UTI 842–3
- prescribing see drug prescribing
- prochlorperazine 895
- Procrit® see epoetin
- Prograf® see tacrolimus
- PROGRESS study 496–7
- propranolol 503
- prostate cancer 766–7
- investigations 768
- management 774, 774–6
- screening 772–3
- staging 768–9, 770
- prostate-specific antigen (PSA) 772
- prostatectomy 763, 775
- prostatic enlargement 79
- prostatitis, bacterial 711
- protein catabolic rate, normalized 287
- protein electrophoresis 119
- protein intake, CKD 258
- protein restriction 208
- proteinuria 20–2, 58–9, 60–1, 77
- benign 59
- causes 29
- CKD 197, 200
- diabetic nephropathy 613
- dipstick-positive 530
- with haematuria 530
- management 61
- microalbuminuria 60, 61
- nephrotic syndrome 60, 554
- pathological 58
- post-transplant 422
- pregnancy 857
- quantification 197
- reduction of 556
- renal biopsy 82
- selectivity 60
- proton pump inhibitors 896
- proximal convoluted tubule 924–5, 925
- prune belly syndrome 715
- pseudaldosteronism 480
- pseudohypoaldosteronism 797
- pseudohypokalaemia 796
- pseudohyponatraemia 780
- psychotropic drugs 896–7
- pulmonary artery catheter 13
- pulmonary oedema 134–5
- pulmonary renal syndrome 72–3
- pulse contour analysis 13
- pulse pressure 451
- pure red cell aplasia 225
- purines, dietary 723
- pyelonephritis 707, 709
- antimicrobial therapy 882
- chronic 712–13
- emphysematous 711
- pregnancy 842, 843
- xanthogranulomatous 711
- pyridoxamine 617
- pyuria, sterile 24

R

- radiopharmaceuticals 54
- ramipril 523
- rapamycin see sirolimus
- rapidly progressive glomerulonephritis (RPGN) 71
- rasburicase 895
- RAVE study 648
- 5 α -reductase inhibitors, benign prostatic hyperplasia 761
- reflux nephropathy 712–13
- pregnancy 857
- renal agenesis 714
- renal amyloid 632–3, 668
- AA amyloidosis 630–1
- AL amyloid 628–9
- hereditary amyloidosis 632
- inherited fever syndromes 632
- β_2 -microglobulin-related dialysis amyloid 632–3
- renal angiography 56
- renal artery stenosis 403
- renal biopsy 80–1
- AKI 121
- complications 84–5
- contraindications 80
- indications 80, 82–3

- renal biopsy (*Cont'd*)
 preparation for 80
 technique 81
- renal calcification 45
- renal cell carcinoma 744–5
 clinical features 746
 follow-up 749
 genetics 744
 investigations 746–7
 management 748–9
 paraneoplastic syndromes
 with 746
 pathological/molecular
 subtypes 745
 prognosis 747
 staging 747
 and transplantation 358
- renal colic 724–5
- renal coloboma
 syndrome 602
- renal denervation in
 hypertension 514
- renal disease
 and ethnicity 8
 inherited 6
- renal failure
 diuretics 793
 HIV 675
- renal failure index 116
- renal function tests 30–1
 creatinine 32–3
 GFR see glomerular
 filtration rate
 immunological and
 serological 40–2
 older patients 38–9
- renal fusion 714–15
- renal masses 742, 742–3
- renal medullary
 carcinoma 637
- renal pelvis tumours 756–7
- renal physiology 913–14
 see also *specific parts*
- renal replacement
 therapy 9–8
 adequacy of 181–3
 AKI 133, 172–4
 anticoagulation 182–3,
 184–6, 187
 indications 172, 173
 modalities 174–5, 176–7
 peritoneal dialysis 188–9
 prescription 178–81
 ANCA-associated
 vasculitis 647
 anticoagulation 182–3, 184
 citrate regional 186–7
 haemodialysis 290
 CKD 267
 decision not to have 270
 withdrawal of 270
 continuous 176
 anticoagulation 184
 prescription 179
 diabetic patients 619
 dialysis disequilibrium 177
 drug prescribing 876–7
 haemodialysis see
 haemodialysis
 haemofiltration 174, 175,
 279, 906
 haemoperfusion 907
 hepatorenal syndrome 159
 high-dose 181
 history 274
 lupus nephritis 663
 peritoneal dialysis see
 peritoneal dialysis
 phosphate balance 247
 post-transplant 398
 pre-transplant 393
 pregnancy 862–3
 prevalence 276, 276–7
 survival 277
 treatment of poisoning
 906–7
 vascular access 180
 when to start 334
- renal stones see
 nephrolithiasis
- renal tubular acidosis
 76–8, 826
 distal 718–19
 proximal 825–6
- renal vein thrombosis 590
- renin 456
- renin inhibitors 208, 511
- renin-angiotensin system
 456, 456–7
 in diabetic
 nephropathy 609
- renin-secreting tumours 479
- renovascular disease 586–7,
 590, 591, 618
 see also *individual
 conditions*
- renovascular
 hypertension 475
- repaglinide 894
- respiratory acidosis 822, 834
- respiratory alkalosis 831, 834
- retinol-binding protein 95
- retrograde
 ureteropyelography 57
- retroperitoneal fibrosis
 738–9
 management 740, 741
- rhabdomyolysis 152–3
 causes 153
 compartment
 syndrome 155
 management 154–5
 prognosis 154
 rheumatoid arthritis 668–9
- rheumatoid factor 119
- rheumatoid-associated
 vasculitis 669
- RITAZAREM study 648
- ritonavir 898
- rituximab 385
 ANCA-associated
 vasculitis 644
 lupus nephritis 660
 nephritic syndrome 543
 thrombotic thrombocyto-
 penic purpura 577
- RITUXVAS study 648
- ruboxistaurin 617
- ## S
- salicylate poisoning 908–9
 treatment 909
- Salmonella typhi* 695
- salt balance 778–9
- salt intake
 and blood pressure 453
 low-sodium diet 472
 restriction of 259, 538, 556
- salt-losing nephropathy 583
- sarcoidosis 670–2
- Schistosoma haematobium* 24
- schistosomiasis 700–1
- scleroderma renal crisis
 666–7
- sclerosing encapsulating
 peritonitis 326
- screening
 CKD 197
 diabetic nephropathy 610
 haematuria 68
 prostate cancer 772–3
- Senior-Løken syndrome
 599, 601
- Sensipar[®] see cinacalcet
- sepsis 878–1
 AKI 166–7
 management 168–70
 antifungals 879–80
 antimicrobials 878–9
 antivirals 879
 high-dose renal replace-
 ment therapy 181
 severe 168
- sepsis syndrome 166
- septic abortion 845
- serotonin-specific reuptake
 inhibitors (SSRIs) 896
- serum free light chain
 assay 621
- Sevelamer-HCl 248
- sexual dysfunction,
 CKD 262
- sexual history 8
- short daily
 haemodialysis 304

shunt nephritis 549
 SIADH 782
 management 785
 sickle cell nephropathy 636–7
 sildenafil, benign prostatic hyperplasia 762
 sirolimus 390, 866
 Sjögren's syndrome 669
 skin cancer, post-transplant 440–1
 smoking, and CKD 205
 social history 4–5
 sodium
 crystalloid solutions 125
 haemodialysis dialysate
 concentration 283
 homeostasis 301
 hypernatraemia see hypernatraemia
 hyponatraemia see hyponatraemia
 reabsorption 922, 924, 930, 931
 salt/water balance 778–9
 urinary 116
 sodium aurothiomalate 668
 sodium bicarbonate 124
 in hyperkalaemia 131
 sodium ferric gluconate 231
 sodium nitroprusside 524
 sodium pump 923
 SOLUTION study 648
 sotalol 503
 spironolactone 793, 931
 squamous cell carcinoma, and transplantation 358
 statins 485, 893
 stone disease see nephrolithiasis
 STOP-2 study 496–7
Streptococcus pneumoniae 695
 stress management 473
 struvite stones 718
 prevention 723
 sulfasalazines 903
 sulfonylureas 894
 sulodexide 208, 617
 surgery
 bowel preparation 943, 944
 parathyroidectomy 254–5
 patient preparation 942–4
 post-operative care 942
 transplantation see various transplantation procedures
 sympathetic nervous system, in blood pressure control 455

symptoms 4
 syndrome of inappropriate antidiuretic hormone secretion see SIADH
 SYST-EUR study 496–7
 systemic disease, renal involvement 602–603
 see also *individual conditions*
 systemic inflammatory response syndrome (SIRS) 168
 systemic lupus erythematosus see lupus nephritis
 systemic sclerosis 666–8
 systemic vasculitis 638, 639
 clinical trials 648
 rheumatoid-associated 669
 see also ANCA-associated vasculitis
 systolic blood pressure 451

T

T cell activation 347, 348
 T cell-mediated rejection 408–9
 tacrolimus 387, 866
 tadalafil, benign prostatic hyperplasia 762
 Takayasu's arteritis 638, 653
 Tamm-Horsfall mucoprotein 25, 622
 teicoplanin 886
 tenofovir 898
 thiazide diuretics 486, 498–9, 792
 thiazolidinediones 894
 thin membrane disease 568, 570
 thoracic electrical bioimpedance 13
 thrombocytopenia, heparin-induced 184, 290
 thrombolytics 893
 thrombotic microangiopathy 412, 574, 575
 thrombotic tendency, pre-transplant assessment 357
 thrombotic thrombocytopenic purpura 576–7
 pregnancy 845
 thyroid disease and hypertension 475, 483
 prescribing 894–5
 thyroid function, CKD 262
 tigecycline 887
 timolol 503
 tissue typing 360–1
 TNF receptor-associated periodic syndrome 632
 tolerance 349
 topiramate 897
 total body water 778
 regulation of 779
 tramadol 380
 transitional cell tumours 757
 transplantation see *individual organs*
 transurethral incision of prostate (TUIP) 763
 transurethral microwave therapy (TUMT) 764
 transurethral needle ablation (TUNA) 764
 transurethral resection of prostate (TURP) 762–3
 TREAT trial 226–7
Treponema pallidum 695
 triad syndrome 715
 triamterene 792, 931
 tricyclic antidepressants 896
 trimethoprim 888
 troponin 948
 TSAT 230
 tuberculosis
 end-stage renal disease 699
 genitourinary 696–7
 prophylaxis 395
 renal 696–7
 tuberculous interstitial nephritis 698–9
 tuberos sclerosis 600
 tubular function 922, 922–3
 in pregnancy 841
 see also *specific areas*
 tubular syndromes 76–7
 tubuloglomerular feedback 920
 tubulointerstitial nephritis
 acute 580–1
 chronic 582–3
 tubulointerstitial nephritis and uveitis syndrome 581
 tubulointerstitial scarring 200
 tumour lysis syndrome 160–1
 diagnosis 160
 tunneled dialysis catheters 296, 940
 Turner syndrome 601

U

ultrafiltration 313
 failure 332, 333
 ultrasound 46
 AKI 120
 obstruction 732, 733

- uraemia 70
 uraemic cardiomyopathy 212
 uraemic syndrome 212–13
 urea:creatinine ratio 116
 urea 37, 116, 929
 ureter
 colic 75
 obstruction 727
 stenosis 403
 tumours 756–7
 ureterocele 715
 ureterorenoscopy 57
 ureteroscopy 57, 725
 urethral obstruction 727
 urethrography 56
 uric acid crystals 28, 29
 uric acid nephropathy 160
 uric acid stones 717–18
 urinalysis 16–17, 18–19
 AKI 116–17
 bilirubin and
 urobilinogen 18
 casts 25, 26
 crystals 28, 29
 glucose 18
 ketones 18
 leucocyte esterase and
 nitrites 18
 leucocytes 24
 microorganisms 24
 osmolality 16, 116
 pH 16, 17
 protein see proteinuria
 red blood cells see
 haematuria
 sediment 22, 23
 specific gravity 16, 116
 test strips 19
 see also *specific tests*
 urinary calculi 45
 urinary tract, pain 75
 urinary tract infection (UTI)
 706–7
 asymptomatic bacteriuria
 706, 710
 bacterial prostatitis 711
 bacteriology 707
 catheter-related 710
 cystitis 707
 interstitial 711
 diabetes mellitus 618
 diagnosis 707
 host factors 706
 investigations 708
 post-transplant 438–9
 pregnancy 842–3
 prophylaxis 711
 pyelonephritis
 bacteriuria 707, 709
 emphysematous 711
 xanthogranuloma-
 tous 711
 recurrent 710
 treatment 709
 antimicrobials 882
 urine
 alkalization 154
 appearance 14, 15
 culture 25
 leakage
 post-transplant 402
 low output 397–8
 odour 14, 15
 production 915
 timed 24h collections 21
 volume 74
 urobilinogen, urinary 18
 uro-radiology 56–7
 useful resources 954–6
 uterine carcinoma, and
 transplantation 358
 UTI see urinary tract
 infection
- V**
 vaccination
 hepatitis B 685
 post-transplant 428
 VACTERL association 601
 valaciclovir 898
 valganciclovir 395
 cytomegalovirus 433
 dose 889
 nephrotoxicity 898
 valproate 897
 VALUE study 496–7
 vancomycin 882
 dose 886
 vascular calcification 242–3,
 308, 311
 dialysis-related 308, 311
 and osteodystrophy 242–3
 vascular thrombosis 402
 vasculitis
 ANCA-associated see
 ANCA-associated
 vasculitis
 systemic 638, 639
 vaso-peptide
 inhibitors 464
 vaso-peptide inhibitors 208
 vasopressin 931, 933–4
 VATER association 601
 venesection, pulmonary
 oedema 135
 Venofer® see iron III
 hydroxide sucrose
 complex
 venous thromboembolism,
 prophylaxis 395
 vesicoureteric junction
 obstruction 737
 vesicoureteric reflux 712
 classification 712
 vigabatrin 897
 viral haemorrhagic
 fevers 165
 vitamin D
 CKD 208
 CKD-MBD 236, 250
 treatment 250–1
 side effects 250
 vitamin D analogues 251
 von Hippel-Lindau
 disease 745
 voriconazole 890
- W**
 Waldenström's
 macroglobulinaemia 635
 warm ischaemic time 365
 water
 balance 778–9
 handling 779
 loading 779
 restriction 538, 556, 779
 total body see total
 body water
 WGET study 648
 white coat hypertension
 460
 Williams syndrome 601
 Wilms' tumour 749
 wound infection 402
- X**
 X-rays 44–5
 xanthogranulomatous
 pyelonephritis 711