OXFORD SPECIALIST HANDBOOKS IN PAEDIATRICS

PAEDIATRIC NEPHROLOGY

Lesley Rees
Paul A. Brogan
Detlef Bockenhauer
Nicholas J.A. Webb

SECOND EDITION

PAEDIATRICS

Oxford Specialist Handbooks in Paediatrics

Paediatric Nephrology

Second edition

Lesley Rees MD, FRCPCH

Consultant Paediatric Nephrologist
Gt Ormond St Hospital for Children NHS Trust
London, UK

Paul A. Brogan MSc, PhD, MRCP, FRCPCH

Senior Lecturer and Honorary Consultant Paediatric Rheumatologist
Gt Ormond St Hospital for Children NHS Trust
London, UK

Detlef Bockenhauer PhD, FRCPCH

Consultant Paediatric Nephrologist
Gt Ormond St Hospital for Children NHS Trust
London, UK

Nicholas J.A. Webb DM, FRCP, FRCPCH

Consultant Paediatric Nephrologist
Royal Manchester Children's Hospital
Manchester, UK

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford OX2 6DP
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First edition published 2007
Second edition published 2012

Impression: 1

British Library Cataloguing in Publication Data

Data available

Library of Congress Cataloging-in-Publication Data

Paediatric nephrology / Lesley Rees . . . [et al.].—2nd ed.
p. ; cm.—(Oxford specialist handbooks in paediatrics)
Rev. ed. of: Paediatric nephrology / Lesley Rees, Nicolas J.A. Webb,
Paul A. Brogan. 2007.
Includes bibliographical references and index.
ISBN 978–0–19–960137–0 (alk. paper)
I. Rees, Lesley, 1951-II. Rees, Lesley, 1951-Paediatric nephrology. III. Series: Oxford
specialist handbooks in paediatrics.
[DNLM: 1. Kidney Diseases—Handbooks. 2. Child. 3. Infant. WS 39]

LC classification not assigned
618.92'61–dc23 2011033028

ISBN 978–0–19–960137–0

Printed in China
on acid-free paper by
Asia Pacific Offset

Preface to second edition

Following on from the success of the first edition of our handbook, we have produced a second edition which has been totally updated. In particular, we have brought in our colleague, Dr Bockenhauer. We have used his expertise to ensure that this second edition is fully up-to-date in genetics. In addition, he has developed and simplified the concepts of electrolyte balance by going back to basic renal physiology.

Our original aim in producing a handbook that is a comprehensive and clinically-orientated guide to the management of children with all forms of renal disease remains. We have continued to try to make the text as practical as possible in the expectation that this will become the first text that the paediatrician refers to when presented with a child with an acute or chronic kidney disorder.

The book provides up-to-date information for the general paediatrician and the paediatric nephrologist. It is pocket sized so that it is easily referred to in the clinical setting and uses a system of bullet points to facilitate this. It covers both common conditions seen by all paediatricians during the day-to-day care of patients on a general paediatric ward or in the outpatient clinic, and also those seen rarely and usually in specialized paediatric nephrology centres in collaboration with local units.

The focus is heavily on investigation and management and there is intentionally little emphasis on basic pathogenesis and disease mechanisms. Where possible we have made evidence-based recommendations, though in the many instances where high quality evidence is lacking, we make recommendations based on the authors' personal experience and current best practice.

All of the chapters have been written by the four authors, who are experienced consultants at two large UK Children's Hospitals, although we have received significant input from a number of our colleagues (listed on pages vi and vii) to whom we are most grateful. We would also like to thank Helen Liepman at Oxford University Press for seeing the handbook through from conception to delivery.

LR, PB, DB, and NW
2011

This page intentionally left blank

Contents

Contributors

Staff at Gt Ormond St Hospital for Children NHS Trust:

Dr William van't Hoff
Consultant Paediatric Nephrologist

Dr Kjell Tullus
Consultant Paediatric Nephrologist

Dr Steven Marks
Consultant Paediatric Nephrologist

Professor Neil Sebire
Consultant Paediatric Pathologist

Ms Vanessa Shaw
Chief Paediatric Renal Dietician

Ms Sue Patey
Senior Paediatric Renal Pharmacist

Ms Eileen Brennan
Nurse Consultant in Paediatric Nephrology

Ms Michelle Cantwell
Clinical Nurse Specialist in Peritoneal Dialysis

Ms Liz Wright
Clinical Nurse Specialist in Extracorporeal Treatments

Mr David Fisher
Nurse Counsellor

Dr Vic Larcher
Consultant Paediatrician

Professor Robert Kleta
Professor of Paediatric Nephrology

Professor Michael Dillon
Emeritus Professor of Paediatric Nephrology

Dr Despina Eleftheriou
Honorary Consultant Paediatric Rheumatologist

Dr Despoina Maritsi
Clinical Fellow in Paediatric Rheumatology

Staff at Royal Manchester Children's Hospital:

Dr Mohan Shenoy
Consultant Paediatric Nephrologist

Ms Hong Thoong
Lead Pharmacist—Paediatric Medicine

Dr Bernadette Brennan
Consultant Paediatric Oncologist

Mr Alan Dickson
Consultant Paediatric Urologist

Dr Malcolm Lewis
Consultant Paediatric Nephrologist

Dr Nick Plant
Consultant Paediatric Nephrologist

Dr Neville Wright
Consultant Paediatric Radiologist

Elsewhere:

Dr Declan de Freitas
Consultant Nephrologist
Manchester Royal Infirmary,
Manchester, UK

Dr Judith E Worthington
Principal Clinical Scientist
Manchester Royal Infirmary,
Manchester, UK

Dr Bronwyn Kerr
Consultant Clinical Geneticist,
St Mary's Hospital,
Manchester, UK

Dr Kay Metcalfe
Consultant Clinical Geneticist,
St Mary's Hospital,
Manchester, UK

Dr Jonathan Evans
Consultant Paediatric Nephrologist
Queens Medical Centre,
Nottingham, UK

Dr Ian Roberts
Consultant Renal Histopathologist
John Radcliffe Infirmary,
Oxford, UK

Dr Annett Birgitta Kranz
Consultant Paediatric
Nephrologist
Universitätsklinikum
Münster Klinik u.Poliklinik
f.Kinderheilkunde, Germany

Symbols and abbreviations

γ-GT	gamma-glutamyltransferase
AA	amyloid-A
AAV	ANCA-associated vasculitis
Ab	antibody
ABMR	antibody-mediated rejection
ABPM	ambulatory blood pressure monitoring
ACEI	angiotensin converting enzyme inhibitor
aCGH	array comparative genomic hybridization (assay for chromosomal microdeletions/insertions)
ACL	anticardiolipin antibody
ACR	American College of Rheumatology
AD	autosomal dominant
ADH	anti-diuretic hormone
ADPKD	autosomal dominant polycystic kidney disease
AFP	alpha fetoprotein
AG	anion gap
AKI	acute kidney injury
AL	amyloid-L
ALG	anti-lymphocyte globulin
ALMS	Asprevas Lupus Management Study
ALP	alkaline phosphatase
ALT	alanine transaminase
ANA	antinuclear antibodies
ANCA	anti-neutrophil cytoplasmic antibody
anti-ds-DNA	anti double stranded DNA
AP	alternative pathway
APA	antiphospholipid antibodies
APC	antigen-presenting cells
APD	automated peritoneal dialysis
APS	antiphospholipid syndrome
APTT	activated prothrombin time
AQ2	aquaporin 2
AR	autosomal recessive
ARB	angiotensin II receptor blocker
ARPKD	autosomal recessive polycystic kidney disease
AS	Alport syndrome
ASOT	anti-streptolysin O titre

AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
ATN	acute tubular necrosis
AV	arteriovenous
AVP	arginine vasopressin
AXR	abdominal X-ray
BCG	Bacille Calmette-Guérin
bd	twice daily
BHS	British Hypertension Society
BKV	BK virus
BM	basement membrane
BMI	body mass index
BMT	bone marrow transplant
BNF-C	British National Formulary for Children
BOR	branchio-oto-renal
BP	blood pressure
BSA	body surface area
BTS	British Transplantation Society
BVAS	Birmingham vasculitis activity score
CAA	coronary artery abnormality
CAKUT	congenital abnormalities of the kidney and urinary tract
cANCA	cytoplasmic anti neutrophil cytoplasmic antibody
CAPD	continuous ambulatory peritoneal dialysis
CAPS	catastrophic antiphospholipid syndrome
CaSR	calcium sensing receptor
CAVH	continuous arteriovenous haemofiltration
CBD	chronic beryllium disease
CCF	congestive cardiac failure
CCPD	continuous cycling peritoneal dialysis
CD	collecting duct
CD20	cluster differentiation
CF	cystic fibrosis
CFB	complement factor B
CFH	complement factor H
CFI	complement factor I
CFTR	cystic fibrosis transmembrane regulator
CFU	colony-forming units
CGH	comparative gene hybridization
CIC	clean intermittent catheterization
CIMT	carotid intima media thickness
CINCA	chronic infantile neurological, cutaneous, and articular (syndrome)

CK	creatine phospho/kinase
CKD	chronic kidney disease
CKD 1 to 5	CKD stage 1 to 5
CKD-MBD	CKD mineral and bone disorder
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system or congenital nephrotic syndrome
CNV	copy number variation
CPACNS	childhood primary angiitis of the central nervous system
CPK	creatine phosphokinase
CrAPS	cryopyrin-associated periodic fevers syndrome
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CSS	Churg–Strauss syndrome
CT	computed tomography
CTL	cytotoxic T lymphocytes
CVD	cardiovascular disease
CVVH	continuous veno-venous haemofiltration
CVVHD	continuous veno-venous haemodialysis
CXR	chest X-ray
CYC	cyclophosphamide
D	dialysate
DCT	distal convoluted tubule
DDAVP	1-desamino-8-D-arginine vasopressin (desmopressin)
DDS	Denys-Drash syndrome
DEXA	dual energy x-ray absorptiometry
DHA	docosahexaenoic acid
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DM	diabetes mellitus
DMS	diffuse mesangial sclerosis
DMSA	dimercaptosuccinic acid
DNA	deoxyribonucleic acid
DP	D-penicillamine
D/Pcr	dialysate/plasma creatinine
DPLN	diffuse proliferative lupus nephritis
DRI	dietary reference intake
dRTA	distal renal tubular acidosis
DRVVT	dilute Russell's viper venom time
DS	Down syndrome
ds-DNA	double-stranded DNA

DSA	digital subtraction arteriography or donor specific antibodies
DTPA	diethylene triamine pentaacetic acid
EBER	Epstein–Barr early RNA
EBV	Epstein–Barr virus
ECF	extracellular fluid
ECG	electrocardiogram
EDTA	ethylenediaminetetra-acetic acid
EEG	electroencephalogram
EM	electron microscopy
EMG	electromyography
EMU	early morning urine
ENA	extractable nuclear antibodies
ENaC	epithelial sodium channel
EOS	early-onset sarcoidosis
EPA	eicosapentaenoic acid
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
ESI	exit site infection
ESR	erythrocyte sedimentation rate
FBC	full blood count
FBS	fasting blood sugar
FDA	Food and Drug Administration
Fe	iron
FEK	fractional excretion of K
FEMg	fractional excretion of Mg
FENa	fractional excretion of sodium
FFP	fresh frozen plasma
FGF	fibroblast growth factor
FISH	fluorescent in-situ hybridization
FMF	familial Mediterranean fever
FRNS	frequently relapsing nephrotic syndrome
FSGS	focal segmental glomerulosclerosis
FVL	factor V Leiden
GAD	glutamic acid decarboxylase
GBM	glomerular basement membrane
GDP	glucose degradation products
GFR	glomerular filtration rate
GH	growth hormone
GI	gastrointestinal
GN	glomerulonephritis
GRA	glucocorticoid remediable aldosteronism

GS	Goodman's syndrome
GWAS	genome-wide association study
H&E	haematoxylin & eosin
HAS	human albumin solution
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HD	haemodialysis
HDF	haemodiafiltration
HDL	high-density lipoprotein
Hg-D	Mercury-Doppler
HIDA scan	hepatobiliary imino-diacetic acid scan
HIDS	hyper IgD syndrome
HIV	human immunodeficiency virus
HIVAN	human immunodeficiency virus-associated nephropathy
HLA	human leucocyte antigen
HLH	haemophagocytic lymphohistiocytosis
HMA	homovanillic acid
HPV	human papilloma virus
HSP	Henoch–Schönlein purpura
HSV	Herpes simplex virus
Ht	height
HTN	hypertension
HUS	haemolytic uraemic syndrome
HVA	homovanillic acid
ICF	intracellular fluid
ICU	intensive care unit
IEM	inborn errors of metabolism
IF	immunofluorescence
IgA	immunoglobulin A
IgAN	immunoglobulin A nephropathy
IGF	insulin-like growth factor
IGRA	interferon gamma-releasing assays
IHC	immunohistochemistry
IL-2	interleukin-2
INR	international normalized ratio
IP	intraperitoneal
IPPN	International Pediatric Peritoneal Dialysis Network
IPV	inactivated polio vaccine
IRMA	immunoradiometric assays
ISKDC	International Study of Kidney Disease in Children

ISN	International Society for Nephrology
IUGR	intrauterine growth retardation
IV	intravenous
IVC	inferior vena cava
IVCYC	intravenous cyclophosphamide
IVIG	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
IVP	intravenous pyelogram
JDM	juvenile dermatomyositis
JIA	juvenile idiopathic arthritis
JVP	jugular venous pressure
KD	Kawasaki disease
KDOQI	Kidney Disease Outcomes Quality Initiative
LA	lupus anticoagulant
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFTs	liver function tests
LKM	liver kidney microsomal
LM	light microscopy
LMP	latent membrane proteins
LMW	low molecular weight
LMWP	low-molecular weight proteinuria
LN	lupus nephritis
LPD	lymphoproliferative disease
LRD	living related donor
LUQ	left upper quadrant
LVH	left ventricular hypertrophy
LVM	left ventricular mass
MAG3	mercapto acetyl tri glycine
MAHA	microangiopathic haemolytic anaemia
MAOI	monoamine oxidase inhibitors
MAP	mean arterial pressure
MBD	mineral and bone disorder
MBL	mannose binding lectin
MC&S	microscopy, culture, and sensitivity
MCD	minimal change disease
MCDK	multicystic dysplastic kidney
MCGN	mesangiocapillary glomerulonephritis
MCP	membrane cofactor protein
MCR	mineralocorticoid receptor
MCUG	micturating cystourethrogram

MEFV	Mediterranean fever gene
MELAS	myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
MERFF	myoclonic epilepsy with ragged red fibres
MESNA	2-mercaptoethanesulfonic acid sodium salt
Mg	magnesium
MHC	major histocompatibility complex
MIBG	meta-iodobenzylguanidine (radiolabelled agent for detection of neuroblastoma and pheochromocytoma)
MLPA	multiplexed ligation-dependent probe amplification (gene dosage assay)
MMA	methylmalonic acidaemia
MMF	mycophenolate mofetil
MMR	mumps, measles and rubella
MN	membranous nephropathy
MNS	neuroleptic malignant syndrome
MPA	microscopic polyangiitis or mycophenolic acid
MPG	∝-mercaptoproprionyl-glycine
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MRA	magnetic resonance angiography
MRI	magnetic resonance image
MRV	magnetic resonance venography
MSB	Martius scarlet-blue
MST	morphine sustained release tablets
MTHFR	methylenetetrahydrofolate reductase
MTX	methotrexate
MVK	mevalonate kinase
MW	molecular weight
Na	sodium
NAG	N-acetyl glucosaminidase
NARP	neuropathy, ataxia, and retinitis pigmentosa
NBT	nitroblue tetrazolium
NDI	nephrogenic diabetes insipidus
NF	neurofibromatosis
NHE3	sodium–hydrogen exchange
NHSBT-ODT	NHS Blood and Transplant Organ Donation and Transplantation Directorate
NIH	National Institutes of Health
NIPD	nightly intermittent peritoneal dialysis
NODAT	new onset diabetes mellitus after transplantation
NPHP	nephronophthisis
NS	nephrotic syndrome

NSAID	non-steroidal anti-inflammatory drugs
NSIAD	nephrogenic syndrome of inappropriate antidiuresis
od	once daily
OPV	oral polio virus
P	plasma
PAN	polyarteritis nodosa
pANCA	perinuclear anti neutrophil cytoplasmic antibody
PAS	periodic acid Schiff
PCR	polymerase chain reaction
PD	peritoneal dialysis
PEG	percutaneous endoscopic gastrostomy
PEqT	peritoneal equilibrium test
PET	positron emission tomography
PH	primary hyperoxaluria
PHA2	pseudohypoaldosteronism type 2
PK	pharmacokinetics
PM	primary megaureter
po	orally
PPE	personal protective equipment
PPV	pneumococcal polysaccharide vaccine
pr	per rectum
PR3	proteinase 3
PRA	panel reactivity
prn	as required
pRTA	proximal renal tubular acidosis
PT	proximal tubule
PTH	parathyroid hormone
PTLD	post-transplant lymphoproliferative disease
PTT	prothrombin time
PUJ	pelviureteric junction
PUJO	pelviureteric junction obstruction
PUV	posterior urethral valves
PVC	polyvinyl chloride
qds	four times daily
RA	rheumatoid arthritis
RBC	red blood cells
RBP	retinol binding protein
RCT	randomized controlled trial
RF	rheumatoid factor
rhGH	recombinant human growth hormone
RNI	recommended nutrient intake
ROMK	rat outer medulla K-channel

RPGN	rapidly progressive glomerulonephritis
RPS	Renal Pathology Society
RRT	renal replacement therapy
RTA	renal tubular acidosis
RtF	reaction frequency
RVT	renal venous thrombosis
Rx	treatment
SAA	serum amyloid A
sACE	serum angiotensin-converting enzyme
SAP	serum amyloid P
SC	subcutaneous
SCUF	slow, continuous ultrafiltration
SD	standard deviation
SDNS	steroid dependent nephrotic syndrome
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosus
SNP	single nucleotide polymorphism
SPA	suprapubic aspiration
SRNS	steroid-resistant nephrotic syndrome
SSNS	steroid-sensitive nephrotic syndrome
SSRI	selective serotonin reuptake inhibitors
TA	Takayasu arteritis
TAL	thick ascending limb
TBMN	thin basement membrane nephropathy
TBV	total blood volume
TCMR	T cell-mediated rejection
THAM	tris(hydroxymethyl)aminomethane
THBD	thrombomodulin
TIN(U)	tubulointerstitial nephritis (plus uveitis)
TLS	tumour lysis syndrome
TMA	thrombotic microangiopathy
TMP	trans-membrane pressure
TmP/GFR	transport maximum for phosphate, corrected for GFR
TNF	tumour necrosis factor
TPA	tissue plasminogen activator
TPD	renal pelvic transverse anteroposterior diameter
TPMT	thiopurine s-methyltransferase
TRAPS	TNF-α receptor associated periodic fever syndrome
TRP	tubular reabsorption of phosphate
TS	tuberous sclerosis
TSAT	transferrin saturation

TTG	tissue transglutaminase
TTKG	transtubular K gradient
TTP	thrombotic thrombocytopenic purpura
U	urine
U&E	urea and electrolytes
Ua:Ucr	urine albumin to creatinine ratio
Uca:Ucr	urine calcium to creatinine ratio
UF	ultrafiltration
UKGTN	UK Genetic Testing Network
UKM	urea kinetic modelling
ULN	upper limit of normal
Unag:Ucr	urine n-acetyl glucosaminidase to creatinine ratio
Upr:Ucr	urine retinol binding protein to creatinine ratio
URR	urea reduction ratio
US	ultrasound
UTI	urinary tract infection
V/Q	ventilation perfusion
VATER	vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, renal defects, and radial dysplasia
VATERL	vertebral, anal atresia, cardiac, trachea, esophageal, renal, and limb defects
VDR	vitamin D receptors
VEGF	vascular endothelial growth factor
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
VTEC	verotoxin producing *Escherichia coli*
VT PCR	verotoxin polymerase chain reaction
VUJ	vesicoureteric junction
VUJO	vesicoureteric junction obstruction
VUR	vesicoureteric reflux
vWF	Von Willebrand factor
VXm	virtual cross-match
VZ	Varicella zoster
VZIG	Varicella zoster immune globulin
VZV	Varicella zoster virus
WBC	white blood cells
WCC	white cell count
WG	Wegener's granulomatosis
WHO	World Health Organization

Oxford Specialist Handbooks published and forthcoming

General Oxford Specialist Handbooks

A Resuscitation Room Guide
Addiction Medicine
Day Case Surgery
Perioperative Medicine, 2e
Postoperative Complications, 2e
Renal Transplantation

Oxford Specialist Handbooks in Anaesthesia

Anaesthesia for Medical and Surgical Emergencies
Cardiac Anaesthesia
Neuroanaethesia
Obstetric Anaesthesia
Ophthalmic Anaesthesia
Paediatric Anaesthesia
Regional Anaesthesia, Stimulation and Ultrasound Techniques
Thoracic Anaesthesia

Oxford Specialist Handbooks in Cardiology

Adult Congenital Heart Disease
Cardiac Catheterization and Coronary Intervention
Cardiac Electrophysiology and Catheter Ablation
Cardiovascular Computed Tomography
Cardiovascular Magnetic Resonance
Echocardiography, 2e
Fetal Cardiology
Heart Failure
Hypertension
Inherited Cardiac Disease
Nuclear Cardiology
Pacemakers and ICDs
Pulmonary Hypertension
Valvular Heart Disease

Oxford Specialist Handbooks in Critical Care

Advanced Respiratory Critical Care

Oxford Specialist Handbooks in End of Life Care

End of Life Care in Cardiology
End of Life Care in Dementia
End of Life Care in Nephrology
End of Life Care in Respiratory Disease
End of Life Care in the Intensive Care Unit

Oxford Specialist Handbooks in Neurology

Epilepsy
Parkinson's Disease and Other Movement Disorders
Stroke Medicine

Oxford Specialist Handbooks in Paediatrics

Paediatric Dermatology
Paediatric Endocrinology and Diabetes
Paediatric Gastroenterology, Hepatology, and Nutrition
Paediatric Haematology and Oncology
Paediatric Intensive Care
Paediatric Nephrology, 2e
Paediatric Neurology, 2e
Paediatric Radiology
Paediatric Respiratory Medicine
Paediatric Rheumatology

Oxford Specialist Handbooks in Pain

Spinal Interventions in Pain Management

Oxford Specialist Handbooks in Psychiatry

Child and Adolescent Psychiatry
Forensic Psychiatry
Old Age Psychiatry

Oxford Specialist Handbooks in Radiology

Interventional Radiology
Musculoskeletal Imaging
Pulmonary Imaging
Thoracic Imaging

Oxford Specialist Handbooks in Surgery

Cardiothoracic Surgery
Colorectal Surgery
Hand Surgery
Hepatopancreatobiliary Surgery
Neurosurgery
Operative Surgery, 2e
Oral Maxillofacial Surgery
Otolaryngology and Head and Neck Surgery
Paediatric Surgery
Plastic and Reconstructive Surgery
Surgical Oncology
Urological Surgery
Vascular Surgery

Chapter 1

Patient assessment

History and examination in children with or with suspected renal disease

Important points in the history

Antenatal history

- *Amniotic fluid volume:*
  - low in fetuses with low urine output e.g. obstruction or severe renal impairment; congenital nephrotic syndrome (CNS);
  - high in polyuric states, e.g. neonatal Bartter syndrome.
- *Alpha-fetoprotein level:* high in CNS and spina bifida.
- *Antenatal ultrasound (US) scan:* when was an abnormality first detected? Did the abnormality worsen through pregnancy? Important anomalies may be missed without a 3rd trimester scan, e.g. posterior urethral valves (PUV). Antenatal bright kidneys may be associated with glomerulocystic diseases.
- *Previous pregnancies/miscarriages:* for a genetic condition.
- *Presence of fetal distress:* associated with renal venous thrombosis, and tubular and cortical necrosis.
- *Maternal drug history.*
- *Maternal diabetes:* associated with sacral agenesis and, occasionally, HNF1 beta mutation and many other renal anomalies, including multicystic dysplastic kidney (MCDK), etc.

Birth history

- *Type of delivery:* any evidence of fetal distress/hypoxia.
- *Apgar score:* evidence of fetal hypoxia.
- *Birth weight small or large:* evidence of intrauterine problems, e.g. low birth weight may be associated with low nephron number; high birth weight with Beckwith–Wiedemann syndrome.
- *Number of umbilical vessels:* single umbilical artery is associated with a renal abnormality in 3% of cases, e.g. aplasia, hypoplasia, extrophy of the bladder.
- *Gestation and birth weight:* increased incidence of intrauterine growth retardation (IUGR) with renal abnormalities.
- *Weight of placenta:* large placenta, >25% of birth weight, in CNS.

Neonatal history

- *Respiratory symptoms:* associated with oligohydramnios and abnormal lung development.
- *Use of umbilical catheters:* associated with renal and arterial thrombosis.
- Timing of passage of urine after birth.

General questions

- Consanguinity.
- Urinary stream.
- Urinary tract infections (UTI).
- Family history, particularly of renal disease, deafness, or diabetes.
- Previous central lines.
- Polyuria and polydipsia.
- Enuresis primary or secondary.

Examination specific to renal disease

- Number of umbilical arteries.
- Height, weight, head circumference, pubertal stage.
- Blood pressure (BP).
- Congenital dislocation of the hips.
- Other congenital abnormalities include, e.g.:
  - eyes, e.g. aniridia, coloboma, retinitis pigmentosa, tapetoretinal degeneration, uveitis;
  - ear deformities;
  - pre-auricular pits;
  - branchial fistulas and cysts;
  - abnormal facies;
  - absence of abdominal muscles;
  - cryptorchidism;
  - spine;
  - genital abnormalities.
- *Palpable kidneys:* enlarged with autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD), tuberous sclerosis (TS), MCDK, severely obstructed kidneys, renal venous thrombosis, renal tumour.
- *Evidence of renal osteodystrophy:* thickened wrists, rickety rosary, lower limb deformities.
- *Oedema, jugular venous pressure (JVP), core-peripheral temperature gap, pulse, and respiratory rate:* needed if assessing fluid balance.
- *Pulses and evidence of collateral circulations:* if previous intravascular lines or hypertension.
- *Handedness of child:* if contemplating a fistula.
- *Markers of systemic disease:* e.g. rash and arthropathy.

Abnormalities of the urine and urinalysis

Visual inspection of urine

Red urine

- Macroscopic haematuria:
  - causes the urine to develop a pink to red colour;
  - only a small amount of blood may be necessary to produce discoloration;
  - fresh heavy bleeding is more likely to be of lower urinary tract origin, particularly when haematuria is greatest at either the end or at the beginning of micturition;
  - contact with acidic urine causes haem pigment to become oxidized to a methaem derivative, giving the urine a brown colour. Generally, the longer the contact and the more acidic the urine, the darker the colour.
- Red urine not due to haematuria may be due to:
  - foods, e.g. beetroot, fruits containing anthocyanins (e.g. blueberries, plums, cherries) and food dyes;
  - haemoglobinuria, e.g. in intravascular haemolysis;
  - myoglobinuria, e.g. in rhabdomyolysis;
  - urate crystals (a cause of pink discoloration of nappies);
  - drugs, e.g. rifampicin, phenothiazines, desferrioxamine, phenindione;
  - inborn errors of metabolism e.g. porphyria and alkaptonuria.

Urine microscopy is therefore mandatory following the detection of red urine. This should occur promptly to avoid red blood cell (RBC) lysis. Whilst Munchausen syndrome by proxy is rare, deliberate contamination of the urine with maternal blood is a frequent presentation of this disorder.

Cloudy urine

May be secondary to the presence of pyuria (white blood cells), calcium phosphate crystals or a combination of calcium salts, uric acid, cysteine, or struvite. Precipitation of phosphates and urates is enhanced by refrigeration.

Dipstick examination of urine

Blood

- Haemoglobin is detected through its ability to catalyse a reaction between hydrogen peroxide and o-tolidine.
- Spotted positivity indicates intact RBCs, whereas uniform positivity indicates free haemoglobin (e.g. in intravascular haemolysis or red cell lysis in the urinary tract).
- Causes of false positive haematuria include:
  - myoglobinuria;
  - oxidizing agents contaminating urine specimen (e.g. hypochlorite, povidone and bacterial peroxidases);
  - heavy bacterial contamination.
- Causes of false negative haematuria include reducing agents in the urine, e.g. ascorbic acid.

Urine microscopy is therefore mandatory following the detection of blood on dipstick analysis. This should occur promptly to avoid RBC lysis.

Protein

- Dipsticks undergo colour change from yellow to green following binding with proteins.
- Dipstick analysis is not a good quantitative test because of the effect of urinary concentration (more concentrated urine will show higher protein concentration), and where proteinuria is detected, formal quantification with a protein to creatinine (Upr:Ucr) or albumin to creatinine (Ua:Ucr) ratio is indicated.
- Approximate estimates of urine protein concentration according to the dipstick result are shown in Table 1.1.

Table 1.1 Approximate estimates of urine protein concentration according to the dipstick result

Dipstick result	Approximate urine protein concentration
Trace	0.15g/L
1+	0.3g/L
2+	1g/L
3+	3g/L
4+	20g/L

- Albumin is better detected than other urinary proteins (globulins, tubular proteins, etc.).
- First morning samples should be assessed to rule out any element of orthostatic proteinuria.
- If there is dipstick positivity for protein, but insignificant albuminuria on quantification, consider tubular proteins and send urine retinol binding protein and n-acetyl glucosaminidase/creatinine ratios (see 🕮 Chapter 7, 'Tubulointerstitial nephritis', p.168).
- Causes of false positive proteinuria include:
  - concentrated urine;
  - alkaline urine;
  - gross haematuria;
  - dipstick left in urine too long or delay in reading;
  - contamination with secretions from the urinary tract (during UTI) or vagina;
  - contamination with antiseptics, chlorhexidine, benzalkonium.
- Causes of false negative proteinuria:
  - dilute urine;
  - acid urine.

Glucose

Lower limit of detection is 4–5mmol/L.

Leucocytes

- Some sticks may detect leucocyte esterase, indicating the presence of pyuria.
- Microscopy should be used to confirm this finding.
- Pyuria is not diagnostic of UTI, and may occur secondary to fever or infection of non-UTI origin.

Nitrites

- The majority of pathogenic bacteria produce nitrite that can be detected on urinalysis.
- The test has a high specificity, but a low sensitivity for the diagnosis of UTI. As such, the test is of limited usefulness.
- Where UTI is suspected or needs to be excluded, a urine culture is necessary to determine the bacteriological cause and antibiotic sensitivities or to confidently rule out UTI.

Microscopy of urine

Casts

- Produced by the aggregation of Tamm–Horsfall protein with cells or cellular debris in the renal tubule and, therefore, can be a normal finding.
- Best seen in unspun urine. Centrifugation may damage casts. In centrifuged urine, casts are most frequently seen at the edge of the coverslip.

Hyaline casts

Present in proteinuric states, although may be found in concentrated specimens of urine from normal individuals.

Cellular casts

- Red cell casts are always pathological and indicate glomerular bleeding.
- White cell casts indicate renal inflammation due to pyelonephritis or immunologically-mediated disease.
- Epithelial cell casts (often present with red and white cell casts) are produced from shed tubular epithelial cells and may be seen during recovery from acute tubular necrosis.

Red blood cells

- Normal red cell excretion increases with age and after exercise.
- The persistent presence of $>5 \times 10^6$ red cells/L in uncentrifuged urine is abnormal.
- Microscopy (phase contract microscopy is best, though possible with ordinary light microscopy (LM)) can distinguish anatomically normal RBCs of lower urinary tract origin from dysmorphic RBCs of glomerular origin that have been distorted during their passage through the filtration barrier.
- The presence of acanthocytes (>5% of RBC population) may indicate the presence of a glomerulonephritis.
- RBCs deform and lyse in urine of high tonicity. It is therefore important that microscopy is performed on a fresh urine specimen.

White blood cells

- The presence of $>10 \times 10^6$ white cells/L is abnormal.
- Neutrophils are detected in UTI, but also in contamination, proliferative glomerulonephritis and interstitial nephritis.
- Eosinophils may be detected in the urine in children with acute tubulointerstitial nephritis (see 📖 Chapter 7, 'Tubulointerstitial nephritis', p.168).

Bacteria and other organisms

- Bacteria may be clearly visible without Gram staining.
- Their detection may be enhanced by the use of phase contrast microscopy.
- Fungi, e.g. *Candida* and *Schistosoma* species (a rare cause of haematuria) may also be detected.

Epithelial cells

- Presence may represent desquamation from the urinary tract.
- Tubular cells may be seen following tubular injury (acute tubular necrosis (ATN), acute transplant rejection).
- Squamous cells are commonly exfoliated from the urethra and are a normal finding.

The approach to the child with haematuria

Presenting symptoms

May present with:

- *Macroscopic haematuria:*
  - symptomatic with dysuria (e.g. UTI), renal colic (e.g. renal calculus), loin pain (e.g. pelviureteric junction (PUJ) obstruction);
  - asymptomatic.
- *Microscopic haematuria:*
  - detected during screening (routine or because of a family history);
  - during an intercurrent infection.

Important points in the history

- Is the haematuria at the beginning or end of the stream (suggestive of a bladder or urethral cause)?
- Is the urine red (more likely to be a local cause) or tea/coca cola coloured (more likely to be glomerular)?
- Symptoms suggestive of UTI, calculi, acute nephritis (see 🕮 Chapter 4, p.75, 🕮 Chapter 8, p.173, 🕮 Chapter 9, p.181 and 🕮 'Acute nephritis', p.186).
- A family history of renal disease or deafness (familial haematurias) or sickle cell disease.

Causes of macroscopic and persistent microscopic haematuria

- *UTI:* the commonest cause.
- *Lower tract bleeding:* e.g. urethral trauma, polyp.
- *Structural abnormalities:* such as PUJ obstruction, usually associated with pain.
- *Calculi:* also associated with pain.
- *Hypercalciuria* (diagnosis of exclusion).
- *IgA nephropathy* (see 🕮 Chapter 9, p.181).
- *Other glomerular disorders:* e.g. membranoproliferative glomerulonephritis (MPGN).
- *Familial haematurias* (see 🕮 'Alport syndrome and thin basement membrane nephropathy', p.184).
- *Sickle cell disease* (see 🕮 Chapter 10, p.225).
- *Schistosomiasis* (see 🕮 Chapter 12, p.315).
- *Renal tumours* (see 🕮 Chapter 15, p.347).
- *Renal tract vascular malformation.*
- *Clotting abnormalities:* as a cause, very rare.

Investigation of macroscopic and persistent microscopic haematuria (see Fig. 1.1)

- Asymptomatic intermittent microscopic haematuria does not need investigation.
- *Urine microscopy, culture and sensitivity (MCS):* haematuria needs to be confirmed by urine microscopy prior to any further investigation to ensure that a positive dipstick test is not false.

- Urine phase contrast microscopy for deformed red cells (glomerular bleeding).
- Ua:Ucr or Upr:Ucr, and urine calcium to creatinine ratio (Uca:Ucr).
- Renal US (and abdominal X-ray if calculi suspected).
- Urea & electrolytes (U&Es), creatinine, and albumin.
- Full blood count (FBC).
- Sickle cell screen (if appropriate).
- Clotting (if history of bruising).
- Anti-streptolysin O (ASO) titre, C3, C4, anti-double-stranded deoxyribonucleic acid (DNA) binding, hepatitis B and C (if acute nephritis suspected).
- IgA levels if asymptomatic episodes.
- Check urine of parents and siblings for blood and protein.
- Urology referral if non-glomerular bleeding suspected; may need cystourethroscopy.
- Renal biopsy if raised creatinine, proteinuria, a low albumin or family history.

Follow-up

- Will depend on cause.
- Asymptomatic microscopic haematuria without a clear diagnosis may resolve or is likely to be benign, and does not warrant biopsy. Annual follow-up is recommended to check for the development of proteinuria or hypertension.
- If proteinuria or hypertension develop, the creatinine, and serum albumin should be checked.
- If there is either a raised creatinine, proteinuria, or a low albumin, biopsy should be undertaken.

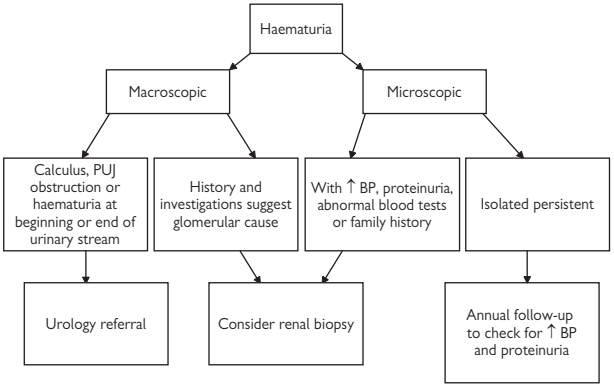

Fig. 1.1 Investigation of macroscopic and persistent microscopic haematuria.

The approach to the child with proteinuria

Quantification of proteinuria

- Because of the inherent difficulties associated with 24-h urine collection in children, this has been superceded by the use of the first morning Upr:Ucr or Ua:Ucr. Here, urine protein or albumin concentration is expressed as a factor of urine creatinine concentration, thus providing a correction for variation in urine concentration.
- A Upr:Ucr in the first urine passed after rising (to rule out any orthostatic element) should be <10mg/mmol, which equates to <60mg/m^2/day. However, these values may be higher in the first 2 years of life.
- 40mg/m^2/h equates to a value of 250mg/mmol, which some define as nephrotic range proteinuria.
- Microalbuminuria will not be detected by dipsticks and is defined as a Ua:Ucr > 2.5mg/mmol.

Causes of proteinuria

It is important to decide whether proteinuria is benign, and therefore, by definition, isolated and not associated with abnormal BP or renal function, or pathological.

Benign proteinuria

Intermittent proteinuria is benign and does not need further investigation. Causes are:

- False positive stick results (see 📖 'Abnormalities of the urine and urinalysis', p.4).
- Increased filtration of plasma proteins due to changes in renal haemodynamics.
  - Without identifiable cause or after severe exercise, cold exposure or intercurrent febrile illnesses.
  - Orthostatic proteinuria, which occurs when the child is ambulant, but not when recumbent. Can be diagnosed by giving the family Albustix to test the very first urine passed immediately (i.e. before doing anything else) on rising. Results will be persistently negative despite positive results in the day. The main features are:
  - occurs mostly in adolescents, particularly boys;
  - proteinuria is mild;
  - usually decreases with time and disappears.

Pathological proteinuria

Proteinuria that is persistent or associated with haematuria, hypertension, or renal dysfunction is pathological.

Causes include:

- *Glomerular disease* due to:
  - glomerulosclerosis or reduced nephron mass from any cause, resulting in hyperfiltration;
  - all causes of glomerulonephritis;
  - all causes of nephrotic syndrome;
  - familial haematurias.

- *Tubular disease:* although there is proteinuria, quantification shows albumin excretion to be low as the majority of the urine proteins are of tubular origin.

Investigations

- Urine microscopy and culture.
- Ua:Ucr or Upr:Ucr.
- Urine n-acetyl glucosaminidase or retinol binding protein to creatinine ratio (Unag:Ucr and Urbp:Ucr) if tubular disease suspected.
- Renal US.
- U&Es, creatinine, and albumin.
- FBC.
- ASO titre, C3, C4, anti-double-stranded DNA binding, hepatitis B and C (if acute nephritis suspected).
- Immunoglobulin A (IgA) levels.
- Check urine of parents and siblings for blood and protein.
- Renal biopsy.

Radiological investigations

The key to obtaining successful and informative imaging of the urinary tract is close liaison between clinician and radiologist. The higher the quality of clinical information given to the radiologist, the higher the quality of the resulting report.

Ultrasound

- Radiation-free, painless, easily available, and low cost.
- Can be used to measure renal lengths, for which there are normal ranges (see Fig. 1.2), although there may be considerable inter-observer error.
- Excellent for the detection and measurement of hydroureteronephrosis, renal masses including tumours, renal cystic disease and calculi (including non-radio-opaque calculi).
- Allows for evaluation of the bladder wall and lumen including measurement of pre- and post-micturition bladder volumes (Fig. 1.3).
- May be useful in the diagnosis of acute pyelonephritis (enlarged echo-bright kidney with loss of corticomedullary differentiation).
- Its role in the detection of permanent renal parenchymal scarring is controversial, although the large majority of series have found it to be of low sensitivity.
- May detect changes secondary to vesicoureteric reflux (VUR; ureteric or renal pelvic dilatation).
- Doppler studies allow measurement of blood flow in the renal artery and veins, and are useful in the diagnosis of renal venous thrombosis. Resistive index measures resistance to blood flow, e.g. in renal artery stenosis. Power Doppler increases sensitivity.
- A number of sonographic contrast agents have recently been introduced, which may allow reflux to be detected in experienced hands. However, catheterization is still required, and anatomical information about the posterior urethra is not obtained.

Plain abdominal X-ray

- Useful for detecting calculi, abdominal masses, calcification (including more severe nephrocalcinosis), sacral agenesis.
- Will detect the presence of spina bifida occulta in around 30% of individuals. This finding is nearly always of no clinical significance.
- Should not be used for the routine diagnosis of constipation.

Intravenous urogram

- Now used relatively infrequently, although easy to perform. Does not require specialist equipment.
- Provides information about renal anatomy, including visualization of the calyces, the presence of malrotation, and may be useful in identifying the site of urinary tract obstruction, e.g. congenital PUJ or vesicouteric junction (VUJ) obstruction and that secondary to renal calculi.
- Has been replaced by radioisotope imaging and, more recently, by magnetic resonance imaging (MRI).

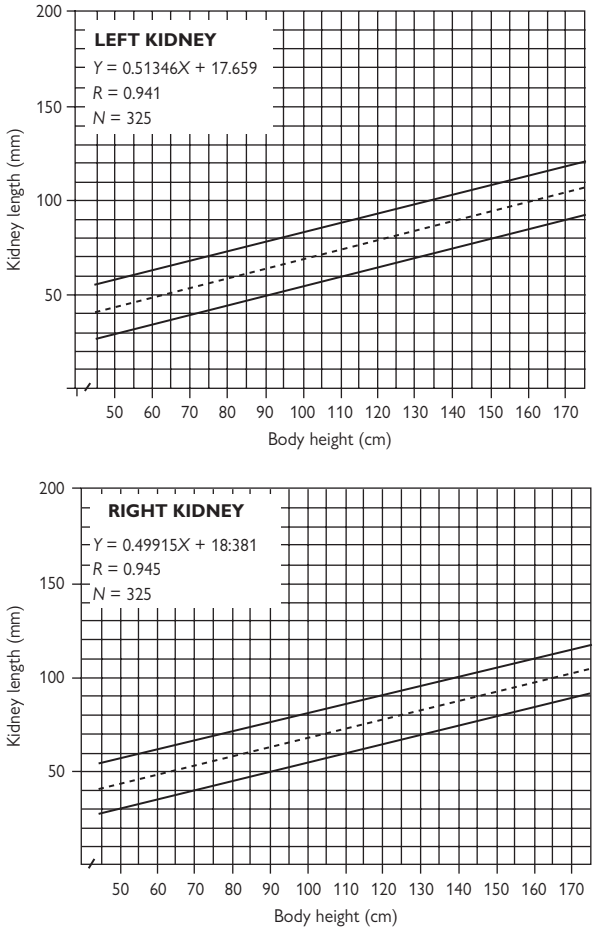

Fig. 1.2 Renal length vs height showing mean, 5th, and 95th centile values. Data based on measurements performed in 325 children with no evidence of renal disease.

Data from Dinkel E, Ertel M, Dittrich M, et al. (1985). Kidney size in childhood. Sonographical growth charts for kidney length and volume. *Pediatr Radiol* **15:** 38–43.

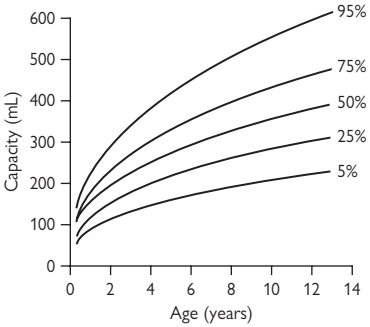

Fig. 1.3 Relationship between bladder capacity and age.
Data from Kaefer M, Zurakowski D, Bauer SB, et al. (1997). Estimating normal bladder capacity in children. *J Urol* **158:** 2261–4.

Micturating cystourethrogram

- Gold standard investigation to detect and grade VUR and posterior urethral valves.
- The frequency with which this investigation is performed has fallen significantly, especially following the recent NICE UTI guidelines.
- Early filling films should be obtained to identify ureterocoeles, which become compressed once the bladder fills.
- Oblique or lateral films, and views of the urethra without the catheter are necessary to detect PUV.
- Requires catheterization of the bladder and can be distressing, even with experienced operators. Radiation dose relatively high (Table 1.2).
- The procedure is associated with a 2–3% risk of UTI, therefore should be covered with antibiotic therapy, particularly in neonates and those shown to have VUR. There is no evidence base to guide therapy; recommended treatment trimethoprim 4mg/kg bd for 3 days (day before until day after procedure).

Table 1.2 Radiation exposure associated with specific radiological investigations

Procedure	Radiation dose (mSv)	Background radiation (equivalent)	CXR (equivalents)
Abdominal XR	1.0	161 days	50
IVU	2.5	403 days	125
DMSA scan	1.0	161 days	50
CT abdomen/pelvis	10	1613 days	500
Ultrasound scan	0	0 days	0
MR scan	0	0 days	0
MCUG	1.5 (boy)/0.9 (girl)	242/145 days	75/45

Nuclear medicine cystography

- *Direct cystography* involves the instillation of ^{99}Tc pertechnetate into the bladder. The procedure is associated with a lower radiation dose than an X-ray micturating cystourethrogram (MCUG) and may have greater sensitivity. Many consider it to be the method of choice in girls. It does not, however, give information about posterior urethral anatomy (essential in boys to rule out PUV) and still requires catheterization.
- *Indirect cystography* can be performed using intravenous (IV) MAG3 (separately or as part of a dynamic investigation), thus avoiding the need for catheterization:
  - the child needs to be fully continent;
  - scanning performed during voiding detects the presence of isotope in the ureters and renal pelvis;
  - lower grades of VUR may be missed, and the investigation does not generate information about posterior urethral anatomy;
  - may be useful as a follow-up investigation in those with known MCUG proven VUR.

DMSA (^{99}Tcm dimercaptosuccinic acid) scan

- DMSA is taken up, although not excreted by (predominantly proximal) renal tubular cells.
- The image produced is that of functioning renal cortical mass and the technique is the gold standard investigation for the detection of renal cortical scarring.
- May also be helpful in identifying ectopic kidneys and confirming non-function (e.g. in the MCDK).
- Information is also generated about differential renal function (the relative contribution of each kidney to total renal function).
- Duplex kidneys (often of little clinical significance) are often detected by DMSA scan.
- Sedation is not generally necessary.
- Controversy exists over the optimum timing of DMSA scanning following UTI:
  - early scans performed within the first few weeks post-UTI will detect changes secondary to acute parenchymal inflammation in up to 50% of children with pyelonephritis, which may be indistinguishable from those of cortical scarring;
  - these acute changes may persist for up to 6 months, and many advocate delaying the scan until 6 months post-UTI. However, in children with recurrent UTIs, this policy may result in major delays in the investigation being performed.
- It is increasingly recognized that the congenitally dysplastic kidney (associated with intrauterine VUR and other factors) may have a DMSA scan appearance which is identical to that of acquired renal scarring. Many children labelled with renal scarring may, in fact, have congenitally dysplastic kidneys. It is therefore preferential to use the term ‘renal defects’, rather than ‘renal scarring’.

Dynamic renography (^{99m}Tc-DTPA or ^{99m}Tc-MAG3 scans)

- These scans are used to assess renal blood flow, and to detect the presence and site of urinary tract obstruction.
- DTPA is excreted by glomerular filtration and, therefore, gives additional information about GFR.
- MAG3 is excreted primarily via proximal tubular secretion; consequently, its clearance is a measurement of tubular cell function. Renal clearance of MAG3 is substantially greater than the renal clearance of DTPA so clearance curves are steeper, assisting in interpretation where obstruction is suspected.
- The child needs to be well hydrated for the scan and the isotope is injected with furosemide (much variation in the timing of the latter, although most give the two together to avoid multiple injections). This increases urine flow, maximally challenging the drainage system.
- Time-activity curves are generated showing uptake of the isotope by the kidneys with subsequent excretion.
- Analogue pictures in the nephographic phase may show renal cortical scarring, although with less sensitivity than the DMSA scan.
- Renographic curves may show:
  - normal uptake and excretion;
  - reduced uptake by either or both kidneys where function is poor;
  - normal uptake, but poor subsequent excretion where obstruction is present;
  - normal uptake with equivocal excretion.
- Poor clearance of isotope from very dilated pelves or ureters may give the artificial appearance of obstruction. This will be exacerbated by dehydration. The child should be sat up, as change of posture can normalize drainage.

Cross-sectional imaging

CT scanning

- Excellent modality for imaging renal parenchyma.
- Usually more readily available than MRI so often the method of choice for assessment of renal masses and renal trauma.
- May provide additional information to US in acute pyelonephritis and pyonephrosis, particularly where drainage of the latter is being considered.
- Renal calculi are clearly identified. These may have been missed on US examination where there is significant obesity or skeletal deformity.
- Xanthogranulomatous pyelonephritis is one of the more significant differential diagnoses of Wilms tumour. The calculi and fatty lesions within the involved kidney are clearly identified by CT.
- There is a significant radiation dose (see Table 1.2).
- Modern rapid image acquisition reduces motion artifact and removes the need for sedation in most cases.

MRI

- Is not associated with any radiation burden.
- Good for the evaluation of renal masses and cystic lesions.
- Can be used for the assessment of renal parenchyma and function (MR renography) or the drainage systems (MR urography).

- Magnetic resonance angiography (MRA) and venography (MRV) are useful non-invasive alternatives to formal angiography for the assessment of renal artery stenosis and other vascular abnormalities.
- MR urography can produce detailed 3D images of the urinary tract for the assessment of complex congenital urological anomalies.
- The use of gadolinium-based contrast is significantly less nephrotoxic than iodine-based contrasts, although there is a risk of nephrogenic systemic fibrosis in those with chronic kidney disease (CKD). This appears to occur almost exclusively in those with CKD 5 and severe CKD 4, in whom its use should be avoided.
- Sedation is often required for MR imaging.

Arteriography and venography

- Advances in MRA techniques have resulted in these investigations being performed less frequently, although MRA is still unable to reliably detect changes in medium-sized arteries (see 📖 'Investigation of primary systematic vasculitis', p.279).
- The techniques require direct arterial or venous puncture. Requires general anaesthesia in the large majority of children.
- Arteriography may be used to assist in the diagnosis of the systemic vasculitides, particularly large vessel vasculitis, such as Takayasu disease, but is less reliable for medium vessel vasculitis, such as polyarteritis nodosa (PAN).
- Renal artery stenosis in a native or transplanted kidney may be diagnosed using formal catheter arteriography and, during the same procedure, it may be possible to perform angioplasty to correct the lesion.
- Interventional techniques may be used to treat arteriovenous fistulae that have occurred, e.g. after renal biopsy where these are causing bleeding or haemodynamic complications.

Recommendations for ultrasound screening for renal abnormalities

Many chromosomal and genetic abnormalities and syndromes are associated with renal abnormalities of all types. Some structural abnormalities are familial.

Recommendations

US screening is recommended when there is

- Structural renal disease, renal agenesis, or VUR with renal defects in first degree relatives.
- Single umbilical artery: this occurs in approximately 0.3% of births and is associated with a slightly increased risk of VUR.
- Significant congenital external ear abnormalities with or without hearing defects.
- Any of the retinal dystrophies.
- Chromosomal abnormalities.
- Syndromes or associations with known renal abnormalities.
- Screening of children for ADPKD is discussed in 📖 'Autosomal dominant polycystic kidney disease', p.324.
- Conversely, parents (and siblings if the disease has complications that may need treatment) of children with renal cystic disease should be screened.
- Screening of patients with a predisposition for Wilms tumour is described in 📖 'Wilms tumour', p.348.

Percutaneous renal biopsy

Indications

Native kidney

- *Nephrotic syndrome:*
  - atypical features at initial presentation (see 🕮 'Nephrotic syndromes: definitions', p.192);
  - primary steroid resistance (no response to 28 days of steroid therapy);
  - secondary steroid resistance (the development of steroid resistance in a previously steroid sensitive patient);
  - monitoring calcineurin inhibitor (CNI) therapy. It is recommended that biopsy is performed after 2 years of therapy to exclude CNI nephrotoxicity: where significant interstitial damage is detected, the CNI should be discontinued.
- Acute kidney injury (AKI) of uncertain aetiology (not where diagnosis is clear cut, e.g. diarrhoea-associated haemolytic uraemic syndrome(HUS) or AKI in intensive care unit (ICU) patients with a history very suggestive of ATN).
- Rapidly progressive renal failure.
- CKD of uncertain aetiology (not if kidneys <5cm bipolar length; increased risk of complications).
- Acute nephritic syndrome with low C3 persisting beyond 8 weeks.
- Henoch-Schönlein purpura with heavy proteinuria, renal impairment, or hypertension (see 🕮 'Henoch-Schönlein purpura', p.288).
- Suspected vasculitis (beware the risk of biopsy of intrarenal artery aneurysm in polyarteritis nodosa).
- Systemic lupus erythematosus (SLE) with renal involvement.
- Macroscopic or microscopic haematuria (if associated with proteinuria, hypertension or impaired renal function).
- Subnephrotic proportion proteinuria: in general, biopsy in children with isolated proteinuria and a Upr:Ucr of <100mg/mmol is unlikely to yield results that significantly alter clinical management.

Transplant

- Acute deterioration in graft function.
- Chronic deterioration in graft function.
- Delayed graft function.
- Stable, but poor graft function.
- Proteinuria.
- Diagnosis of recurrent or *de novo* glomerular disease.
- Routine surveillance biopsies: an increasing number of centres now performing routine protocol biopsies at, e.g. 12 months post-transplantation.

Contraindications

These are all relative; assessment has to be made of the risks and benefits of the procedure. Open biopsy can be performed where the risk of complications is thought to be excessive.

- Large cysts or abscesses (risk of spreading infection along the track of the biopsy needle).

- Bleeding diatheses.
- Solitary native kidney.
- Horseshoe or other fused/anatomically abnormally-sited native kidney.
- Severe hydronephrosis.
- Polycystic kidneys.
- Abnormal vascular supply.
- Severe CKD (need to control BP and abnormal bleeding tendency).
- Uncontrolled hypertension.
- Severe oedema.
- Obesity.

Pre-biopsy investigations

- FBC.
- Clotting studies (prothrombin time (PTT), activated prothrombin time (APTT), and fibrinogen) and history to exclude coagulopathy.
- Group and save blood.
- Perform renal US to confirm the presence of two kidneys, exclude hydronephrosis, etc. (may be performed at time of procedure).
- Bleeding time if urea >40mmol/L; in uraemic patients, desmopressin, a synthetic derivate of arginine vasopressin (AVP) has been shown to shorten the prolonged bleeding time significantly while increasing factor VIII-coagulant activity. IV infusion of 300ng/kg diluted in 50mL of 0.9% saline over 30 min may normalize the bleeding time for 4–8h in most uraemic patients, so allowing renal biopsy (unlicensed indication).

Sedation/anaesthesia

- General anaesthesia may be preferable in smaller children and those in whom sedation has previously failed. This subject is reviewed well at http://www.sign.ac.uk. This document recommends that all renal biopsies in children should be performed under general anaesthesia.
- Alternatively, sedation and analgesia may be given as per local policy. *Example*: an IV infusion of chlorpromazine (1mg/kg body weight—maximum 50mg) given over 60min and slow IV injection of pethidine (1mg/kg body weight—maximum 75mg). Additional sedation, if required at the time of the biopsy with IV diazepam (0.2–0.4mg/kg body weight) or IV midazolam (0.1mg/kg body weight; e.g. chlorpromazine 1mg/kg—max dose 50mg).
- Older children with extraperitoneal transplants can often be biopsied with local anaesthesia +/– Entonox® alone.

Procedure

- Children undergoing native renal biopsy should be placed in the prone position.
- A rolled sheet or firm sponge bolster placed under the lower ribs/upper abdomen will help to 'fix' the position of the kidneys.
- Real time US guidance will:
  - allow pre-biopsy confirmation of the presence of two kidneys;
  - confirm the absence of severe hydronephrosis/other abnormality;
  - allow the tip of the needle to be visualized, so the direction may be altered to avoid the calyceal system and major vessels;
  - reduce the complication rate.

- The use of automated spring-loaded biopsy devices (e.g. Biopty gun) are associated with lower incidence of complications and smaller number of passes required to obtain an adequate tissue sample. 14–18G needles should be used in children; smaller needles are associated with fewer complications, but volume of tissue obtained is also smaller.
- Strict asepsis should be maintained.
- Local anaesthetic should be infiltrated at the biopsy site and along the proposed route of the biopsy needle to the pericapsular region.
- The biopsy needle should be passed under real-time US guidance to the site of biopsy: this should be at the lower pole of the native kidney, or the most accessible pole of a transplanted kidney, with care taken to identify and avoid the main renal vessels.
- Two adequate cores of renal tissue (see 📖 'Tissue handling', p.21) should be obtained.
- More than three passes of the biopsy needle should be avoided as this increases the risk of complications.
- Fine needle aspiration of the transplant kidney has been advocated by some for the diagnosis of acute rejection by the study of intragraft gene expression. At present, the use of this technique, which may be associated with a lower rate of complications, is generally restricted to research protocols.

Tissue handling

- The specimen should be checked under a low power dissection microscope to ensure adequate cortical tissue has been obtained.
- The quality of a renal biopsy depends on the number of glomeruli: it is generally agreed that 10–15 glomeruli are optimal; very often 6–10 glomeruli are sufficient; in some cases, even one glomerulus is enough to make a diagnosis, but if the percentage of glomerular involvement in a biopsy is used to determine the severity of a focal glomerular lesion, a small biopsy sample size will lead to considerable misclassification of disease severity. In addition, a small biopsy sample size will make the exclusion of focal disease difficult.
- Banff transplant biopsy criteria define adequacy as the presence in the sample of 10 glomeruli and 2 arteries.
- The sample should be divided into three portions, for LM, immunofluorescence and electron microscopy (EM).

Post-biopsy observations

- Bed rest for 4 h if possible.
- Encourage adequate fluid intake to ensure good diuresis (unless oliguric renal failure is present).
- Monitor pulse, BP, respiratory rate, and O_2 saturations for 6 h post-procedure.
- Monitor urine for macroscopic haematuria.
- FBC should be checked if there are abnormal observations or macroscopic haematuria.
- Activity post-biopsy should be restricted as follows:
  - stay off school for 48 h;
  - avoid lifting, strenuous activity, and running for a week after biopsy;
  - avoid contact sports for 6 weeks.

Complications

- Pain over the biopsy site.
- Complications of analgesia/sedation.
- *Macroscopic haematuria (5–7%):*
  - although transient macroscopic haematuria is seen in 0.8–12% of biopsies, massive haematuria leading to serious complications necessitating surgical intervention is not usually seen in the well selected patient population with normal pre-biopsy screening;
  - haematuria generally settles conservatively—bed rest and fluids are recommended to encourage a good urine output. The haemoglobin needs regular monitoring;
  - only 1–2% of cases require blood transfusion or are severe enough to cause clot colic or ureteral/bladder outlet obstruction.
- Microscopic haematuria is almost universal (and many will have had pre-biopsy microscopic haematuria).
- Asymptomatic subcapsular or perirenal haematomas occur in up to 85% of biopsies:
  - more commonly seen if routine post-biopsy US is performed;
  - around 1% are symptomatic with pain or anaemia due to blood loss and, very rarely, collection of subcapsular blood can cause compression of renal tissue to occur.
- *Arteriovenous fistula formation:*
  - incidence depends on how hard they are looked for, but up to 15% are found with routine angiography;
  - most resolve spontaneously;
  - very rarely cause hypertension or high output cardiac failure necessitating embolization or heminephrectomy.
- Inadvertent extrarenal organ puncture.
- Mortality rate 0.12% in adult series.
- Requirement for surgery or interventional radiological procedure 0.3%.
- The risk of kidney loss is less than 0.1%.

A recent study from the UK proposed that a major complication rate of less than 5% is an acceptable standard. Major complications were defined as macroscopic haematuria requiring monitoring and/or intervention, a prolonged hospital stay due to the need for analgesia, and hypoxia requiring intervention and or oxygen post-procedure.

Day-case versus overnight stay

More units are now performing percutaneous renal biopsy as a day-case procedure, given that most complications that develop will present within the immediate post-biopsy period. Criteria for discharge might be that:

- The observations are normal.
- The biopsy site looks satisfactory.
- The patient passes urine twice, neither sample of which is heavily blood-stained.

Renal histology

Glossary of terms

Table 1.3 lists terms used by pathologists describing renal biopsy material.

Table 1.3 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 (Fig. 1.4).
Proliferation	Increase in cell numbers, may be mesangial, endocapillary or extracapillary (which may form crescents), e.g. mesangial proliferation = >4 cells per mesangial area (Fig. 1.7).
Exudation	Infiltrated by neutrophils. Example acute post-streptococcal nephritis (Fig. 1.13).
Membranous	Specific type of glomerular basement membrane thickening associated with subepithelial immune deposits, e.g. idiopathic membranous nephropathy (Fig. 1.10).
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', this table).
Sclerosis	Scar tissue, a fibrous matrix obliterates normal structure so that capillaries collapse and normal cell nuclei are lost (Fig. 1.6).
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; Fig. 1.12).
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 (Fig. 1.13).
'Spikes'	Projections of basement membrane between regular sub-epithelial deposits, typical of membranous nephropathy.

Table 1.3 (*Contd.*)

Term	Definition
Foam cells	Lipid laden cells, usually histiocytes but also mesangial or tubular cells, seen in nephrotic syndrome and Alport's syndrome.
H&E	Routine histological technique that 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 that 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', this 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 BM disease	*Age 3–15 years:* Thin GBM: 181–236 nm; normal: 242–333nm.
	Age 9–68 years: Thin GBM: 262–335nm. Normal: 331–547nm.
"Basket weave" GBM	The disordered replication of lamina densa of the GBM in Alport's Nephropathy (Fig. 1.18)

Modified with permission from Taylor CM, and Chapman S (1989). Renal biopsy. In: Taylor CM and Chapman S (eds) *Handbook of renal investigations in children*. Wright, London: 160–71.

Examples of commonly encountered paediatric renal disease

Fig. 1.4 shows the normal human glomerulus. Figs. 1.5–1.18 show examples of relatively common or classical renal pathology in children.

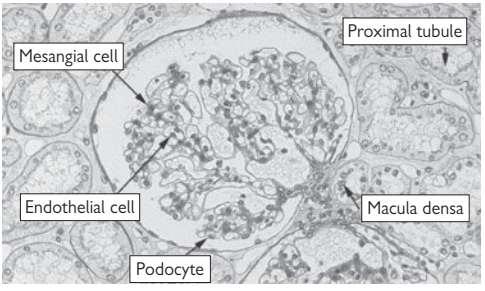

Fig. 1.4 Normal renal biopsy. See Plate 1.

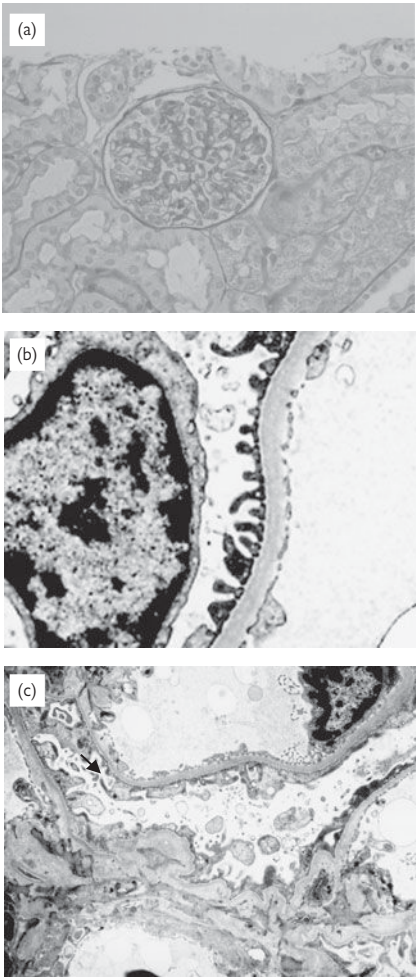

Fig. 1.5 Minimal change disease. Minimal changes on light microscopy (a). EM of normal foot-processes (b). Minimal change disease with effacement of podocyte foot processes (c). See Plate 2.

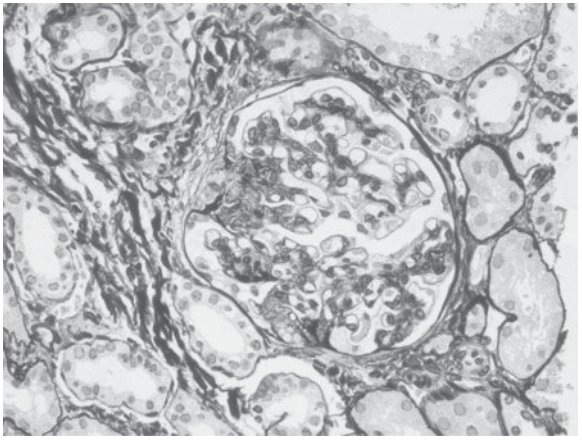

Fig. 1.6 Focal and segmental glomerulosclerosis: sclerosis of part of a glomerulus, not all glomeruli affected (silver stain). A capsular adhesion is present. There is a propensity for FSGS to affect predominantly the deep, juxta-medullary glomeruli, so cortical glomeruli may not demonstrate the lesion (false negative renal biopsy). See Plate 3.

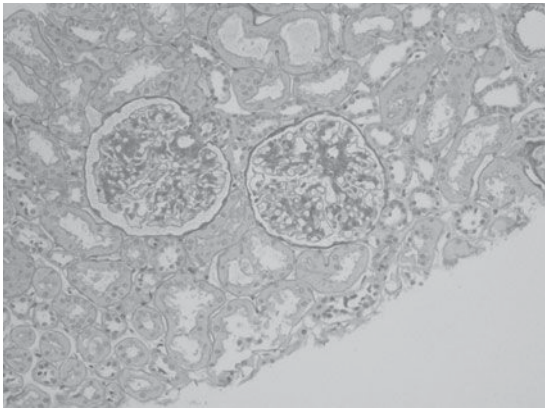

Fig. 1.7 Mesangial proliferative glomerulonephritis. Increase in mesangial cells and matrix (>4 cells/mesangial area), but without peripheral capillary loop involvement (PAS). This pattern is most characteristic of Henoch–Schonlein nephritis, IgA nephropathy, IgM nephropathy and SLE, but may be present in many other conditions. See Plate 4.

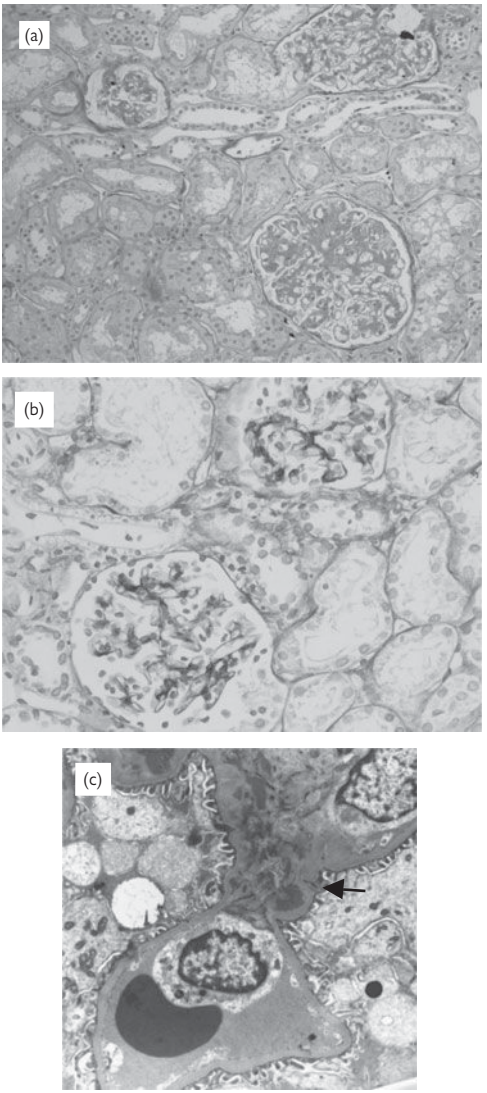

Fig. 1.8 IgA nephropathy. (a) Mesangial proliferation (PAS). (b) Granular immune complexes containing predominant IgA in the mesangium of most or all glomeruli (immunohistochemistry) (c) Electron microscopy showing electron-dense deposits in the mesangium. See Plate 5.

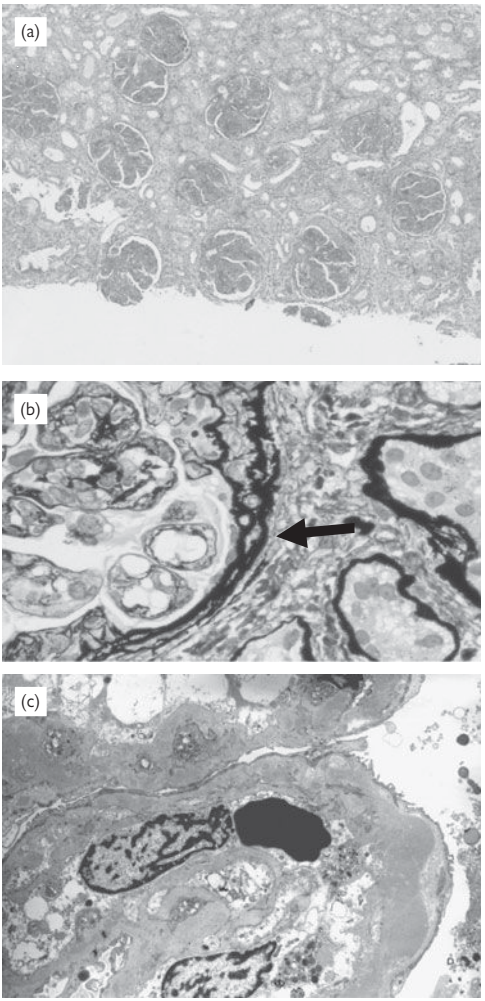

Fig. 1.9 Membranoproliferative glomerulonephritis type 1. (a) Diffuse increase in glomerular cellularity with mesangial cell proliferation and lobulation of the glomerular tufts (PAS). (b) Thickening of the capillary wall caused by circumferential interposition of mesangial cells and matrix between the endothelium and GBM, resulting in capillary luminal narrowing and 'double-contour' formation on silver staining. (silver) (c) EM revealing separation of the endothelial cells from the GBM by interposed mesangial cell cytoplasm and sub-endothelial deposits, resulting in narrowing of the capillary lumen. See Plate 6.

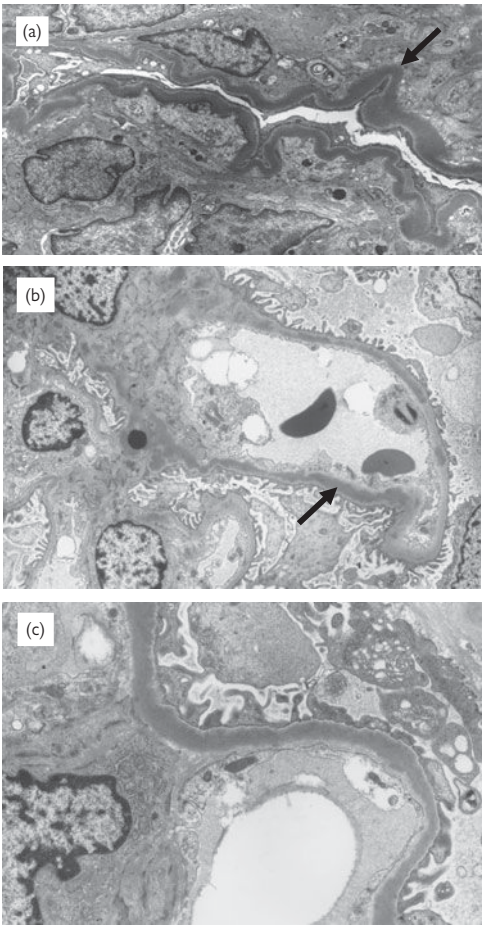

Fig. 1.10 Membranoproliferative glomerulonephritis type 2, dense deposit disease. A wide spectrum of LM appearances may be seen, but the diagnosis is made on EM examination, which reveals replacement of the lamina densa of the capillary basement membrane by electron dense material, which may also be observed in other areas.

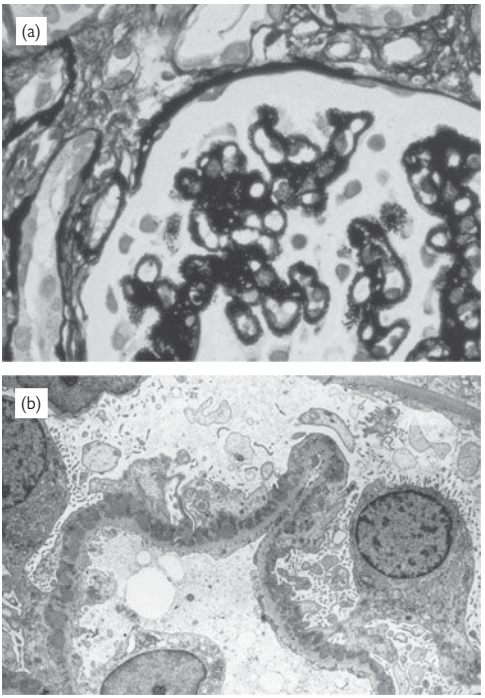

Fig. 1.11 Membranous glomerulonephritis. (a) LM demonstrating thickening of the glomerular basement membranes with 'spike' formation (silver). (b) EM of membranous glomerulonephritis with thickened glomerular basement membrane and numerous, regular subepithelial electron dense deposits. See Plate 7.

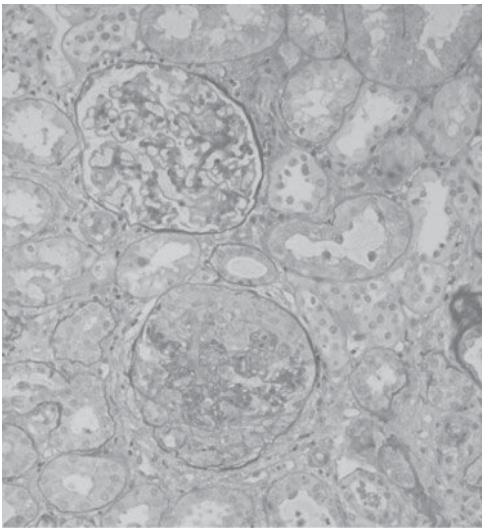

Fig. 1.12 Crescentic nephritis. Cellular crescent impinging on glomerulus. (PAS) Immunohistochemistry was 'pauci-immune–' compatible with ANCA vasculitis (in this case Wegener's granulomatosis). See Plate 8.

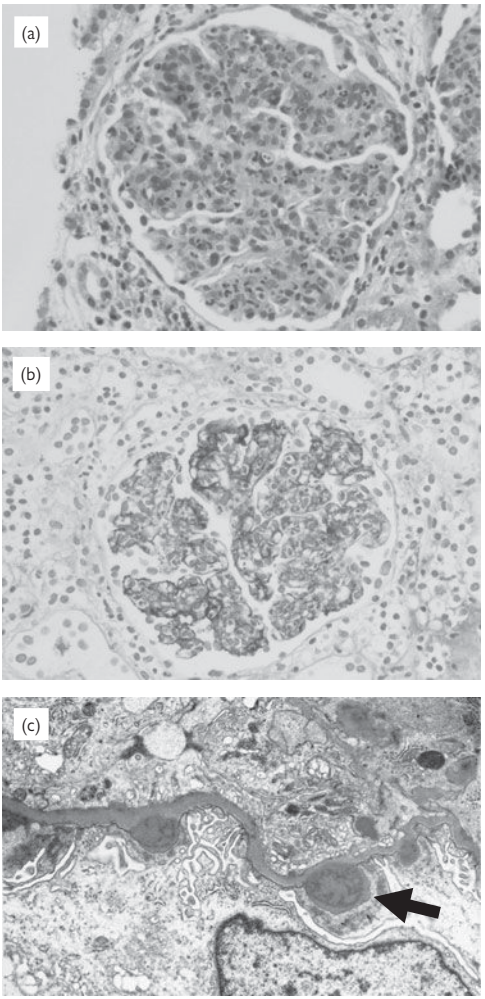

Fig. 1.13 Post-infectious glomerulonephritis (acute diffuse proliferative glomerulonephritis). (a) Glomeruli show hypercellularity. There is obliteration of the capillary lumens (endocapillary proliferation). Some polymorphonuclear leucocytes can be seen. (PAS.) (b) Coarse granular pattern of staining with IgG in the glomerular basement membrane ('lumpy bumpy' pattern), typical of post-infectious GN (IHC). (c) EM showing large subepithelial deposits (humps) in the glomerular basement membrane (arrows). See Plate 9.

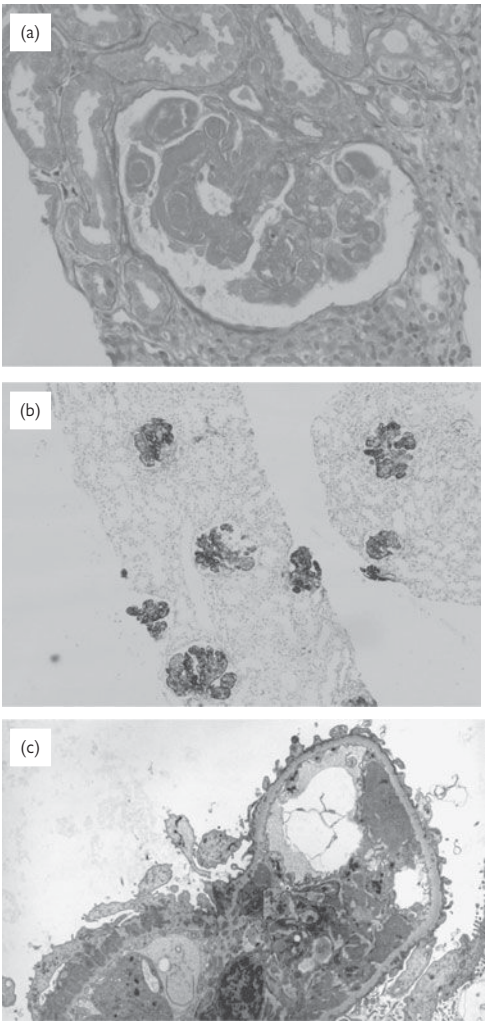

Fig. 1.14 Systemic lupus erythematosus. (a) Diffuse proliferative (WHO class 4) lupus nephritis with endocapillary cellular proliferation and massive subendothelial deposit forming 'wire-loop' and 'hyaline-drop' lesions. (b) Immunostaining in such cases often shows a 'full-house' pattern with deposition of IgG, IgM, IgA, and complement (c) Large electron dense deposits are seen in the subendothelial region of the glomerular basement membrane (arrow). See Plate 10.

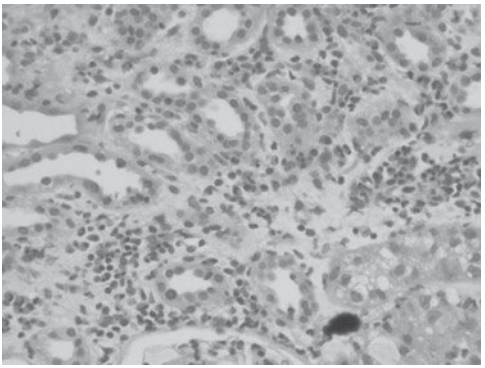

Fig. 1.15 Tubulointerstitial nephritis. Extensive interstitial infiltration of mononuclear inflammatory cells and eosinophils with tubular damage. See Plate 11.

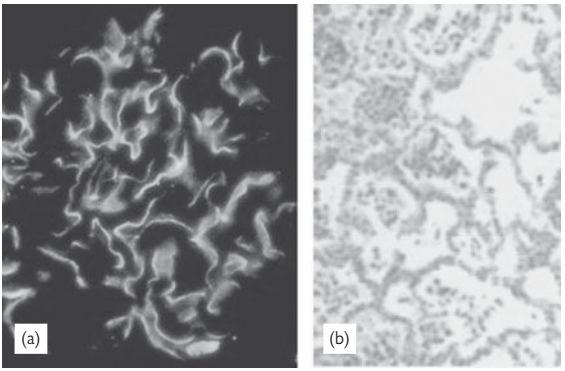

Fig. 1.16 Goodpasture's disease. (a) Linear staining of immunoglobin deposited in the glomerulus. In Goodpasture's disease, the autoantibody is directed against an antigen in the glomerular basement membrane and is deposited in a linear fashion, in contrast to immune complex mediated disease. (b) Lung of a patient with evidence of intra-alveolar haemorrhage. See Plate 12.

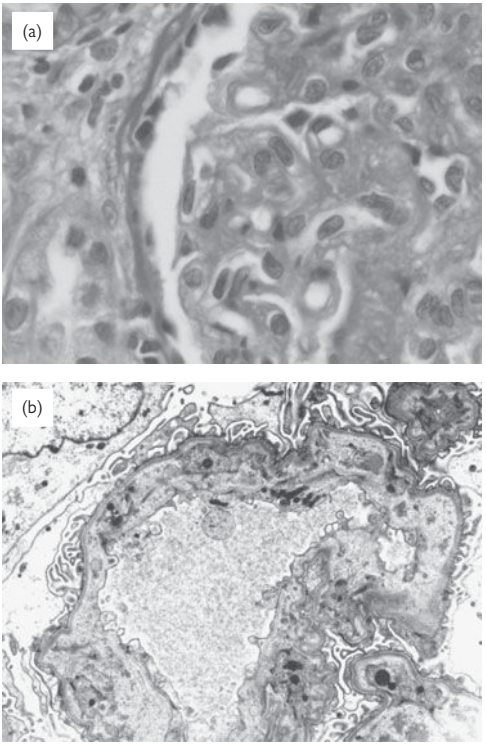

Fig. 1.17 Haemolytic uraemic syndrome. (a) A glomerulus affected by thrombotic microangiopathy with luminal reduction and double-contour formation (silver) (b) Electron micrograph demonstrating subendothelial widening containing fibrin-like material. See Plate 13.

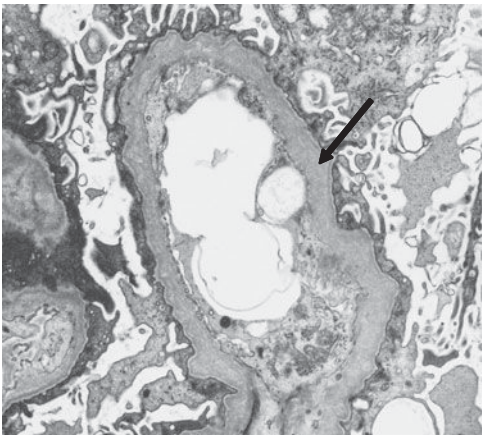

Fig. 1.18 Alport's syndrome. EM demonstrating irregularity of the basement membranes and the characteristic lamination ('basket weave') of the lamina densa.

Further reading

Taylor CM, and Chapman S. (1989). Renal biopsy. In: Taylor CM and Chapman S (eds) *Handbook of renal investigations in children*. Wright, London: 160–71.

Genetic testing and antenatal diagnosis

The discovery of genes coding for new diseases has increased rapidly since the decoding of the human genome. The genetic predisposition for many disorders is increasingly recognized but the ability to test for these genes in a clinical context is lagging behind. The dramatically reduced costs through the advent of new sequencing technologies (see 📖 'Tests used in making a genetic diagnosis', p.39), should enable testing for most genetic disorders in the near future.

Copy number variations

Increasingly, so-called copy number variations (CNV) are recognized as causes of inherited diseases. In most cases it is a deletion, so that instead of the usual 2 copies of a gene, only one copy is present, e.g. half of all mutations identified in HNF1B are whole gene deletions. An excess number of copies (3 or more) can cause disease.

Clinical genetic testing

This differs from research testing:

- Clinical genetic testing is performed in an accredited laboratory that has been demonstrated to fulfil the necessary quality criteria.
- Research testing is performed in a research laboratory not accredited for clinical testing, ∴ research test results should not be used for clinical decision making.
- In the UK, clinical genetic tests are performed under the umbrella of the UK Genetic Testing Network (UKGTN; 🖱 http://www.ukgtn.nhs.uk/gtn/Home).
- Genetic tests approved by the UKGTN are usually covered under the NHS. However, for tests not available under this network, extra funding must be secured. Even if a test is available, genetic testing should be considered carefully.

Reasons for genetic testing

Precise diagnosis

Apart from the psychological benefit to patient and family of being recognized as suffering from a specific disease, a precise diagnosis is critical to the instigation of proper treatment and counselling.

Supporting clinical management

The most important reason.

Example: in steroid-resistant nephrotic syndrome, if a patient with this diagnosis is found to have to pathogenic mutations in NPHS2 (podocin), this has immediate consequences for further treatment for a number of reasons:

- Obviates the need for a kidney biopsy.
- Influences the choice of medications (see 📖 'Overview of inherited glomerular diseases', p.182).
- Informs discussions regarding suitability of living donor transplantation.

Increased availability of genetic testing and thus more genetic diagnosis will enable correlation between genotype and phenotype, which can then inform the prognosis and management of other affected patients.

Precise genetic counselling

Identification of a specific mutation allows determination of carrier or affected status in other family members. In some conditions, early diagnosis is critical for optimal outcome, e.g. cystinosis or nephrogenic diabetes insipidus. Parents can also be offered prenatal testing for selected disorders with appropriate counselling.

Concerns about genetic testing

Psychological burden

Presenting someone with a genetic diagnosis can be very distressing, especially if the person has experience of the diagnosis from other family members. Genetic testing should only be considered if the diagnosis can have beneficial consequences. In children, it is advisable to wait until they are old enough to decide for themselves. A typical example is genetic testing in autosomal dominant polycystic kidney disease (see 📖 'Autosomal dominant polycystic kidney disease', p.324). If therapeutic interventions are available, then the diagnosis should be established to allow affected patients to benefit.

Discrimination

Making the diagnosis of an inherited condition could stigmatize a person and affect their ability to obtain insurance, a job, or a mortgage. Some countries have legislation against this discrimination, but enforcement is difficult.

Tests used in making a genetic diagnosis

Karyotype

A well-established method in which chromosomes are stained and ordered according to size from 1 to 23, plus 2 sex chromosomes. This test can detect abnormalities in chromosome number (such as trisomy 21), as well as major structural abnormalities in a chromosome.

Sequencing

This refers to the determination of the order of the nucleotide bases in a molecule of DNA. Typically, this is used to identify a mutation in a gene associated with the patient's disease. Different methods are in use.

- Sanger sequencing: conventional form of sequencing that can decode nucleotide sequence for typically 500–800 base pairs. Is expensive and labour-intensive. To reduce costs, sometimes only specific regions of a gene known to harbour most mutations are assessed. If this limited mutation screening is unsuccessful or mutations are known to be scattered throughout the whole gene, the entire gene must be sequenced.

Sanger sequencing has been frequently replaced by:

- *'Next-generation' sequencing:* various technologies for next-generation sequencing exist, but they all share key features—they dramatically reduce the cost for sequencing but can only decode short stretches of DNA (20–400 base pairs, depending on technology). For sufficient accuracy these stretches need to be sequenced many times over (also called 'resequencing') and the results are assembled by computer software. The cost reduction of these new technologies can be substantial:

- the decoding of the first human genome using Sanger sequencing was completed in 2005: it took 15 years at a cost of $2.7 billion;
- in 2010, a study was published in which an individual genome was sequenced in a few weeks using next-generation sequencing for less than $50.000.

Multiplex ligation-dependent probe amplification

Multiplex ligation-dependent probe amplification (MLPA) is a technique used to assess CNV (or gene dosage) of a defined stretch of DNA (e.g. an exon of a gene).

Fluorescent in situ hybridization

Fluorescent *in situ* hybridization (FISH) is another technique used to assess CNV for a defined region of DNA. Typically used in the diagnosis of diseases caused by a defined microdeletion, such as Williams syndrome.

Both MLPA and FISH are increasingly being replaced by:

Array comparative genomic hybridization

Comparative genomic hybridization (CGH) is a technique used to assess CNV of longer stretches of DNA (e.g. a gene or several neighbouring genes ('microdeletions'). The advantage of this technique is that the whole genome is assessed, rather than specific stretches and so it is an extension of the karyotype with a much finer resolution. Especially useful in patients with unclear syndromic features, but can also detect known microdeletion syndromes.

Linkage analysis

Mostly used in research to identify new disease genes, but can also be used to assess individual patients, in conjunction with other affected family members. Rather than identifying a specific mutation, identifies whether an individual has inherited a given stretch of DNA harbouring the mutation.

Example: in a family with ADPKD, linkage analysis could identify whether a patient has inherited the same copy of the *PKD* gene that all the other affected family members share. Next-generation sequencing and thus the ability to cheaply assess even very large genes means that linkage analysis will become less commonly used for diagnostic purposes, although still is an important research tool in identifying disease-causing genes in single-gene disorders.

Single nucleotide polymorphisms array

Tests for single nucleotide polymorphisms (SNP), which by definition are common sequence variations (present in >1% of the population). Modern arrays can test for more than a million SNP simultaneously. Variations have occurred over time and accumulated in the genome and it is important to understand that:

- The vast majority have little or no functional effect.
- They are located anywhere in the genome, mostly outside of coding regions.
- If they had a substantial functional effect, there would have been evolutionary pressure for this variation to disappear (if it was a deleterious) or to become common (if it was a beneficial).

- Only rarely has an identified SNP actual functional significance (especially important in interpreting the results of the commercial SNP array tests).
- Having a SNP associated with a given disease does not mean that the disease will actually develop, but only that in previous studies a statistically significant higher percentage of patients with the disease have this SNP compared with controls and it is most probable that the SNP is often inherited together (i.e. 'in linkage disequilibrium') with a functionally relevant sequence variation, still to be identified.
- Mainly tag a block of DNA in their immediate genomic vicinity that is commonly inherited together (a so-called haplotype), which may harbour the true disease-causing mutation.
- SNP arrays are used in both linkage analysis and in genome-wide association studies.
- Some SNP may have a disease-modifying effect or can be causal in association with other sequence variations (often in other genes) or environmental factors.

Example: R229Q polymorphism in NPHS2—patients homozygous for this variation do not develop steroid-resistant nephrotic syndrome, but in combination with a true pathogenic mutation this variation is thought to be disease-causing. Associated with microalbuminuria in the general population.

Genome-wide association

Genome-wide association (GWA) study is a research tool used to identify the genetic contribution in multi-factorial diseases. In contrast to linkage analysis, GWA is used if a disease is thought to have a genetic contribution, but is caused by the interplay of several genes or environmental factors.

Recent examples: the identification of several SNP associated with diabetes or membranous nephropathy. Important to understand that the identified SNP only have a statistical association with the disease, but usually are not causal themselves, but are in close vicinity to the actual underlying sequence change and thus inherited together.

Antenatal diagnosis

A fetal abnormality

May be:

- Detected on US during routine screening.
- Specifically looked for using US because of a family history.
- Diagnosed using molecular techniques.

Molecular studies are justified if early intervention or treatment improves the outcome or when the condition has a poor prognosis and the family would opt for termination of pregnancy.

DNA from the fetus

Can be obtained by:

- Chorionic villus sampling:
  - is undertaken at 10–12 weeks gestation;
  - the villi contain ample DNA for analysis;
  - there is a risk of miscarriage of 1–2%.
- Amniotic fluid:
  - can be obtained from 15 weeks gestation;
  - 3 weeks are needed for the amniotic cells to grow to obtain enough DNA;
  - there is a risk of miscarriage of 0.5%.

Chapter 2

The neonate

The fetus and birth

Kidney development commences at 5 weeks gestation. By week 9 the first glomeruli are formed and by week 34 nephrogenesis ceases, when there are around 1 million glomeruli in each kidney. A bladder is detectable by week 9, and thereafter fetal urine contributes to over 90% of liquor volume.

Important factors in the antenatal and birth history

- See 🕮 'History and examination in children with or with suspected renal disease', p.2.
- 90% of infants pass urine within 24h.
- Weight loss over 10% of birth weight is significant.
- Transient proteinuria may occur in the first days of life.
- Plasma creatinine reflects maternal levels at birth.
- Plasma creatinine may rise in the first 3 weeks of life in premature infants due to tubular reabsorption.
- Plasma bicarbonate may be lower than expected as the renal threshold for bicarbonate is 18–20mmol/L, rising to 24–26mmol/L by 1 year of age.

Commonly used drugs administered during pregnancy that affect the fetal kidney

- Angiotensin converting enzyme inhibitors (ACEIs) affect placental perfusion and inhibit nephrogenesis.
- Non-steroidal anti-inflammatory drugs (NSAIDs) affect fetal renal perfusion. May cause renal cysts and chronic kidney disease (CKD).

Polyhydramnios

Polyhydramnios occurs in approximately 1% of pregnancies. In the majority of cases there is no underlying fetal abnormality, but maternal problems such as diabetes may be present. If a fetal abnormality is present, the majority are in the gastrointestinal (GI) tract (decreased swallowing of liquor). Only a small proportion of polyhydramnios is caused by fetal renal disease, typically Bartter's syndrome (see 🕮 Chapter 7, p.139).

Oligohydramnios

- Bilateral urinary tract obstruction.
- Renal agenesis.

Raised alfa-fetoprotein

Present in all conditions with leakage of fetal protein, such as:

- Neural tube defects.
- Congenital nephrotic syndrome (CNS).
- Epidermolysis bullosa.

'Bright' kidneys

Causes of 'bright' kidneys diagnosed on antenatal ultrasound scans

- Renal dysplasia (usually small ± cysts): may be isolated; in association with vesicouteric reflux (VUR) or obstruction; or as part of a syndrome.
- Autosomal recessive polycystic kidney disease (ARPKD; usually large with small cysts).
- Autosomal dominant polycystic kidney disease (ADPKD; usually large with large cysts and may be asymmetrical).
- Glomerulocystic disease (typically HNF1β deletions/mutations; usually large).
- Beckwith–Wiedemann syndrome (visceromegaly, macroglossia, hemihypertrophy, hypoglycaemia).
- CNS.
- Congenital infection.

Causes of 'bright' kidneys diagnosed on postnatal ultrasound scans

All of the causes diagnosed by antenatal ultrasound, and also:

- Bright cortices may be normal in the neonate.
- Acute tubular necrosis.
- Renal venous thrombosis (see 📖 'Renal venous thrombosis', p.47).
- Neonatal nephrocalcinosis:
  - common in preterm infants, particularly if they have been on diuretics or IV feeding;
  - distal renal tubular acidosis;
  - for other causes of nephrocalcinosis, see 📖 Chapter 8, p.173.
- Nephroblastomatosis.
- Primary hyperoxaluria.
- May be transient, due to protein precipitation in the renal tubules.
- Neonatal Bartter syndrome (see 📖 'Disorders of renal salt handling: thick ascending limb', p.148).

Neonatal disorders of fluid balance

Fluid homeostasis in the neonate is compromised because

- The kidneys receive only 15–20% of the cardiac output (25% in adults).
- The GFR (ml/min/1.73m^2) in the premature infant is 10–15 and 15–20 in the term infant. These values double over the first 2 weeks after birth and reach adult values of 80–120 by 1–2 years of age.
- Maximum urine concentrating capacity is low at birth (up to 600mOsm/kg) and increases over the first 2 months of life and then progressively over the first year of life.

Neonatal hypernatraemic dehydration

- A complication of inadequate breast milk production that may go unrecognized, particularly in the first child who is exclusively breast fed.
- If severe, venous and/or arterial thrombosis, and AKI may occur.

Neonatal acute kidney injury

See 🕮 Chapter 17, p.377.

- A common problem in the neonatal intensive care unit (ICU).
- May be associated with perinatal asphyxia, circulatory insufficiency due to sepsis, dehydration, or cardiac disease, drug therapy, bilateral renal arterial, or venous thrombosis (see 🕮 'Renal venous thrombosis', p.47), congenital or structural renal disease.
- The principals of management are the same as for the older child, except that urinary sodium <20mmol/L, FeNa <2.5% and urine osmolality >400mOsm/kg suggests pre-renal acute kidney injury (AKI) in neonates, compared with <10mmol/L, <1% and >500mOsm/kg, respectively, in older children.

Renal venous thrombosis

Renal venous thrombosis (RVT) may occur wherever there is vessel wall damage, reduction in blood flow, alteration in blood composition, or an inherited procoagulant tendency. Thrombosis starts in the arcuate or interlobular veins of the kidney, and then spreads to the main renal vein. This is why anticoagulation is often unsuccessful when a clot is already identified in the main renal vein, and why the term renal venous thrombosis (RVT), rather than renal vein thrombosis should be used.

- RVT is the commonest form of venous thrombosis in neonates.
- It may develop antenatally in association with fetal stress so perinatal RVT may be a more appropriate term than neonatal RVT.
- Predisposing factors are dehydration, sepsis, maternal diabetes, birth asphyxia, umbilical venous catheters, and procoagulant defects.
- RVT presents with haematuria, renal mass(es), fall in haemoglobin, and thrombocytopaenia.
- AKI with a rising creatinine will occur if bilateral.

Investigations

- Urgent US including Doppler studies when decreased renal blood flow will be seen. It is important to look in the arcuate and interlobular veins, as well as the main renal veins, inferior vena cava (IVC), and heart. Measurement of renal length at presentation is important as there is evidence that the most swollen kidneys are the ones that fare worst.
- US can be used to give ongoing information on the restoration or lack of renal blood flow and of renal length, which will show shrinkage if the kidney has infarcted. Calcification may be seen in infarcted tissue after 6 weeks.
- Procoagulant screen including: protein C/S, antithrombin levels, Exner, DRVVT, and anticardiolipin levels, Factor V Leiden (1691GA), methylenetetrahydrofolate reductase (MTHFR) and prothrombin (2021GA) mutations.
- It is important to note that the clot, any acute phase process, and anticoagulants may affect the protein C, S, and antithrombin levels. Therefore, if levels are low acutely, they need to be repeated after recovery.
- DMSA scan after 3–6 months for evidence of renal damage.
- CKD management is necessary in those with bilateral damage on DMSA scan.

Treatment

- There is no evidence regarding who may benefit from anticoagulation in RVT, so each case is considered on an individual basis. Heparinization may prevent extension of the thrombus. Some advocate tissue plasminogen activator (TPA/alteplase) if the clot is bilateral or extends into the IVC (see Box 2.1).
- Before considering anticoagulation, intracranial bleeds (which may be made worse) must be excluded using intracranial US, particularly in very premature infants.

Box 2.1 Administrative protocols

Protocol for administration of recombinant tissue plasminogen activator:
- Heparin must be stopped for at least 3h.
- Give 0.1mg/kg over 10min then 0.3mg/kg/h over 3h.
- If the treatment is not completely successful, TPA (alteplase) can be repeated at an increased dose of 0.4mg/kg/h over 3h after 12–24h.
- All invasive procedures should be avoided.
- The plasma fibrinogen should be maintained at ≥1.5g/L during the infusion.
- Heparin is started at the end of the infusion at 100units/kg/day.
- Contraindications are recent surgery, intracerebral, or other severe bleeding.
- Correct thrombocytopenia and other coagulation deficiencies.
- Normalize the blood pressure (BP) as far as possible.

Long-term complications

- Hypertension.
- CKD (may be progressive if bilateral).
- If IVC clot, the development of collaterals, which may make difficult the future use of the femoral veins for dialysis access and the use of the IVC for renal transplantation. Such babies will need imaging of their abdominal vessels pretransplant.

Chapter 3

Congenital abnormalities

Antenatal diagnosis of structural renal abnormalities

Before antenatal ultrasound (US) scanning became routine, few congenital malformations of the kidneys and urinary tract were diagnosed until they caused symptoms in infancy, childhood, or occasionally adult life. Now the great majority are identified *in utero* and can be managed prospectively. They are potentially important because they may:

- Be associated with abnormal renal development or function.
- Predispose to postnatal infection.
- Cause urinary obstruction that requires surgical treatment.
- Occasionally be associated with aneuploidy or syndromes.

The antenatal detection and early treatment of urinary tract anomalies provide an opportunity to minimize or prevent progressive renal damage. A disadvantage is that minor abnormalities are also detected, most commonly mild unilateral renal pelvic dilatation, which do not require intervention, but may lead to over investigation, unnecessary treatment and unwarranted parental anxiety. It must be remembered that the management of the child who presents with symptoms is not the same as those that present with abnormalities on the antenatal scan.

Classification of antenatal ultrasound abnormalities

- Renal tract dilatation, which may be of the renal pelvis and/or calyces (hydronephrosis) and/or ureter (hydroureteronephrosis); see Table 3.1.
- The bladder may have diverticulae, be thick walled and/or show poor emptying; a dilated posterior urethra may be seen.
- Absent kidney(s).
- Large, small, echogenic, or cystic kidneys.

Table 3.1 Major causes of antenatal renal tract dilatation

Transient hydronephrosis (normal postnatal scan)	50%
Hydronephrosis with no evidence of obstruction; or extrarenal pelvis	15%
PUJ obstruction	11%
VUR	9%
Megaureter (obstructed, refluxing, non-refluxing and non-obstructed or both refluxing and obstructed)	4%
Renal dysplasia	3%
MCDK	2%
Duplex kidney +/– ureterocoele	2%
PUV	1%
Others	5%

Key points

- High resolution 2-D US allows detailed assessment of the kidneys and urinary tract from the second trimester of pregnancy.
- The incidence of antenatal renal tract dilatation (hydronephrosis) is around 1 in 200 pregnancies.
- There are many causes of antenatal renal tract dilatation; detection does not necessarily indicate the presence of obstruction in the affected kidney.
- Abnormalities of other organ systems may sometimes co-exist with renal anomalies.
- It is important to remember that following the detection of antenatal renal tract dilatation, around 50% of postnatal scans will subsequently be normal.
- Whenever a fetus or infant is being assessed, it is essential to take a complete antenatal history including details of all of the investigations performed to date.

Technical issues

- Antenatal US scans are usually undertaken routinely at 12–14 and 20 weeks gestation. Many abnormalities appear early, but PUV and others may be missed without a third trimester scan.
- Measurement of renal length. Allow 1mm per week of gestation, e.g. the length of the kidney in a 34-week gestation fetus is approximately 34mm.
- Renal pelvic dilatation is assessed by measurement of the maximum antero-posterior (AP) pelvic diameter in the transverse plane (not including the calyces), known as the transverse pelvic diameter (TPD).
- There is much debate regarding cut-off points for isolated renal pelvic dilatation above which postnatal investigation should be initiated:
  - AP diameters of between 5 and 15mm have been proposed as the cut-off point above which postnatal investigation should be performed;
  - lower cut-off points will increase the number of investigations performed postnatally (higher false positive rate) and enhance parental anxiety. Number of abnormalities detected will increase, but these are likely to be cases of mild non-dilating vesicoureteric reflux (VUR), which are unlikely to be of clinical significance.
- Careful assessment of the bladder and ureters should be performed:
  - detection of calyceal and/or ureteric dilatation is of great significance as their presence increases the likelihood of a significant urological abnormality being present; more intensive postnatal investigation is therefore warranted;
  - detection of bilateral pelvic dilatation at any time must be considered significant and increases the likelihood of significant urological abnormality being present; more intensive postnatal investigation is therefore warranted.
- Liquor volume needs careful assessment.
- It is possible to mistake the adrenal gland for the kidney in cases where the latter is absent.

Indications for antenatal referral to a fetal therapy unit

The following antenatal abnormalities need referral to a fetal therapy unit for discussion with a nephrologist/urologist (see Figs. 3.1–3.3):

- Oligohydramnios.
- Abnormal bladder: thick wall, ureterocoele, absent bladder.
- Abnormal renal parenchyma: echogenic, large or small kidneys, cystic change.
- Bilateral renal tract dilatation where the TPD is >15mm.
- Solitary kidney where the TPD is >15mm.
- Other major anomalies.

The management of antenatally-detected renal tract dilatation is outlined in Figs. 3.1–3.3.

This protocol recommends that postnatal investigations are restricted to those infants in whom hydronephrosis (TPD diameter of ≥10mm) is detected at 32 weeks gestation (see Fig. 3.2).

All infants where bilateral hydronephrosis (TPD diameter of ≥6mm), hydronephrosis in a single kidney (TPD diameter of ≥6mm) or hydronephrosis associated with ureteric dilatation is detected should undergo postnatal investigation (see Fig. 3.3).

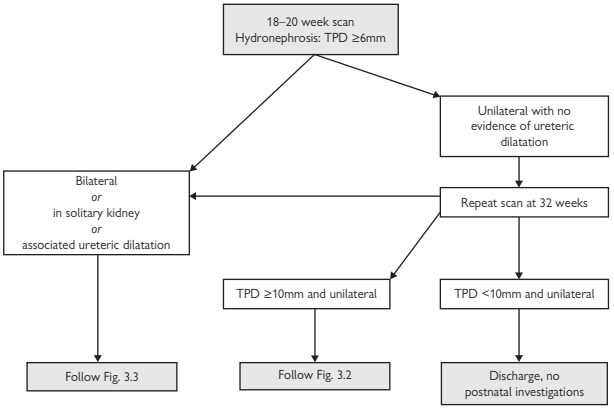

Fig. 3.1 The antenatal scan findings, indicating those that require further follow-up and investigation and those that can be discharged.

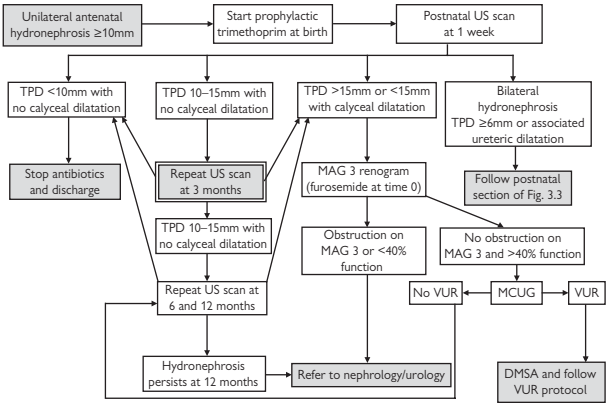

Fig. 3.2 Postnatal management for unilateral hydronephrosis diagnosed antenatally.

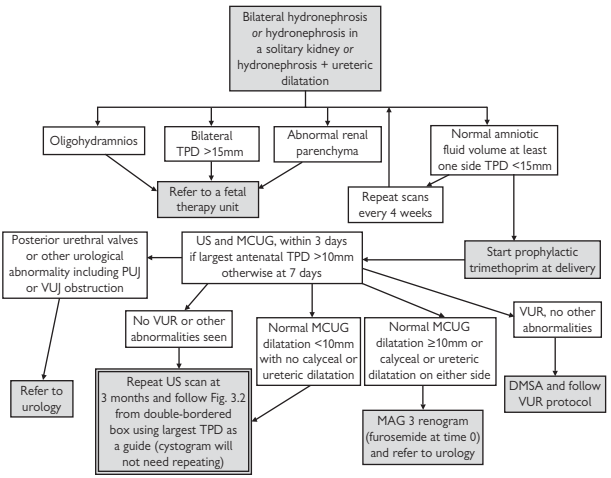

Fig. 3.3 Postnatal management for bilateral hydronephrosis, hydronephrosis in a solitary kidney or associated ureteric dilatation detected antenatally.

Ultrasound

- The difficulty is to distinguish neonates with abnormalities that need further assessment and treatment from those who need conservative management. US is the first investigation:
  - where unilateral hydronephrosis is present without ureteric dilatation (see Fig. 3.2), this should be performed at 1 week as the neonate is relatively oliguric for the first few days of life;
  - where hydronephrosis is bilateral, present in a solitary kidney or associated with ureteric dilatation (see Fig. 3.3) this should be performed along with a micturating cystourethrogram (MCUG) within 3 days of birth if the largest TPD was >10mm, otherwise within 7 days. This is the case even if the hydronephrosis was shown to subsequently resolve during later pregnancy.
- US should include:
  - measurement of renal length, and assessment of appearance and echogenicity;
  - measurement of the maximum renal pelvic diameter in the transverse plane (not including the calyces) and ureteric dilatation. A dilated renal pelvis with no dilatation of the ureter may signify a pelviureteric junction abnormality. Dilatation of the pelvis and ureter may signify a vesicoureteric junction (VUJ) abnormality or VUR;
  - Assessment of the calyces;
  - Appearance of the bladder with measurement of wall thickness, presence of ureterocoeles and, if the baby passes urine during the examination, post micturition residue. Views of the posterior urethra can be obtained in boys;
  - Spinal views can be obtained if a neuropathic bladder is suspected.

MCUG

Indications for an MCUG:

- Bilateral hydronephrosis or ureteric dilatation in a solitary kidney (Fig. 3). This should be performed within 3 days of birth if the largest TPD was >10mm and otherwise within 7 days. This is the case even if the hydronephrosis was shown to subsequently resolve during later pregnancy.
- Distended or thick walled bladder.
- Duplex kidney associated with hydronephrosis.

MAG3

The MAG3 scan can be undertaken at 1 to 2 months of age. It gives information on the function of each kidney relative to total.

- Good function is >40%.
- Moderate 20–40%.
- Poor <20%.

It must be noted that the drainage curve is unreliable in the neonate and will over diagnose obstruction because it is dependent upon:

- Renal function.
- Hydration and urine flow rate.
- Bladder fullness.
- Posture and pooling in a dilated system.

Long-term outcome studies of renal pelvic dilatation secondary to pelviureteric junction (PUJ) obstruction have provided the following information:
- All kidneys that showed deterioration in function had a TPD >20mm.
- A sustained increase in dilatation may precede deterioration in function.
- There is a very high risk of deterioration in function (60%) if the TPD is >30mm and pyeloplasty in the first 6 months of life is recommended.
- Of infants with renal pelvic measurements between 20 and 30mm with good function one-quarter remain stable, and some may improve by the age of 3–4 years.
- The more severe the calyceal dilatation the greater the risk of deterioration.

Surgery is recommended:
- In infants who develop symptoms.
- When there is progressive dilatation as measured by US.
- When there is deterioration in function on MAG3 scan.
- If the renal pelvic transverse diameter is >30mm.

Other renal anomalies

The following may also be detected and are discussed elsewhere: note that where evidence of one or more of these is detected antenatally, this should prompt referral to a fetal therapy unit:
- Cystic kidneys.
- Echobright kidneys.
- Multicystic dysplastic kidney (MCDK).
- Solitary kidney.
- Ectopic, horseshoe, and duplex kidneys.

Further reading

Dhillon HK (2002). In: Thomas DPM, Rickwood AMK, and Duffy PG (eds) *Prenatal Diagnosis. Essentials of Paediatric Urology*. Martin Dunitz Ltd, London, 97–104.

Burge D, Griffiths M, Steinbrecker H, and Wheeler R (2005). *Paediatric Surgery*, 2nd edn. Hodder Arnold, London, pp. 435–9.

Renal agenesis

Introduction

- True unilateral renal agenesis is caused by a failure of the ureteral bud to communicate with the metanephric blastema in the first few weeks of gestation.
- A number of cases of apparent renal agenesis will represent multicystic dysplastic kidneys that have undergone spontaneous regression.
- The reported incidence is 1 in 500 to 1 in 3,200.
- Diagnosis is now most commonly made on antenatal renal US.
- May go undetected and be diagnosed incidentally later in life, e.g. at time of US scan for unrelated issues, particularly if antenatal scanning is not performed.
- May occur in association with anomalies in other organ systems, e.g. vertebrae, genitalia, intestines, anus, limbs, heart, trachea, ear, and CNS.
- Almost 50% of children have associated congenital abnormalities of the contralateral kidney:
  - VUR in 28%;
  - PUJ and/or vesicouteric junction (VUJ) obstruction in 20%.
- There is an increased incidence of asymptomatic renal malformation (9%), most frequently unilateral agenesis (4.5%) in first-degree relatives of patients with bilateral renal agenesis, bilateral severe dysplasia, or agenesis of one kidney and dysplasia of the other. US examination of first degree relatives may therefore be warranted.

Investigation

- Ultrasound:
  - for renal size-a solitary kidney should show compensatory hypertrophy (>2SD above the mean, see Table 3.2 and 📖 'Radiological investigations', p.12);
  - to search for a previously undetected ectopic kidney;
  - to detect hydronephrosis or hydroureter in the single kidney suggestive of obstruction or VUR.
- Consider performing a DMSA scan to confirm absence of functioning renal tissue and to look for ectopically sited kidneys that have not been detected by US examination. Experienced ultrasonographers may argue that this is unnecessary and that ectopically sited kidneys can always be identified.
- Consider performing a MCUG where ureteric dilatation is or has been present (antenatally) to exclude VUR.
- MAG3 where there is suspicion of either PUJ or VUJ obstruction because of pelvic or ureteric dilatation on US without a dilated ureter or VUR on MCUG.
- The contralateral kidney should show compensatory hypertrophy. Where compensatory hypertrophy does not occur, this suggests the presence of dysplasia, and assessment of renal function should be performed (measurement of plasma creatinine or formal measurement of GFR, dependent upon local centre preference).
  - where there is evidence of compensatory hypertrophy and no other abnormality on US examination the outcome is likely to be very good and the child can be discharged from hospital follow-up;

- it is probably sensible that such children have their BP and an early morning urine dipstick assessed by their family doctor on an annual basis;
- where there is absence of compensatory hypertrophy, with or without evidence of abnormality of renal function, the child should remain under long-term follow-up.

Outcome

Long-term outcome is dependent upon the status of the single kidney.

- Where this is entirely normal, the long-term outlook appears to be excellent.
- Where dysplasia is present it is likely that progressive deterioration in renal function will develop in the long-term.

Bilateral renal agenesis

- Rare and almost uniformly fatal. Many fetuses die *in utero*.
- Fetal anuria results in oligohydramnios from around 16 weeks gestation, causing the Potter sequence (characteristic facial appearance with low-set malrotated ears, facial and nasal flattening, and an underdeveloped chin).
- Reduced intrauterine movement results in the development of arm and leg flexural deformities.
- Death within hours of birth usually occurs secondary to pulmonary hypoplasia.
- The small number of survivors require CKD 5 management from birth and have a tendency to develop recurrent pulmonary problems.
- Siblings should have a renal tract US.

Table 3.2 Mean and SD of renal length for age in patients with single functioning kidneys. Reproduced with permission from Rottenberg (1996). *American Journal of Roentegenology*, 167, 1255–9. Copyright © 1996 by American Roentgen Ray Society

Age range (weeks)	Mean age (weeks)	Mean length (mm)	SD	Number of patients in age group
0–4	2	51.0	5.8	13
5–15	9	56.8	6.3	40
17–34	23	62.8	5.6	25
34–52	46	69.6	6.8	18
53–94	63	71.7	7.9	33
103–153	112	78.0	8.0	32
156–207	172	79.6	8.2	17
208–258	225	86.7	9.5	14
260–312	279	91.0	7.9	12

Horseshoe kidney, renal ectopia, and duplex kidneys

Horseshoe kidney

- The lower poles (95% of cases) of the kidneys are fused over the midline by a narrow isthmus of renal parenchyma or fibrous tissue.
- The kidneys are sited more caudally than normal.
- Incidence 1:500 live births. More common in males.
- Associated with Turner's syndrome, trisomy 13, 18, 21, and 22, VATER (VACTERL) association.
- Also seen in fetal alcohol syndrome and the infant of a diabetic mother.
- The large majority are asymptomatic and are often undetected (incidental finding at post-mortem).
- A small percentage may be associated with other congenital anomalies of the urinary tract and other organ systems.
- UTI, haematuria, and abdominal pain are the commonest presenting features.
- Complications of the horseshoe kidney include:
  - PUJ obstruction due to the abnormal path of the ureter;
  - UTI associated with VUR, which may be present in as many as 50% of cases;
  - renal calculi secondary to stasis and infection;
  - trauma to the isthmus (situated anterior to the spine);
  - increased risk of Wilms' tumour in children and renal cell carcinoma in adults; adenocarcinoma, transitional cell carcinoma, malignant teratoma, oncocytoma, angiomyolipoma, and carcinoid have all been reported;
  - an increased incidence of hypertension is reported (this is likely to be secondary to renal cortical scarring resulting from VUR obstruction or dysplasia, rather than the horseshoe kidney itself).
- The identification of the isthmus and demonstration of its continuity with both lower poles may be difficult and missed with US. Diagnosis can be made by IVU, DMSA, computed tomography (CT) or magnetic resonance (MR) with a high degree of accuracy. Most would advocate a DMSA scan in the first instance.

Ectopic kidney

- Failure of ascent of the kidney during embryogenesis results in an ectopic kidney.
- Most cases are pelvic kidneys, although rare cases of thoracic kidney have been reported.
- May be unilateral or bilateral.
- They are not reniform in shape and may have associated ureteric abnormalities, but are usually asymptomatic.

Crossed renal ectopia

- One kidney crosses the midline and lies in an abnormally rotated position, below and medial to the normally sited one.
- There may be fusion, the upper pole being fused to the normal kidney's lower pole.
- The ectopic kidney is usually hypoplastic.
- The ureter from the ectopic kidney inserts in its normal position.
- It is often associated with ureteric and lower tract lesions.
- It is common in association with cloacal and anorectal abnormalities.

Duplex kidneys

- These occur in around 1% of the population, are familial and usually of no significance.
- May be bilateral, although unilateral duplication is 5–6 times more common that bilateral.
- Duplication of the ureteric bud results in a duplex kidney and collecting system, and may be complete or partial. In both cases, the kidney is usually larger than normal.
- If duplication is complete, the kidney has two moieties, each with its own ureter: the upper pole ureter may be ectopic, draining into the vagina (causing dribbling of urine) or posterior urethra, and may have a ureterocoele (which can cause obstruction); the lower pole ureter may have VUR. Very occasionally, a PUJ obstruction may occur in the lower pole or a moiety may be dysplastic.
- Incomplete duplication results in an 'uncomplicated' duplex kidney, with either simply a divided pelvis or two ureters that join before entering the bladder.
- They may present as kidneys of different sizes during US examination. In this situation it is important to have an estimate of renal centiles in order to distinguish between a normal and a small kidney, or a large and a normal-sized kidney. If there is no dilatation of the collecting system (uncomplicated) no further imaging is necessary.

The multicystic dysplastic kidney

Introduction

The MCDK

- Developmental abnormality due to failure of union of the ureteric bud with the renal mesenchyme resulting in a non-functioning kidney that is replaced by large, non-communicating cysts of varying sizes with no renal cortex and an atretic ureter. By definition, therefore, it can only be unilateral in a surviving infant.
- Sporadic condition with an incidence of 1 in 2000–4000.
- Twice as common in males.
- Previously presented as a unilateral abdominal mass on routine neonatal examination. Now is most frequently detected during antenatal US examination.

Investigation and diagnosis

- US (repeated in the early newborn period where the abnormality has been detected antenatally) shows large non-communicating cysts of varying size with no renal parenchyma.
- DMSA scan will confirm absence of renal function on the affected side. If function is present, the diagnosis may be a severely obstructed PUJ, the apparent 'cysts' being dilated calyces.
- The contralateral kidney should show compensatory hypertrophy (defined as renal length >2 SD above mean; see 🕮 Appendix, p.599). Where compensatory hypertrophy does not occur, this suggests the presence of dysplasia, and assessment of renal function should be performed (measurement of plasma creatinine or formal measurement of GFR, dependent upon local centre preference).
- If there is no other abnormality on US, no further imaging need be undertaken.
- As up to 25% of cases have VUR into the contralateral kidney, an MCUG should be considered if there is evidence of calyceal or ureteric dilatation.
- There is an increased incidence of PUJ obstruction in the contralateral kidney (3%).

Complications

- *Malignancy:*
  - whilst case reports of malignant transformation to Wilms' tumour, adenocarcinoma and embryonic carcinoma exist, the risk of malignancy has probably previously been overstated;
  - it is not possible to calculate a precise risk of malignancy from existing data, although it has been estimated that 1600–8000 MCDKs might need to be removed to prevent one Wilms' tumour.
- *Hypertension:* MCDK is associated with a slightly increased risk of hypertension which can be cured by nephrectomy.
- Infection, bleeding into or rupture of cysts if large.

Management

Conservative

- Most authorities recommend conservative management of the MCDK. 15-year follow-up of a large cohort of conservatively-managed patients in Nottingham has shown that 62% of antenatally-detected MCDKs will undergo involution by 10 years (see Fig. 3.4). Kidneys greater than 5cm were less likely to undergo involution (21 vs. 76% in those <5cm).
- Absence of detection on US does not equate with true disappearance of renal tissue, and the risk of hypertension and other complications may persist.
- Nephrectomy may be indicated for kidneys that have not adequately involuted by the age of 2 years or if infection, hypertension, or other complications develop.
- Conservatively managed cases should be reviewed with annual BP and urine stick testing for protein. US, to look for involution of the MCDK and also for growth of the contralateral kidney, which should grow above the 50th centile for height and age, should be annual until 2 years of life and then can be repeated at the age of 5 years if all is well.

Early nephrectomy

- The major advantage of surgery is that it allows the child to be discharged from all ongoing follow-up (if the contralateral kidney is normal).
- Some have advocated elective nephrectomy for all patients at around 12 months of age.
- Advances in laparoscopic nephrectomy allow the operation to be performed as a day-case procedure.
- Surgery has a very low complication rate.

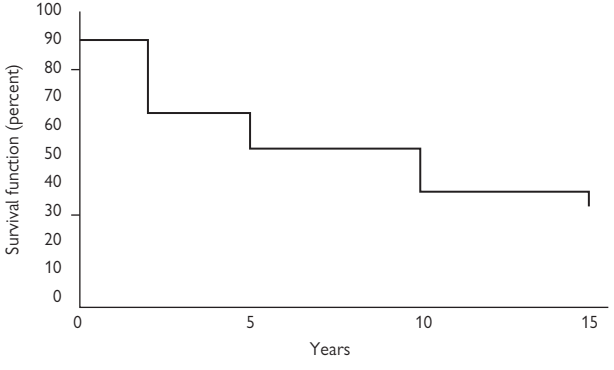

Fig. 3.4 Involution of all MCDK kidneys.

Pelviureteric junction abnormalities

Introduction

- PUJ anomalies are the commonest abnormality of the upper urinary tract.
- Incidence is around 1:1000.
- More common in boys (2–3:1).
- Not all cases of renal pelvic dilatation have a significant outflow obstruction; i.e. the pelvis may be dilated, but not obstructed.
- Most cases of obstruction are primary and due to obstruction secondary to a dysfunctional segment at the PUJ, which is generally narrower than the normal surrounding ureter (histologically, disordered bundles of smooth muscle with an excess of extracellular matrix).
- Lower pole aberrant blood vessels crossing the pelvis may sometimes produce a secondary PUJ obstruction (extrinsic obstruction).
- Other causes of secondary PUJ obstruction include ureteral polyps (intrinsic obstruction).
- More common on the left (2:1).
- May be bilateral in up to 40% of cases.
- The lumen is nearly always patent, albeit narrow and irregular.
- May be intermittent, depending on the rate of urine flow.
- May be associated with other renal anomalies, e.g. ectopic kidneys.
- May affect the lower pole PUJ in a duplex kidney.

Presentation

- The large majority of cases are now detected in the antenatal period during routine US assessment; significant PUJ obstruction is more likely when the antenatal hydronephrosis is >20mm.
- Older children may present with acute loin or abdominal pain, haematuria, a palpable flank mass, infection (including pyonephrosis), nausea/vomiting, or pelvic rupture following minor trauma.
- In extreme form, this is termed Dietl's crisis.
- Pain may subside spontaneously.
- PUJ anomalies may occasionally be detected during radiological investigation (e.g. abdominal US or CT scanning) for other clinical problems.

Investigation

The key issue is to distinguish cases of antenatally-suggested PUJ obstruction, which may lead to progressive deterioration in renal function from cases of non-obstructive hydronephrosis, which are very likely to undergo spontaneous resolution.

Ultrasound

- Older children not detected through antenatal US screening will most commonly initially undergo US assessment of the urinary tract.
- Measurements of the renal pelvis should be the antero-posterior pelvic diameter in the transverse plane (not including the calyces). A dilated renal pelvis with no dilatation of the ureter may signify a PUJ abnormality.

- The major differential diagnoses include an extra renal pelvis, a peripelvic renal cyst, non-obstructive hydronephrosis, obstructed or non-obstructed megaureter, and VUR.
- If the calyces are not dilated, obstruction is unlikely.
- US alone cannot diagnose obstruction as functional information is not provided.

MAG3 scan (dynamic renography)

- Required for confirmation of the diagnosis.
- This investigation is dependent upon a number of factors including the hydration status of the patient, the positioning of the patient, and the timing of administration of isotope and diuretic, and can be difficult to interpret.
- Produces information on differential renal function, the clearance of the isotope and analogue pictures, which show the anatomy of the collecting system; this will allow distinction between PUJ (no isotope seen in ureters) and VUJ obstruction (isotope in ureters).
- In the presence of obstruction, isotope accumulates within the kidney and the drainage curve continues to rise even after change of posture or diuretic to encourage drainage (Fig. 3.5).

Intravenous urogram

- Traditionally has been the investigation of choice for the diagnosis of PUJ obstruction in adults and older children, but has now been replaced by radioisotope imaging.
- Provides good anatomical and some functional information (although not quantitative relative function), but the radiation dose is significantly higher than the MAG3 scan.
- Works less well in poorly functioning or immature kidneys.

Indications for surgical intervention

- The presence of clinical symptoms is always an absolute indication for surgery.
- Surgical intervention in antenatally-suggested PUJ obstruction is a controversial subject:
  - only around 25% of such cases will develop clinical problems or evidence of deteriorating renal function requiring surgical intervention;
  - there has therefore been a move away from early intervention to close monitoring with serial imaging;
  - where the renal pelvic transverse AP diameter is <2.0cm, surgery is rarely necessary;
  - few urologists would recommend operative intervention solely on the presence of an obstructive curve on the MAG3 scan;
  - most would operate only if (i) the differential function of the affected kidney falls to <40%, (ii) there is a fall in differential function of >10% during follow-up or (iii) there is increasing dilatation of the kidney during follow-up.
- The aim of surgery is to improve the function or prevent further deterioration of the affected kidney.

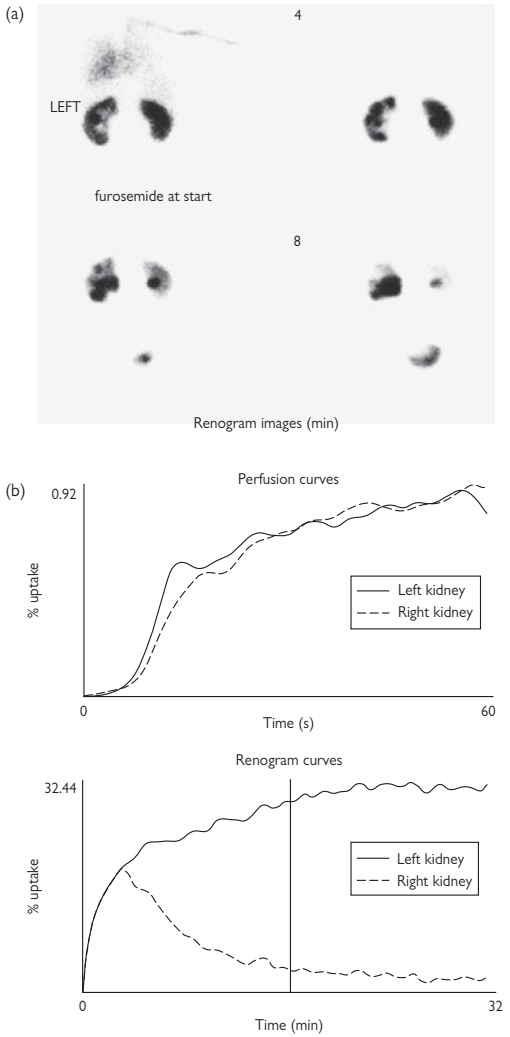

Fig. 3.5 MAG3 isotope renogram, with (a) posterior analogue images and (b) time-activity curves, showing showing rapid uptake of isotope in right kidney with rapid excretion, and rapid uptake but poor drainage with ongoing accumulation of isotope in the left kidney. Findings consistent with a diagnosis of a left PUJ obstruction.

- It has been suggested that the chances of improving renal function are greatest when surgery is performed in the first year of life.
- Complications associated with the conservative management include:
  - potential for progressive deterioration of the function of the affected kidney;
  - haematuria;
  - loin pain;
  - urinary stasis resulting in UTI and calculus formation (the combination of obstruction and infection has the potential to rapidly destroy renal tissue).

Surgery

- Open pyeloplasty (Anderson Hynes) is the most frequently undertaken surgical procedure.
- Laparoscopic techniques are increasing in popularity.
- Where differential function is very poor (<10–15%), there is a case for draining the kidney via a nephrostomy: if function improves, a pyeloplasty is indicated; whereas if function remains poor nephrectomy should be considered.
- Recommended follow-up: US scanning (at around 2 months) and MAG3 scanning (at around 6–12 months). These should show improvement in hydronephrosis with improved drainage with stabilization or improvement in differential renal function.

Megaureter

Megaureter describes an abnormally wide ureter and is classified as obstructed, refluxing, obstructed and refluxing, or non-refluxing/non-obstructed.

Primary megaureter (PM)

- Includes cases of obstructed and non-obstructed megaureter where secondary causes (urethral obstruction, bladder outlet obstruction, etc.) have been excluded.
- More common in boys.
- More often involves the left ureter.
- 25% of cases are bilateral.
- Where unilateral, 10–15% of cases have an absent or dysplastic contralateral kidney.
- Most frequently diagnosed on routine antenatal US.
- Other cases (primarily obstructed PM) present in infancy, often with significant illness and urinary sepsis.
- Renal calculi can form within the dilated system causing pain and haematuria.

Non-obstructed primary megaureter

- The majority of PM is non-obstructed with no evidence of VUR.
- The aetiology is unclear.
- Can be managed conservatively as the risk of deterioration of renal function is very low.

Obstructed primary megaureter

- Functional obstruction occurs because of an aperistaltic section of distal ureter that cannot adequately transport urine.
- Requires surgical correction (re-implantation of distal ureter).

Investigation

- PM is most frequently detected during routine antenatal US assessment.
- Postnatal US will show and quantify the extent of hydronephrosis and hydroureter.
- A MCUG should be performed to diagnose or exclude VUR, and help eliminate secondary causes of megaureter (posterior urethral valves, bladder dysfunction). VUR may occasionally be seen in association with an obstructed PM.
- Further investigation should aim to distinguish obstructed PM from non-obstructed PM:
  - MAG3 scan is the most useful investigation, although interpretation of the drainage curve may be difficult because of pooling of isotope in the dilated ureter;
  - significant obstruction is more likely where the differential function of the affected kidney is reduced to <40%.
- An obstructed PM may occasionally be associated with PUJ obstruction; an IVU may be helpful in this situation.

Treatment

The acutely sick patient presenting with pyonephrosis or pyelonephritis requires systemic antibiotic therapy and drainage of the obstructed system with the use of a percutaneous nephrostomy or a double-J stent. Following assessment of the relative function of the kidney, surgery should be performed. A nephrectomy may be necessary for a non-functioning or very poorly functioning kidney (contributing <10% of the overall GFR), although this should be assessed once the acute infection has subsided.

Non-obstructed primary megaureter

- Non-obstructed PM (on the basis of 📖 'Investigations', p.66) should be managed conservatively and the likelihood is that the dilatation will resolve with time:
  - serial US scans (6-monthly initially, then annually) should be performed to ensure there is no increase in hydronephrosis;
  - where increase in hydronephrosis occurs, the MAG3 should be repeated to ensure that evidence of obstruction or a fall in differential function has not developed; this may occur in 1–2%.

Obstructed primary megaureter

- Severe urinary sepsis is an absolute indication for surgery.
- For other cases there is an increasing trend towards conservative management. There is widespread use of prophylactic antibiotic therapy in this clinical situation, although no randomized controlled trial evidence to support this.
- Regular imaging is indicated as described for the non-obstructed PM.
- During follow-up, surgery is indicated for:
  - any symptoms (infection, calculus formation or pain);
  - worsening obstruction with increasing hydronephrosis and deteriorating relative renal function.
- Surgery involves the tapering and re-implantation of the lower ureter.
- Hydronephrosis may take several years to resolve post-operatively.

Posterior urethral valves

Introduction

- PUV are a congenital malformation of the posterior urethra occurring exclusively in male infants, although anterior urethral valves may very rarely affect females.
- Valves exhibit effects on the developing urinary tract from early in pregnancy when fetal urine production commences.
- The back-pressure produced by the valves may result in VUR, hydronephrosis, calyceal rupture (the weakest point) causing a urinoma and renal dysplasia.
- The bladder wall hypertrophies, becoming thickened and trabeculated in response to the obstruction. This may result in secondary VUJ obstruction.
- The effect on renal function is very variable and related to the degree of renal dysplasia, which occurs secondary to the obstruction or may be part of the abnormality itself:
  - some infants will have normal renal function at presentation, whereas in other cases this is markedly deranged. Tubular damage predominates, leading to sodium and bicarbonate losses causing significant hyponatraemia, acidosis, and secondary hyperkalaemia;
  - the extent of improvement in renal function following relief of obstruction is also very variable: in some the plasma creatinine will return to normal, whereas in others, particularly where severe dysplasia is present, the plasma creatinine may remain elevated.

Presentation

- The majority of cases are diagnosed as a result of antenatal US, which may show oligohydramnios with bilateral hydronephrosis and hydroureter, bladder wall thickening and posterior urethral dilatation. A significant proportion will be missed if there has not been a third trimester scan.
- The oligohydramnios which may develop secondary to the urinary tract obstruction may result in pulmonary hypoplasia. This may be fatal in the newborn period.
- Oligohydramnios may also cause postural defects including dislocation of the hip, talipes, receding jaw (Potter-like syndrome).
- Fetuses diagnosed with bilateral hydronephrosis should therefore undergo urgent US assessment in the newborn period. Prophylactic trimethoprim (2mg/kg) should be commenced and an urgent MCUG organized.
- Later modes of presentation include UTI, poor urinary stream, straining to pass urine, palpable bladder or, later in childhood, problems with daytime and night-time wetting, and CKD.

Diagnosis

- Where PUV are strongly suspected on the basis of the preliminary US findings, the infant should be catheterized (5FG feeding tube) under broad spectrum antibiotic cover so that any obstruction can be relieved, whilst radiological investigation is awaited. Where there is a paediatric urology service 'on-site' a suprapubic catheter may be preferable in order to allow accurate diagnosis of the urethral pathology, which may be destroyed by the insertion of a urethral catheter.

- Meticulous attention should be paid to fluid balance, as where obstruction has been present, there may be a marked post-obstructive diuresis. Urine output should be replaced on a mL for mL basis with 0.45% or 0.9% saline (depending on urinary sodium concentration) with added bicarbonate as urinary sodium and bicarbonate losses will be high. Regular weighing of the child and monitoring of plasma and urine electrolytes is mandatory.
- The MCUG is the gold standard investigation for diagnosing PUV. Views of the urethra should be obtained without the catheter *in situ*.
  - this will show posterior urethral dilatation, and the bladder is likely to have an abnormal trabeculated contour and diverticulae;
  - unilateral or bilateral VUR may also be present;
  - it is important to consider obstruction at the VUJ if the system is dilated and there is no VUR.
- A DMSA scan should be arranged 3 months after relief of obstruction and resolution of infection to determine the degree of renal dysplasia, and to measure differential renal function.

Treatment

- Treatment of PUV is surgical.
- Definitive treatment involves the valves being ablated endoscopically by a variety of different surgical techniques. It has been argued that ablation is the preferred initial treatment as spontaneous filling and emptying of the bladder during infancy is crucial to normal development.
- When primary ablation is impossible because of size or if the technique fails, urinary diversion with a vesicostomy or bilateral ureterostomies may be necessary with elective surgical treatment of the PUV later.
- Following relief of lower tract obstruction:
  - a diuresis may occur with resultant abnormalities of fluid balance and biochemistry;
  - a secondary VUJ obstruction may develop due to the presence of the thick-walled bladder. This is suspected where the biochemistry does not improve and an US shows persistent hydroureteronephrosis. It may resolve with time, but may be severe enough to necessitate nephrostomy drainage, ureterostomies or insertion of VUJ stents;
  - a MAG 3 scan, if renal function is adequate, may help to decide if obstruction is present.
- It is technically possible to intervene *in utero* with the insertion of a vesico-amniotic shunt, however, the long-term efficacy and safety of this procedure remains uncertain. A randomized trial (PLUTO) comparing fetal vesico-amniotic shunt insertion with conservative management is currently in progress (http://www.pluto.bham.ac.uk). NICE guidelines (2006) encourage recruitment of patients into this study.
- Early delivery of antenatally-diagnosed patients has not been shown to be of benefit.

Short-term follow-up and complications

- Careful follow-up is necessary with attention to renal function and plasma biochemistry, growth (sodium deficit and acidosis will impair

this and sodium bicarbonate is often routinely added to all feeds) and BP.
- Prophylactic antibiotics are given when VUR is present and UTIs should be treated promptly to prevent further renal damage. It is unclear how long antibiotics should be continued for, though some would recommend until 3–4 years of age.
- A check cystourethroscopy or MCUG is performed at 3 months post-ablation.

Long-term complications of posterior urethral valves

Chronic kidney disease

- The most severe long-term complication of PUV, which are the cause of around 16% of cases of CKD 5 in the United Kingdom.
- 10–22% of boys with PUV will develop CKD 5 during childhood.
- Clinical features predictive of a poor outcome with regards to renal function include:
  - early presentation (where antenatal diagnosis has not been made) as those with more severe urinary obstruction present earlier;
  - failure to achieve a plasma creatinine below 80μmol/l following relief of urinary obstruction;
  - proteinuria;
  - daytime wetting after the age of 5 years.
- When transplantation is being considered, great attention should be paid to bladder function to ensure that the success of the graft is not put at risk by abnormally high bladder pressures.

Wetting

- Boys with PUV have bladders that may behave abnormally and there may be significant continence issues.
- Assessment of continence is clearly difficult in the infant and very young child in nappies and urodynamic studies may be very difficult to interpret in this group.
- Urodynamic studies should be performed in all boys with daytime wetting persisting beyond 5 years of age.
- Some have argued the case for earlier routine urodynamic assessment:
  - more severe valve bladders are small, trabeculated, thick walled, high pressure systems with large residual volumes post-micturition;
  - VUR into the upper tracts may be a large proportion of the bladder capacity, which together with the high urine output due to the decreased concentrating capacity as a result of tubular damage may contribute to the progression of CKD, particularly when the bladder becomes very full overnight.
- Treatment options for the abnormal bladder include the use of anticholinergic agents or clean intermittent catheterization where:
  - bladder pressures are high;
  - there is concern about ongoing renal damage.
- More severe cases may require augmentation cystoplasty; a continent channel to allow catherization of the augmented bladder can be created at the time of surgery with the use of appendix or other tissue (Mitrofanoff).

Urogenital sinus and cloacal abnormalities

Urogenital sinus abnormalities

- A disorder of females—failure of development of the urethrovaginal septum results in the urethra and vagina being a single channel and opening.
- The opening may be stenosed, causing obstruction to both uterine drainage (causing hydrocolpos) and urinary tract drainage.
- Surgical separation of the vagina and urethra is necessary. Colon may be needed to create the vagina.

Persistent cloaca

- A disorder of females—failure of development of the urorectal septum results in the urethra, vagina, and colon opening into a single channel.
- There may be obstruction of drainage of the bladder, uterus, and gastrointestinal (GI) tracts.
- Relief of the obstructions is necessary (may include a colostomy), followed by reconstructive surgery.

Bladder exstrophy

- Failure of infraumbilical mesenchyme to separate the part of the cloaca that will go on to form the bladder from overlying ectoderm. This results in breakdown of the cloacal membrane causing exposure of the posterior wall of the bladder with a shortened abdominal wall, incomplete fusion of the genital tubercles, separated pubic rami and inguinal herniae.
- The baby is born with a defective lower abdominal wall, symphysis pubis diastasis and multiple abnormalities involving the pelvis, bladder, urethra, and external genitalia. The posterior wall of the bladder joins with the edges of the defect in the abdominal wall and has a deficient anterior wall, including the bladder neck and external urethral sphincter. There is epispadias or hemi-clitoris with a widely-spaced scrotum or labia and an anterior anus.
- It is up to six times as common in males.
- Surgery is complex and in the UK is undertaken in only 2 hospitals: Great Ormond St Hospital for Children and the Royal Manchester Children's Hospital. The bladder is closed in the neonatal period; this usually requires pelvic bone osteotomies. Thereafter, multiple operations are necessary to enable urinary continence and to reconstruct the genital tract.

Cloacal exstrophy

As well as bladder exstrophy there is omphalocoele, a rudimentary midgut with imperforate anus and lumbosacral defects.

Absent abdominal musculature syndrome

Introduction

- Triad of:
  - deficiency or absence of anterior abdominal wall musculature;
  - bilateral cryptorchidism (in boys);
  - ureter, bladder, and urethral abnormalities, predominantly megacystis and megaureter, secondary to dysplasia.
- Abnormalities of other organ systems occur in up to 75% of cases.
- Over 95% of cases occur in males (some consider girls to have incomplete or pseudo-Prune belly syndrome).
- Although a genetic basis has not been established, a small number of cases have been documented in siblings and twin gestations.
- The recurrence risk is not, however, generally thought to be increased in subsequent pregnancies.
- An abnormality of mesenchymal development has been proposed.
- Cause of 1.0 and 2.6% of cases of CKD 5 in UK and US, respectively.
- The term 'Prune belly syndrome' is no longer used due to its insensitivity.

Urinary tract abnormalities

Kidneys

- Varying degrees of renal dysplasia may occur and may be severe, resulting in early death from pulmonary hypoplasia.
- Severity of dysplasia is an important determinant of long-term survival.
- Acquired renal damage from UTI early in life in combination with dysplasia will result in progressive CKD.

Ureters

- Dilated and tortuous with associated VUR in the majority.
- Poor or ineffective peristalsis results in poor urinary drainage.
- Significant urinary stasis increases risk of urine infection significantly.
- Kinking of ureters may result in obstruction.
- Obstruction may also occur at the PUJ and VUJ.

Bladder

- Large volume with an irregularly thick (due to fibrosis) although non-trabeculated wall.
- Multiple large diverticulae are common.
- Ureteric orifices are laterally spaced.
- Urachal cyst or patent urachus may be present.
- Has poor contractility and low voiding pressures.
- Significant post-micturition residual volume because of poor contractility and VUR into dilated upper tracts.

Urethra

- May be narrowed just below prostate gland with dilated prostatic urethra.
- Urethral atresia may occur (more common in girls).

Testes/genitals
- Cryptorchidism is universal.
- Empty, hypoplastic scrotum.
- Invariably infertile, although sexual function normal.
- Girls may have vaginal atresia or uterine abnormalities.

Involvement of other organ systems

Gastrointestinal tract
- Increased incidence of malrotation and malfixation.
- Constipation may be a problem.
- Increased incidence of gastroschisis.
- Imperforate anus may occur, particularly in association with urethral atresia.

Heart
- 10% incidence of congenital heart disease.
- Echocardiography screening is warranted in newborns.

Skeletal Increased risk of talipes equinovarus and congenital dislocation of the hip as in all infants when the pregnancy has been complicated by oligohydramnios.

Pulmonary Pulmonary hypoplasia may develop in those where oligohydramnios has been present.

Diagnosis

- Often suspected from antenatal US scans showing severely dilated urinary tract with a distended abdomen. PUV associated with urinary ascites may produce a similar appearance.
- Wrinkled and lax appearance of the neonatal abdomen wall with a palpable urinary tract and cryptorchidism (empty hypoplastic scrotum) are all clinically apparent and should lead to early diagnosis and evaluation.

Assessment

- Initial assessment should involve identifying non-renal anomalies, which may be life-threatening including significant congenital heart lesions and pulmonary hypoplasia.
- The urinary tract should initially be assessed by US.
- MAG3 scan will provide data on differential renal function and evidence of possible obstruction (although the dilated, poorly-draining ureters may produce false positive results).
- MCUG will identify VUR, although there is a significant risk of introducing infection and some have argued that this should be avoided.
- MR urography can produce further anatomical information.
- Urodynamic assessment may be helpful, particularly where there are concerns about bladder drainage.

Treatment

- There is little evidence that reconstructive surgical procedures are of benefit in this condition.
- Any instrumentation of the urinary tract may introduce infection, leading to deterioration in renal function.
- Surgery may be necessary where there is clear evidence of urinary obstruction. Ureteric and bladder drainage is the major source of problems; this may be treated with urinary diversion (cutaneous ureterostomies), clean intermittent catheterization (urethral or via a created continent channel (Mitrofanoff)), reduction cystoplasty or tailoring followed by re-implantation of the ureters.
- There is no evidence to support the use of long-term prophylactic antibiotic therapy.
- Abdominal wall function may develop with increasing age.
- Orchidopexy should be performed, ideally before dialysis or transplant becomes necessary.
- Renal function should be kept under review.
- Where function deteriorates, standard CKD management should be instituted.
- Dialysis and transplantation can be successfully performed, although it is essential to ensure that bladder function is satisfactory prior to transplantation.

Chapter 4

Urinary tract infection

Background and clinical features

Background

Three per cent of girls and 1% of boys have a symptomatic urinary tract infection (UTI) before the age of 11 years, and 50% of them have a recurrence within a year. The highest incidence is in the first year of life. UTI may involve the kidneys (pyelonephritis), when it is associated with fever and systemic involvement, or may be due to cystitis, when fever is absent or low grade. Up to one half of children with a UTI have a structural abnormality of their urinary tract. UTI is important because, if the upper tracts are affected, it may damage the growing kidney by forming a scar, predisposing to hypertension and, if bilateral, CKD.

NICE guidelines published in 2007 have significantly changed clinical practice regarding the diagnosis, clinical management, and subsequent radiological investigation of the child with a UTI. The introduction to these guidelines expressed the view that 'current management—involving imaging, prophylaxis and prolonged follow up—has placed a heavy burden on NHS primary and secondary care resources, and is unpleasant for children and families, costly and not evidence-based'.

Important general points

The commonest error in the management of UTI in children, and especially in infants, is failure to establish the diagnosis properly in the first place. If UTI is not diagnosed, the opportunity to prevent renal damage may be missed, or, if incorrectly diagnosed, may lead to unnecessary invasive investigations.

NICE guidelines recommend the testing of urine in infants and children with:

- Symptoms and signs of UTI.
- Unexplained fever of 38°C or higher (test urine within 24 h).
- An alternative site of infection but who remain unwell (consider urine test after 24 h at the latest).

Clinical features

Presentation of UTI varies with age:

- In the newborn, symptoms are non-specific and include fever, poor feeding, vomiting, failure to thrive, lethargy, and irritability; septicaemia may develop rapidly.
- The classical symptoms of dysuria, frequency, and loin pain become more common with increasing age.
- Dysuria without a fever is often due to vulvitis in girls or balanitis in uncircumcised boys, rather than a UTI.

Collection of urine samples and diagnosis

Collection of urine samples

Urine can be collected by a variety of methods in a younger child in nappies.

NICE recommended techniques

- A 'clean-catch' sample into a waiting sterile pot when the nappy is removed; this is easier in boys.
- Absorbent urine collection pads, e.g. Newcastle sterile urine collection packs, in the nappy (not cotton wool, gauze, or sanitary towels).
- Catheter sample or suprapubic aspiration (SPA), the authors' method of choice in the severely ill infant under 1 year, requiring urgent diagnosis and treatment, and in cases where previous samples have suggested contamination. NICE guidelines recommend this be performed when non-invasive methods are not possible. US imaging should be performed to confirm the presence of urine in the bladder and to guide sampling.

Alternatives (not NICE recommended)

An adhesive plastic bag applied to the perineum after careful washing, although there may be contamination from the skin and the false positive rate is 85%. This method should only be used as a screening test.

In the older child, urine can be obtained by collecting a midstream sample. Careful cleaning and collection are necessary, as contamination with both WBC and bacteria can occur from under the foreskin in boys, and from reflux of urine into the vagina during voiding in girls.

Diagnosis

- Ideally, the urine sample should be microscopically examined for organisms and WBC, then cultured straight away.
- If not possible, refrigerate to prevent overgrowth of contaminating bacteria.
- Presence or absence of urinary WBC alone is not a reliable feature of a UTI, as they may be present in febrile children without a UTI, and in children with balanitis or vulvovaginitis, or absent due to lysis during storage.
- Positive testing of the urine with sticks for leucocyte esterase and nitrite is also suggestive of infection, but there may be both false positive and false negative results. This is because the presence or absence of WBC is not diagnostic of UTI (see 📖 'Background and clinical features', p.76) and urine needs to be in the bladder for at least an hour to allow time for the conversion of nitrate to nitrite. Sticks, in the opinion of some, should only be used as a screening test. The sensitivity and specificity of leucocyte esterase and nitrite sticks have been reported to be 83 and 78, and 53 and 98%, respectively (see 📖 'NICE guidelines', p.78).
- Which urines should be cultured after screening is controversial. Some suggest that culture is only necessary for urine that contains organisms on microscopy. Others recommend culture if stick tests are positive and there are >5 WBC per high power field in a spun sample, or bacteria seen in an unspun Gram-stained sample.

NICE guidelines

- Recommend urgent microscopy and culture, and the immediate commencement of antibiotics if:
  - age <3 months;
  - specific urinary symptoms in children of 3 months to 2 years of age;
  - non-specific symptoms in children of 3 months to 2 years of age at high risk of serious illness.
- If symptoms are non-specific in a child of 3 months to 2 years of age:
  - urine should be collected and sent for urgent microscopy and culture;
  - if bacteriuria positive and pyuria positive or negative treat as UTI with antibiotics;
  - if bacteriuria negative and pyuria positive, treat as UTI if clinically suggestive of UTI;
  - if bacteriuria and pyuria negative do not treat as UTI;
  - if urgent microscopy not available, treat with antibiotics if dipstick nitrites positive; urine should be sent for culture.
- In children 3 years of age and older, NICE recommends that a urine dipstick test should be used to initially diagnose UTI.
- Urine dipstick results should be interpreted as follows:
  - *if leukocyte esterase and nitrite positive:* start antibiotic treatment for UTI; send urine for culture if high or intermediate risk of serious illness or past history of UTI;
  - *if leukocyte esterase negative and nitrite positive:* start antibiotic treatment and send urine for culture;
  - *if leukocyte esterase positive and nitrite negative:* treat only if good clinical evidence of UTI; culture urine and treat depending on result;
  - *if both leukocyte esterase and nitrite negative:* do not treat as UTI or send urine for culture.
- A colony count of any Gram negative bacilli or $>10^3$ colony-forming units (CFUs) per mL of a Gram positive cocci from a suprapubic aspirate of urine gives a 99% probability of infection. A colony count of $>10^5$ CFUs of a single organism per mL in a sample obtained by catheterization gives a 95% probability of infection. A sample with $\geq 10^5$ CFUs of a single organism per mL obtained by clean catch gives an 80% probability of infection, which rises to 90% if the same result is found in a second sample. Mixed organisms usually represents contamination, but if there is doubt, another sample should be collected.
- NICE guidelines recommend that acute pyelonephritis (upper UTI) is distinguished from cystitis (lower UTI) using Table 4.1. This influences which radiological investigations should subsequently be performed.

Table 4.1 Factors distinguishing between upper UTI and lower UTI

Bacteriuria and fever of 38°C or higher	Acute pyelonephritis (upper UTI)
Bacteriuria, loin pain/tenderness and fever of less than 38°C	Acute pyelonephritis (upper UTI)
Bacteriuria, but no systemic features	Cystitis (lower UTI)

Bacterial and host factors that predispose to infection

Infecting organism

- Infecting organisms other than *E. coli* are more likely to be associated with structural abnormalities of the renal tract.
- UTI is usually the result of bowel flora entering the urinary tract via the urethra, except in the newborn, when it is more often haematogenous.
- The commonest organism to do this is *E. coli,* followed by *Proteus* and *Pseudomonas* sp.
- The virulence of *E. coli* is determined by factors including its cell wall antigens, and possession of endotoxin and cell wall appendages called P-fimbriae, which allow the organism to attach to the ureter and ascend to the kidney.
- *Proteus* infection is more commonly diagnosed in boys than girls, possibly because of its presence under the foreskin, and predisposes to the formation of phosphate stones by splitting urea to ammonia and thus alkalinizing the urine.
- *Pseudomonas* infection may indicate a structural abnormality in the urinary tract affecting drainage.

Incomplete bladder emptying

Is the most important cause of UTI and may be due to:

- Infrequent voiding, resulting in bladder enlargement.
- Vulvitis or balanitis.
- Hurried micturition.
- Obstruction by a loaded rectum from constipation.
- Neuropathic bladder (see 📖 'Primary diurnal and secondary enuresis', p.96).
- VUR.

Vesicoureteric reflux

- VUR is the retrograde passage of urine from the bladder into the upper renal tract.
- Primary VUR is a developmental anomaly of the vesicoureteric junction (VUJ). The ureters are displaced laterally and enter directly into the bladder, rather than at an angle, with a shortened intramural course. Primary VUR is, by definition, not associated with overt bladder pathology. It occurs in 1% of young children.
- There is no evidence that primary VUR of uninfected urine at normal pressure damages the kidney.
- There may be associated renal dysplasia in severe cases; indeed, antenatal scanning has revealed that what would have been termed 'reflux nephropathy' in the past is, in fact, due to congenital renal dysplasia with or without additional acquired infection-related damage. The changing definition has led to a decrease in the reported incidence of 'reflux nephropathy' as a cause of CKD 5 and a parallel increase in renal dysplasia with VUR.

- It is frequently familial, with a 30–50% chance of occurring in first-degree relatives.
- Secondary VUR may be due to or associated with bladder pathology, e.g. a neuropathic bladder or urethral obstruction or occur temporarily after a UTI. High-pressure VUR in this situation, with or without infection, may damage the kidneys.
- Its severity varies from reflux into the lower end of an undilated ureter during micturition to the severest form with reflux during bladder filling and voiding, with a distended ureter, renal pelvis, and clubbed calyces. Grading of VUR by MCUG has been popular in the past, but there are differing classifications and apparent severity can vary with the amount of contrast instilled into the bladder, and the speed and pressure applied. Also, more severe VUR occurs during filling, as well as voiding. More important is a description of the findings.
- Mild VUR is unlikely to be of significance, either in causing UTI or renal damage, but VUR associated with a dilated ureter may be associated with intrarenal reflux, the backflow of urine from the renal pelvis into the papillary collecting ducts in compound papillae. In compound papillae the collecting ducts fuse, making access to refluxed urine more likely than in simple, cone-shaped papillae. Compound papillae occur predominantly at the upper and lower poles of the kidney. Intrarenal reflux is associated with a particularly high risk of renal scarring if UTIs occur.
- The incidence of renal defects on scanning increases with increasing severity of VUR; however, half of children with renal defects do not have VUR.
- Conversely, VUR associated with two normal kidneys is very likely to resolve.
- Overall VUR resolves in 10% of cases each year. However, reflux into dilated ureters is less likely to resolve, particularly if associated with abnormal kidneys.

VUR with associated ureteric dilatation is important because:

- Refluxed urine returning to the bladder from the ureters after voiding results in incomplete bladder emptying, which encourages infection.
- The increased work placed upon the bladder may result in bladder dysfunction and decompensation over time.
- The kidneys may become infected (pyelonephritis), particularly if there is intrarenal reflux, resulting in renal scarring.
- Bladder voiding pressure is transmitted directly to the renal papillae; this may contribute to renal damage if voiding pressures are high.
- Renal scarring may lead to high BP (variously estimated at up to 10%) or to CKD if bilateral.

Management

Management of the acute infection

- Prompt identification and treatment reduces the risk of renal scarring.
- Most children can be treated with oral antibiotics, but infants, and children who are severely ill or vomiting, require IV antibiotic therapy until the temperature has settled, when oral treatment can be substituted.
- NICE guidelines regarding antibiotic treatment are as follows:
  - *age <3 months:* IV antibiotics—precise duration not stated, but sensible to administer for 2–3 days prior to switch to oral antibiotics if clinically improved;
  - *age >3 months, but with upper tract UTI:* oral antibiotic with low resistance pattern for 7–10 days; IV antibiotics for 2–4 days if vomiting, then oral antibiotics for a total of 10 days;
  - *age >3 months with lower urinary tract symptoms:* oral antibiotics for 3 days.
- If a child is on prophylaxis, change the antibiotic rather than increasing the dose.
- Most laboratories monitor local bacterial resistance patterns and are able to advise prescribers accordingly.
- NICE does not recommend antibiotic prophylaxis unless UTIs are recurrent.

NICE guidelines have produced a definition of atypical UTI. This is important as the presence of atypical UTI affects the subsequent radiological investigations that are recommended.

Definition of an atypical UTI

- Seriously ill child.
- Poor urine flow.
- Abdominal or bladder mass.
- Raised plasma creatinine level.
- Septicaemia.
- Failure to respond to treatment within 48 h.
- Non-*E. coli* UTI.

Investigations

The extent to which a child with a UTI should be investigated is controversial, not only because of the invasive nature and radiation burden of the tests (see 📖 'Radiological investigations', p.12), but also because of the lack of an evidence base to show that outcome is improved (unless urinary obstruction is demonstrated). Mild VUR usually resolves spontaneously and operative intervention to stop VUR has not been shown to decrease renal damage. There has, therefore, been a move away from traditional protocols that use age alone to determine investigations following a UTI, to protocols that identify children for investigation who are at the most risk of renal damage.

Current NICE guidelines recommend that different investigations are performed according to whether there is a good response to treatment within 48 h, whether there is evidence of atypical UTI (see 📖 'Definition of an atypical UTI', p.81) and whether there is evidence of recurrent UTI (2 or more upper UTI, 1 upper and 1 or more lower UTI or 3 or more lower UTI), as well as the age of the child. Tables 4.2, 4.3, and 4.4 summarize NICE recommended investigations according to severity of UTI and age.

Table 4.2 Investigations following UTI in infants under 6 months of age

	Good response within 48 h	Atypical UTI	Recurrent UTI
US at time of acute infection	No	Yes[b]	Yes
US within 6 weeks	Yes[a]	No	No
DMSA at 4–6 months	No	Yes	Yes
MCUG	No	Yes	Yes

[a]If abnormal consider MCUG once infection adequately treated.

[b]US at 6 weeks if non-*E. coli* UTI, but responding well.

Table 4.3 Investigations following UTI in children of 6 months to 3 years of age

	Good response within 48h	Atypical UTI	Recurrent UTI
US at time of acute infection	No	Yes[b]	No
US within 6 weeks	No	No	Yes
DMSA at 4–6 months	No	Yes	Yes
MCUG	No	No[a]	No[a]

[a]MCUG if dilatation on US, poor urine flow, non *E.coli* UTI, family history of VUR.

[b]US at 6 weeks if non *E.coli* UTI, but responding well.

Table 4.4 Investigations following UTI in children over 3 years of age

	Good response within 48 h	Atypical UTI	Recurrent UTI
US at time of acute infection	No	Yes[ab]	No
US within 6 weeks	No	No	Yes[a]
DMSA at 4–6 months	No	No	Yes
MCUG	No	No	No

[a]US with full bladder (measure pre- and post-micturition volume).

[b]US at 6 weeks if non-*E. coli* UTI, but responding well.

- The initial US will identify:
  - serious structural abnormalities and urinary obstruction;
  - bladder wall thickness and emptying;
  - renal defects, although most studies that have compared US with DMSA have shown US to miss a significant proportion of renal scars. Furthermore, it has to be remembered that there is a degree of operator variability with the use of US, and experienced full-time paediatric ultrasonographers are more likely to detect more minor changes than less experienced operators.
- The DMSA scan is considered the gold standard investigation for the diagnosis of renal parenchymal damage. It should be delayed until 4–6 months after the acute UTI in order to avoid a false positive result due to renal parenchymal inflammation that may resolve.
- The MCUG is considered the gold standard investigation for the diagnosis of urethral abnormalities and VUR.
- See 🕮 'Radiological investigations', p.12 for further details, including recommendations for the use of prophylactic antibiotics for the MCUG.

Long-term management

Medical measures for the prevention of urinary tract infection

- High fluid intake to produce a high urine output.
- Regular voiding.
- Complete bladder emptying using double micturition to empty any residual or refluxed urine returning to the bladder.
- Prevention or treatment of constipation.
- Good perineal hygiene.
- *Lactobacillus acidophilus*, to encourage colonization of the gut by this organism.

The use of antibiotic prophylaxis is a controversial area:

- A recent Australian study (PRIVENT) was the first to show that the use of antibiotics (co-trimoxazole) reduced the incidence of UTI compared with placebo (Hazard ratio 0.61) in children under 18 years with a prior history of UTI (42% had VUR). Earlier studies have shown conflicting findings and a Cochrane review of trials involving 2324 children showed that long-term antibiotic prophylaxis compared to no treatment

or placebo did not significantly reduce symptomatic UTI or febrile UTI at 2 years follow-up. However, at 1–3 year follow-up antibotic prophylaxis did reduce the relative risk of new or progressive damage on DMSA scan (RR 0.35, 95% CI 0.15–0.80).

- NICE guidelines do not recommend the routine use of prophylactic antibiotics in infants and children following a first UTI, although this may be considered in those with recurrent UTI, defined as:
  - two or more upper UTIs;
  - one upper UTI plus one or more lower UTI;
  - three or more lower UTIs.
- Commonly, prophylaxis is used in those under 2 years of age and those with ureters that are dilated up to the renal pelvis. Trimethoprim (2mg/kg at night) is used most often, but nitrofurantoin (1mg/kg at night) or nalidixic acid (7.5mg/kg bd) may be given. Broad spectrum, poorly-absorbed antibiotics, such as amoxicillin should be avoided.
- In children with a prior history of UTI, whether prophylactic antibiotics are used or not, there should be a high suspicion for UTI during acute illnesses. UTIs should be promptly identified and treated.

Follow-up

- NICE guidelines state that children who do not undergo radiological investigation following UTI do not require follow-up.
- Routine urine culture in well children is not necessary.
- There is no evidence for when antibiotic prophylaxis (if used) should be stopped. This should be considered at the age of 2 years (by when maximum renal growth has occurred) or after 1 year free of UTIs.
- Any child with a renal defect requires annual BP checks for life. Hypertension has been reported in up to 10%, but such a high incidence has been questioned.
- Regular assessment of renal function and growth using US, and early morning urine stick testing for proteinuria for those with bilateral renal defects, who are at risk of progressive CKD.
- No further imaging is necessary in a child with no or unilateral defects with no further infections.
- Circumcision may benefit boys with recurrent UTIs. It has been estimated that around 100 circumcisions are required to prevent one UTI.
- Anti-reflux surgery may be indicated if there is progression of scarring with ongoing VUR, but outcome has not been shown to be better than the use of antibiotic prophylaxis. More recently, open re-implantation of the ureters has been replaced by peri-ureteric injection of bulking agents (STING procedure). However, the success rate is less for this procedure than re-implantation of the ureters, and it often needs to be repeated.

If there are further symptomatic UTIs, investigations are required to determine whether there are new scars or continuing VUR. New scars are rare in previously unscarred kidneys after the age of 4, even in the presence of continuing VUR, and reinvestigation is rarely necessary in this group. A suggested schema for the follow-up of children with no further infections is shown in Fig. 4.1 and for those with further symptomatic UTIs in Fig. 4.2.

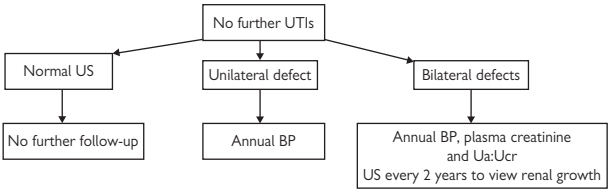

Fig. 4.1 Follow-up of children with no further UTIs.

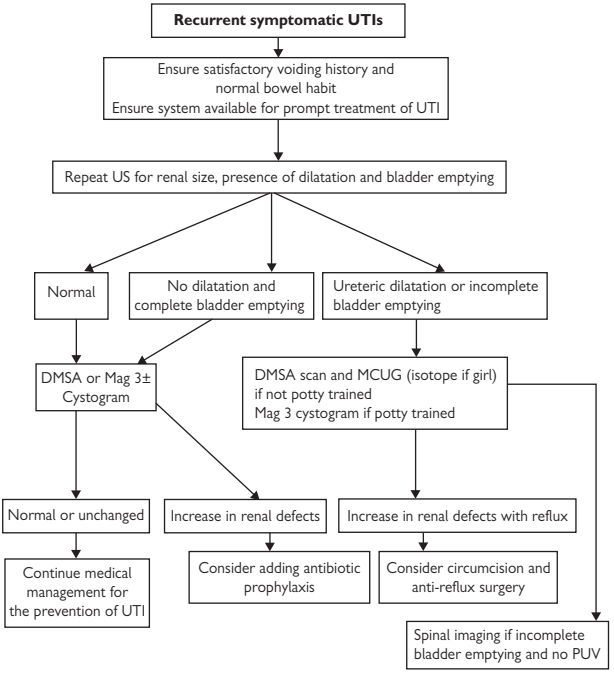

Fig. 4.2 Investigation and follow-up of children with recurrent symptomatic UTIs.

Asymptomatic bacteriuria

Occasionally bacteriuria may be discovered during investigation of another problem in an asymptomatic child. Although treatment with antibiotics will eradicate the bacteriuria, recurrence is common. Asymptomatic bacteriuria does not need treatment as long term follow-up studies have shown that it does not cause renal damage. However, this may not be the case for children with renal transplants (see 🕮 'Urinary tract infection post-transplantation', p.547).

Further reading

National Institute for Health and Clinical Excellence. (2007). *Urinary tract infection in children*. NICE Clinical Guideline 54. NICE, London.

Nagler EVT, Williams G, Hodson EM, Craig JC. Interventions for primary vesicoureteric reflux. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD001532. DOI: 10.1002/14651858.CD001532.pub4.

The penis and foreskin

Introduction

- The foreskin is almost invariably non-retractile in the neonate. It should never be forcibly retracted for cleaning or other reasons.
- The foreskin becomes retractile with increasing age (40% at 1 year, 90% at 4 years, and 99% at 15 years).

The penis should always be examined in boys with UTI because:

- Infection of the foreskin (balanitis) may be misdiagnosed as UTI as there may be white blood cells (WBCs) and bacteria in the urine.
- Obstruction to urine flow by the foreskin can cause UTI.

Inflammation and infection of the foreskin

- Minor inflammation of the foreskin is common and may be caused by soaps, bubble bath, detergents, and other factors.
  - most cases are self-limiting;
  - avoidance of precipitating factors, and the use of barrier or mild topical steroid ointments result in rapid resolution.
- More significant inflammation (balanitis) may be due to bacterial (*Streptococci, Staphylococci, Proteus*, and other Gram negative organisms) or yeast infection.
  - a course of oral antibiotic therapy (amoxicillin, co-amoxiclav) will result in rapid resolution in most cases;
  - topical antifungal therapy should be used where there is evidence of such infection (satellite lesions, etc.);
  - the inflamed foreskin will be painful and analgesia should be given;
  - boys may find that passing urine in the bath is more comfortable;
  - dysuria may lead to incomplete bladder emptying and the development of UTI.
- Where severe cellulitis is present, IV antibiotic therapy should be given and the patient considered for emergency circumcision.
- Elective circumcision should be considered in boys with recurrent severe balanitis.

Phimosis (non-retractile foreskin)

- Forced retraction of the non-retractile foreskin and recurrent balinitis result in the development of scar tissue in the distal foreskin rendering it non-retractile.
- Opening of the foreskin is narrowed with visible scar tissue. Causes ballooning of the foreskin during micturition and a thin urinary stream.
- Topical corticosteroids of increasing potency may resolve matters, although circumcision should be considered when these are unsuccessful.
- Rarely this can be so severe as to cause urinary obstruction.

Circumcision

- This is regularly performed in the neonate for religious reasons, most commonly by a non-medically qualified practitioner. The rate of non-religious routine circumcision varies between countries, the rate in the USA being significantly higher than in the UK.

- There is some evidence of medical benefits of circumcision:
  - incidence of UTI is as much as 10-fold lower in circumcised males;
  - rate of penile cancer (a very rare malignancy) is 3-fold lower in circumcised males;
  - risk of acquiring sexually-transmitted diseases may be reduced.
- These potential benefits are not, however, sufficient to justify the routine circumcision of all male infants, and professional organizations including the American Academy of Pediatrics have issued formal statements to this effect. It has been estimated that around 100 circumcisions are required to prevent one UTI and that of 100 boys circumcised to prevent one UTI, 0.2–5 would develop complications.

Religious circumcision is usually performed without analgesia.

- There is significant evidence that neonates circumcised without analgesia experience pain as indicated by changes in heart rate, BP, and oxygen saturation levels.
- Can be reduced by the use of topical anaesthetic agents, such as eutectic mixture of local anaesthetics (EMLA), regional anaesthesia (dorsal nerve block), or general anaesthesia.

Complications include bleeding, infection, and poor wound healing.

- Bleeding may be the first presentation of vitamin K deficiency, haemophilia, or other disorders of coagulation.
- Occasionally, severe acute problems occur including injury to the glans and urethral trauma.
- In the longer term, meatal stenosis may occur due to local trauma from rubbing on nappies and continuous exposure to urine.
- Injury can lead to incomplete bladder emptying (which can be seen on US scan) and UTIs.

Medical indications for circumcision include:

- *Recurrent UTIs:* circumcision may be considered when more conventional treatment modalities have been unsuccessful, particularly in those with major congenital abnormalities of the urinary tract.
- *Balinitis xerotica obliterans:* a primary non-infective aggressive inflammation of the foreskin, which results in hard fibrotic true phimosis.
- Severe acute or recurrent balanitis.
- *Paraphimosis*: caused by retracting a tight foreskin over the glans so that the ring of the foreskin meatus acts a partial tourniquet around the base of the glans, resulting in glanular oedema and swelling.

References

American Academy of Pediatrics (1999). Circumcision policy. *Pediatrics* **103:** 686–93.

Craig JC, Knight JF, Sureshkumar P, Mantz E, AND Roy LP. (1996). Effect of circumcision on incidence of urinary tract infection in pre-school boys. *J Pediatr* **128:** 23–7.

British Association of Paediatric Surgeons (2007). Consensus statement. Available at: http://www.baps.org.uk/documents/Circumcision_2007.

Vulvovaginitis

Introduction

- Vulvovaginitis is a common problem in pre-pubertal girls.
- Clinical features include soreness, itching, discharge, and bleeding, and urinary symptoms including dysuria and frequency.
- Clinical signs include inflammation of the labia and introitus, and visible discharge.
- May cause cystitis as a result of poor bladder emptying due to pain on voiding.

Causes

- *Poor perineal hygiene:*
  - poor wiping technique;
  - constipation with overflow soiling;
  - wetting.
- *Local irritation:*
  - bubble bath/detergents;
  - friction from wet/nylon underwear.
- *Infection (responsible for only around 20% of cases):*
  - bacterial (Group A β haemolytic *Streptococcus*, *Staphylococcus aureus*, *Haemophilus influenzae*);
  - viral;
  - fungal;
  - sexually transmitted (rare cause though requires consideration);
  - *Enterobius vermicularis* infestation (threadworms) with associated perianal itch.
- Deficient oestrogenization of prepubertal labia.
- *Primary dermatological disease:* lichen sclerosis, eczema.
- Foreign body.
- *Sexual abuse:* rare cause though requires consideration.

Investigation

- Mid-stream urine specimen (MSU).
- *Swab from introitus:* sellotape test to collect threadworm eggs—apply sellotape to perianal region and place on glass microscopy slide to visualize eggs; test is of high specificity, but low sensitivity.

General management

- Improve perineal hygiene.
- Simple symptomatic treatment:
  - front to back wiping;
  - avoid/treat constipation;
  - cotton underwear;
  - salt baths;
  - barrier creams e.g. Sudocrem®;
  - avoid bubble bath and other chemical irritants, use mild bath soap.
- Systemic antibiotics only if swab culture results positive.
- MSU may be falsely positive due to contamination.

- Consider empirical course of mebendazole (treat whole household).
- Some have advocated a trial of oestrogen cream (applied twice daily for 1 week) where bacterial cultures are negative.
- *Candida* infection is a relatively rare cause and empirical treatment is unlikely to be of help.
- Specific dermatological disorders require specialist advice.
- Where symptoms do not resolve or problem becomes recurrent, consider sexually-transmitted infection/sexual abuse, foreign body in vagina. Suspected sexual abuse problems require consultation with appropriately trained specialists.

Chapter 5

Enuresis

Nocturnal enuresis

Introduction

- Most children achieve night-time dryness by 5 years of age, when bladder volume exceeds nocturnal urine production.
- Nocturnal enuresis is defined as the involuntary loss of urine at night, in the absence of physical disease, at an age when the child could reasonably be expected to be dry (developmental age of 5 years by consensus):
  - primary nocturnal enuresis is the term used where the child has never been dry;
  - secondary or onset nocturnal enuresis is the term used where the child has previously been dry at night for 6 months or more after the age of 5 years;
  - monosymptomatic or uncomplicated nocturnal enuresis refers to nocturnal enuresis not associated with other symptoms referable to the urinary or GI tracts;
  - polysymptomatic or complicated noctural enuresis refers to bedwetting associated with symptoms suggestive of lower urinary tract dysfunction (see 📖 'Primary diurnal and secondary enuresis', p.96 and 📖 'Bladder pathology', p.97).
- Nocturnal enuresis is common, affecting 15–20% of 5-year-olds, 5% of 10-year-olds, and 1–2% of 15-year-olds.
- The problem is socially inconvenient to the child and their family, and may result in bullying and stigmatization, with resultant low self-esteem.

Aetiology

- Remains poorly understood despite the high prevalence.
- Delay in maturation of bladder control has been proposed. Children have smaller functional bladder capacity and unstable detrusor contraction.
- There is a strong genetic component: a family history is found in most children. The gene appears to be localized on chromosome 13.
- Studies of sleep patterns have shown variable results, although it appears that children who bed wet have difficulties in waking.
- Some studies have detected loss of the normal nocturnal rise in anti-diuretic hormone (ADH) production, resulting in an increase in nocturnal urine production.
- Upper airway obstruction and constipation may rarely produce wetting.

Assessment and investigation

- History of bed wetting, daytime symptoms, toileting patterns and fluid intake.
- Perform general physical examination, with particular attention to whether the bladder is palpable and the spine and lower limb neurology.
- Routine urinalysis and culture is not necessary unless the child has started bed wetting recently, has daytime symptoms or signs of ill health, and a history suggestive of urinary tract infection or diabetes mellitus.

- Investigate the child's attitudes and motivation.
- Children with primary nocturnal enuresis should *not* be subjected to radiological or urodynamic investigation.

Management

*Indicates evidence-based recommendation.

General

- Primary nocturnal enuresis has a high rate of spontaneous remission: it has been estimated that 10–15% of children will see a resolution of bed wetting each year with no treatment.
- Attempts to treat children under 7 years of age are often unsuccessful, although recent NICE guidelines recommend that younger children are not excluded from the management of enuresis on the basis of age alone.
- Specialist enuresis clinics generally provide the best service for patients. These are often run by specialist nursing staff and sited in local health centres in the community. Details of the location of such clinics are available from ERIC (see 📖 'Information for families', p.95).
- Management strategies are similar for both primary and monosymptomatic secondary nocturnal enuresis. In the child with secondary nocturnal enuresis an exploration of potential psychological or social problems (marital disharmony, bullying at school, etc.) is warranted.
- In general, where daytime wetting is also occurring, this should be investigated and treated prior to addressing nocturnal enuresis.

General measures

- Advise on fluid intake, diet, and toileting behaviour:
  - maintain adequate, but not excessive daytime fluid intake to develop bladder capacity and reduce evening fluid intake. NICE guidelines recommend daily fluid intakes (see Table 5.1);
  - avoid caffeine-based drinks;
  - healthy diet;
  - treatment and avoidance of constipation;
  - pass urine regularly during the daytime and before sleep.

Table 5.1 Daily recommended fluid intake

Age (years)	Total daily intake (mL)
4–8	1000–1400
9–13	1200–2100 girls
	1400–2300 boys
14–18	1400–2500 girls
	2100–3200 boys

Reward systems

This alone may be sufficient in the child who already has some dry nights.

- NICE guidelines recommend that rewards should be given for agreed behaviour (drinking recommended fluid intake, passing urine before sleep, etc.), rather than dry nights; however, *star charts for dry nights with or without night-time lifting or waking have been shown to reduce the number of wet nights and produce longer-term success after treatment.
- Neither lifting (carrying or walking child to the toilet without fully waking the child) or waking will promote long-term dryness.
- Waking should be used only as a practical measure in short-term management.
- Older children with enuresis unresponsive to treatment may find self-instigated waking (alarm clock) helpful.
- Where these measures alone are unsuccessful, there is a need to consider the use of an alarm system or drug treatment.

Alarm systems

- NICE guidelines recommend that alarm treatment be offered to children where bed wetting has not responded to advice on fluid intake, toileting, and an appropriate reward system, ***and*** alarm treatment is desirable and appropriate.
- *Cochrane review has shown alarm systems to be effective, with around 50% of children achieving long-term dryness.
- Immediate alarm systems appear to be more effective than delayed alarm systems.
- Alarm systems are superior to behavioural techniques* and drug therapy.*
- There may be problems with acceptability (embarrassment with system, other family members being woken, etc.).
- Many trials involving alarm systems had high drop-out rates.

Drug therapy

NICE guidelines recommend the use of drug treatment where rapid onset and/or short-term dryness is a priority and where alarm treatment is either undesirable or inappropriate.

*Desmopressin**

200–400 micrograms orally or 120–240 micrograms sublingually at bedtime:

- Superior to placebo (Cochrane review), though there appears to be a high relapse rate upon stopping treatment.
- Response to therapy should be assessed at regular intervals with dose increase where no response seen. Where successful, treatment should be withdrawn every 3 months to assess response.
- Useful agent for short-term use to allow children to attend sleep-overs, school trips, cub or brownie camps, etc. In this situation it is worth having a trial run at home prior to the trip to ascertain the dose required and to instill confidence in the child.
- May be used in conjunction with an alarm system.

- There are a small number of reports of hyponatraemic seizures in children; these appear to be associated with excessive water intake, which should be discouraged.
- The monitoring of weight, plasma electrolytes, blood pressure, and urine osmolality is not necessary.

Anticholinergic agents

Oxybutynin, etc.

- May be considered in combination with desmopressin in children with nocturnal enuresis unresponsive to desmopressin alone or in combination with an alarm system.
- May also be useful in those with both daytime symptoms and nocturnal enuresis.
- *Not* licenced for nocturnal enuresis.
- Should only be used under expert supervision.
- Should never be used in combination with a tricyclic agent.

Tricyclic agents[*]

Imipramine, amitriptyline, viloxazine, clomipramine and desipramine.

- NICE guidelines do not recommend the use of these agents as first-line treatment for nocturnal enuresis—use should be restricted to those who have not responded to alarm and/or desmopressin. Imipramine should be the tricyclic of first choice.
- Superior to placebo, with a reduction of around one wet night per week (Cochrane review).
- Similar to desmopressin, the effect is not sustained upon stopping treatment.
- These drugs have significant adverse-effects. In overdose they are cardiotoxic and hepatotoxic and at therapeutic doses produce anticholinergic adverse effects (dry mouth, postural hypotension, etc.). These adverse effects and the availability of desmopressin has resulted in a very significant fall in the use of these agents.
- If used, imipramine should be withdrawn gradually when stopping treatment.

Information for families

Education and Resources for Improving Childhood Continence (ERIC), http://www.eric.org.uk, telephone helpline (+44) (0)117 9603060 provides information and support for younger children, teenagers, parents, and professionals on nocturnal enuresis and daytime wetting.

Further reading

NICE (2010). *Nocturnal enuresis—the management of bedwetting in children and young people.* NICE Clinical Guidance 111. Available at: http://www.nice.org.uk/guidance/CG111.

Treating nocturnal enuresis in children. Effective Health Care. University of York Centre for Reviews and Dissemination, 2003 8 2.

Nocturnal enuresis. Best Practice Evidence Based Guideline. Paediatric Society of New Zealand. http://www.paediatrics.org.nz.

Paediatric Society of New Zealand (2005). *Nocturnal enuresis.* Best Practice Evidence Based Guidelines. Available at: http://www.paediatrics.org.nz.

Primary diurnal and secondary enuresis

Primary diurnal enuresis

May be due to:

- Delayed bladder maturity.
- Dysfunctional voiding (abnormal bladder habit, often accompanied by abnormal bowel habit).
- True bladder pathology (caused by bladder decompensation due to severe VUR, PUV, neuropathic bladder, non-neuropathic neuropathic bladder) (see 📖 'Bladder pathology', p.97).
- Polyuria (diabetes mellitus or insipidus, CKD) as a cause is rare.
- An ectopic ureter will cause a constant dribble of urine, the volume of which depends on the function of the parenchymal renal segment supplying the ureter. Pooling of urine in the vagina overnight may mean that the child is dry at night, but wets on rising in the morning.

Secondary enuresis

The new onset of incontinence (secondary enuresis) is uncommon and is a symptom to be taken seriously, particularly in a boy. Important points in the history would be:

- The frequency of urination and the volume passed, which may be frequent with polyuric causes; and with a neuropathic bladder may be infrequent, or frequent small volumes, or dribbling due to overflow.
- Urinary stream, which would be abnormal with a PUV, but can also be abnormal with other causes of bladder pathology.
- Bowel habit, abnormalities of which may be due to a neurological defect, but also constipation in itself can cause bladder outlet obstruction due to pressure from a loaded colon on the bladder in the pelvis.
- Circumcision, which can result in damage to the urethra during the procedure leading to urethral stenosis.
- The occurrence of UTIs.
- Accompanying symptoms that might suggest CKD.

Examination should include:

- Abdominal palpation to check for bladder enlargement.
- A check of the foreskin for phimosis and the urethral meatus if circumcised.
- Spine, anal tone, and lower limb neurology.
- BP and signs of CKD (growth, anaemia).

Bladder pathology

Bladder pathology is important to identify because:

- It may result in abnormally high pressures being transmitted to the collecting system and renal tubules.
- Poor bladder emptying predisposes to UTIs.
- If there is high pressure VUR of infected urine, the risk of renal damage is particularly high.
- In the polyuric child with poor bladder emptying, the bladder is particularly vulnerable overnight when it may become distended with urine, leading to poor upper tract drainage and potential renal damage.

Bladder pathology may be due to:

- *Severe VUR:* the bladder in severe cases (particularly male infants who often have associated renal dysplasia) may be refluxing as much urine back into dilated ureters as it expels via the urethra. Sometimes the ureters can be continuous with the bladder and act as part of the urine storage organ. The resultant strain on the bladder musculature can result in decompensation with poor emptying.
- *Absent abdominal musculature syndrome:* bladder is large and atonic.
- Urethral obstruction by PUV results in a thick-walled bladder; usually small volume with high pressures and diverticulae.
- Neuropathic bladder.
- Causes are:
  - spina bifida;
  - sacral agenesis;
  - spinal cord tumour or trauma;
  - transverse myelitis;
  - autonomic neuropathy.
- *Non-neuropathic neuropathic bladder (Hinman syndrome):*
  - the bladder behaves as if neurologically abnormal, but no such defect can be demonstrated;
  - the syndrome evolves over time due to damage to the bladder in association with infrequent or incomplete voiding, often also with abnormal bowel habit, although the cause is poorly understood;
  - high pressure within the bladder results in stretching and damage to the musculature and nerve supply. Spontaneous contractions of the bladder muscle (detrusor) do not co-ordinate with release of the urethral sphincter which takes place when voiding occurs. This causes 'blow outs' in the bladder wall (diverticulae) that cause pocketing of urine (predisposing to infection) and poor bladder drainage;
  - if CKD develops the high urine volumes further contribute to bladder dysfunction and damage;
  - a small subgroup of patients have been identified as having a genetic defect (Urofacial (Ochoa) syndrome) and have a peculiar facial expression, inverted smile, and partial facial palsy, as well as a non-neuropathic neuropathic bladder.

Investigations

- Spinal X-ray and magnetic resonance imaging (MRI) of spine.
- *Urodynamics;* the best simple test of bladder function is an ultrasound (US) taken after micturition. If the bladder empties completely bladder pathology is unlikely. Video urodynamics require bladder catheterization and a rectal pressure monitor. The purpose is to identify causes of renal damage and to inform best management.

Urodynamics

Give information about:

- *Bladder volume:* normal values up to 12 years = 30 × age in years + 50mL (see also Fig. 1.3).
- Urine flow rate.
- Intravesical pressure at rest, during filling, and when voiding.
- VUR.

Abnormal bladder function

Can be broadly divided into three types:

- High pressure contractions that do not co-ordinate with opening of the urethral sphincter, resulting in very high bladder pressures.
- Reduced bladder wall compliance so that there is a continuous increase in bladder pressure.
- Atonic, low pressure bladder with few contractions and overflow.

Management of bladder pathology

- Oxybutinin helps to decrease bladder contractions and, therefore, increases intravesical volume and decreases pressure, but at the expense of bladder emptying.
- *High pressure, small volume or non-compliant bladders:* bladder augmentation and clean intermittent catheterization (CIC) or catheterization through a continent channel (Mitrofanoff) may be necessary.
- The atonic, low pressure bladder with few contractions and overflow can be managed by CIC without augmentation.
- Bladder catheter left in overnight (avoids large volumes of urine accumulating in the bladder during sleep, which can be several litres in patients with polyuric CKD), with intermittent catheterization in the day, usually 2–4 times, depending on whether there is still an ability to void spontaneously and on the volumes of urine passed.

Chapter 6

Homeostasis

Disorders of sodium and water: basic principles

- Sodium (Na) and water homoeostasis are inextricably linked. Na concentration is measured in mmol/L, highlighting the fact that changes in numerator (Na), as well as denominator (water) will alter the concentration. It is impossible to assess a plasma Na measurement without considering plasma volume. Since Na constitutes the major extracellular ion, changes in plasma volume will result in the largest absolute change in Na concentration compared with the other plasma ions. For instance, when starting from a baseline of 140 mmol/L, a decrease in plasma water of 10% will lead to an increase in the plasma Na concentration to 154 mmol/L and vice versa a 10% increase to 126 mmol/L.
- The kidney has no sensors for Na concentration and regulates Na reabsorption purely in response to renal perfusion. Changes in plasma tonicity are sensed by osmoreceptors in the brain and affect renal water handling via antidiuretic hormone (vasopressin).
- In case of conflicting signals, the most important principle is preservation or restoration of a normal plasma volume, rather than a normal Na concentration. Thus, with normal functioning kidneys, urine Na is low in hypernatraemic dehydration and elevated in syndrome of inappropriate antidiuretic hormone (SIADH) or acute water intoxication. Whilst we easily measure Na concentration, there is no simple test for plasma water. Instead, we need to use auxiliary parameters, such as change in weight, BP and perfusion (capillary refill) to determine whether an abnormal Na concentration is the consequence of changes in Na or water.
- In clinical practice, the vast majority of abnormal Na concentrations are due to changes in water, rather than Na. The precise aetiology can be determined by interrogating the kidneys via urine indices (Na, creatinine, osmolality). An absolute urine Na concentration is a useful first guide, but it is much better to calculate a fractional excretion of Na (FENa). FENa = $(U_{Na}/U_{cr})/(P_{Na}/P_{crea})$ (all in mmol/L). Normally, FENa is <1% and in dehydration usually <0.3%.

Disorders of sodium and water: hypernatraemia

Definition

Plasma Na >145 mmol/L.

- Caused by either a deficiency of water (common) or an excess of salt (rare).
- A diagnostic algorithm for the assessment of hypernatraemia is given in Fig. 6.1a,b.

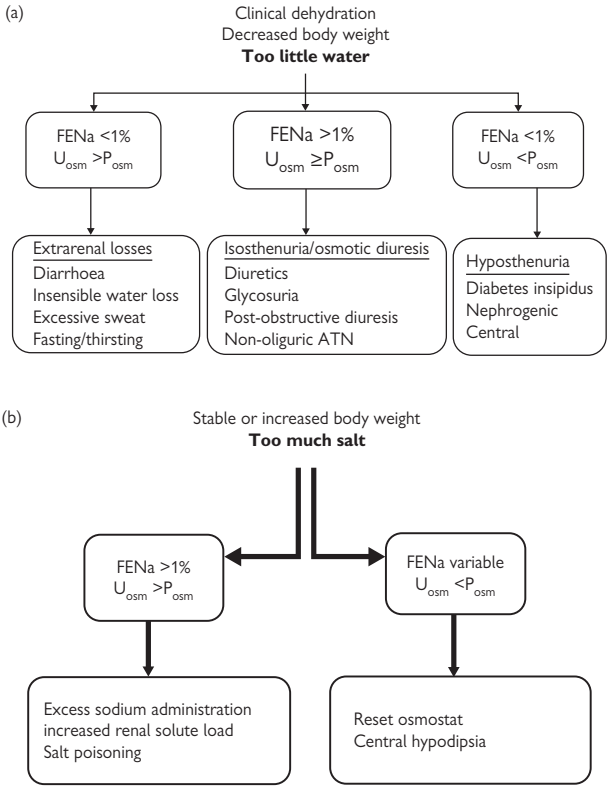

Fig. 6.1 (a) A diagnostic algorithm for hypernatraemia due to a deficiency of water. (b) A diagnostic algorithm for hypernatraemia due to an excess of salt.

The limit for FENa of 1% is not absolute. Neonates have higher FENa due to tubular immaturity. In general, the lower the FENa, the better tubular reabsorption.

Clinical signs and symptoms

- *CNS dysfunction:* lethargy, irritability, nuchal rigidity, seizures, drowsiness, coma. Intracranial haemorrhage (subdural, subarachnoid, intracerebral) may occur due to rapid shift of water from brain cells with associated cerebral vessel distention.
- *Hypernatraemic dehydration:* signs of extracellular fluid (ECF) depletion are masked (even if very dehydrated) because water moves from cells to the extracellular compartment.
- *Salt overload:* may be signs of volume overload, such as oedema, pulmonary venous congestion, and hepatomegaly. In cases of sudden salt ingestion (e.g. deliberate salt poisoning) there is rapid progression to coma often without signs of hypervolaemia, with mortality as high as 30–60%.

Investigations

Plasma and urine U&Es, creatinine, glucose, and osmolality. Always consider the possibility of a urinary concentrating defect (see 📖 'Disorders of renal water handling', p.155 as this alters management).

Management of hypernatraemic dehydration

The general principle is that alterations that have happened acutely can be corrected relatively quickly (24–48h), whereas chronic alterations should be treated slowly. This is because of the adaptive response of brain cells to hypernatraemia—with time they increase intracellular osmolarity, decreasing movement of water out of cells, and preventing intracellular dehydration, by intracellular production of osmotically active low molecular weight organic molecules. This is important because if hypernatraemia is rapidly corrected before the brain cells have had time to adjust back to a normal intracellular osmolarity, then fluid will pass into the cells and catastrophic cerebral oedema will develop. This is the reason that the successful management of hypernatraemia depends on a gradual lowering of the Na.

- Shock should be corrected by 0.9% saline solution 20mL/kg over 30 min and repeated if necessary.
- Never give hypotonic fluids as a bolus! It will lead to a rapid imbalance between extracellular and intracellular tonicity, and movement of water into cells, with the risk of fatal brain oedema and herniation. The plasma Na should be reduced by not more than 15 mmol/day.
- If IV fluids are used then 0.9% saline is usually a good initial starting point, but always consider the possibility of a renal concentrating defect. Check the urine osmolality—this should be well above plasma osmolality in hypernatraemic dehydration. The tonicity of the fluid given (not considering dextrose content) should not exceed the tonicity of the urine. Thus, if the urine osmolality is 150 mosm/kg (as in diabetes insipidus), then fluid given should be dextrose with either water or 0.18% saline.
- Normal hydration should be achieved over 36–48h and perhaps 72h if the initial plasma Na is >170 mmol/L. Fluid volume is calculated by considering maintenance requirement, plus deficit, plus ongoing losses.

Example: a 3-kg neonate with 20% dehydration aiming for correction over 48 h: maintenance: 300 mL/day = 600mL plus deficit of 600mL = 1200mL over 48h = 25mL/h. If there are ongoing losses (diarrhoea, vomiting) this needs to be added. The key is close monitoring of vital signs, weight, fluid balance and electrolytes (6-hourly initially) to adjust treatment if needed.

- In the case of a urinary concentrating defect, administered fluids (except for boluses) should have a Na concentration equal to or lower than that of urine, otherwise hypernatraemia will worsen.
- Oral rehydration therapy in diarrhoeal-induced hypernatraemic dehydration is safe in children who are not shocked, despite a faster fall in plasma Na.
- Persistent oliguria when circulatory impairment has been corrected indicates:
  - acute kidney injury (AKI), due to acute tubular necrosis;
  - possible renal venous thrombosis.

Management of hypernatraemia due to salt excess

- Will correct spontaneously if renal function is normal (salt is excreted by kidneys).
- Avoid too rapid a correction of plasma Na (risk of cerebral oedema- see 🕮 'Management of hypernatraemic dehydration', p.102).
- If AKI is present, dialysis may be indicated.

Disorders of sodium and water: hyponatraemia

Definition

Plasma Na <135 mmol/L. Due to:

- Gain of water in excess of Na (common).
- Loss of Na in excess of water (rare).

Definition of terms

- *Osmolal gap:* the difference between the calculated osmolality and the measured osmolality: (2 × [Na + K] + [urea] + [glucose]) – (measured osmolality).
- *Factitious hyponatraemia*: occurs as a result of a fluid shift between the intracellular fluid (ICF) and ECF compartments due to the presence of abnormal, relatively impermanent solutes in the ECF. Examples of such solutes are glucose in excess, mannitol, sorbitol, and maltose. In factitious hyponatraemia, the measured plasma osmolality is high despite the low plasma Na and, with the exception of hyperglycaemia, the osmolal gap will be greater than 10 mosm/kg.
- *Pseudohyponatraemia*: associated with a normal plasma osmolality and an increased osmolal gap may occur if there is a reduction in the fraction of plasma water. The plasma water fraction may fall below 80% in patients with marked hyperlipidaemia or hyperproteinaemia, and if the technique of flame photometry, which measures electrolyte concentration in whole plasma, is used, the plasma Na is artefactually reduced. Most laboratories now use ion-selective electrodes or other techniques that measure the plasma water electrolyte concentration directly; thus, in most cases, the problem should no longer arise.

A diagnostic algorithm for the assessment of hyponatraemia is given in Fig. 6.2.

Clinical features

- *Acute water intoxication:* low plasma osmolality will cause movement of water into cells. Most important consequences occur in the brain, as space to accommodate cell swelling is confined by the skull, causing nausea, emesis, headaches, disorientation, seizures, coma, death.
- *Chronic hyponatraemia:* adaptive mechanisms to equilibrate intra- and extracellular osmolality (mainly excretion of osmols from cells) have had time to take place; often patients are asymptomatic or have milder, non-specific symptoms, such as malaise, anorexia, and headaches.

Investigations

- Plasma and urine U&Es, glucose, albumin, and osmolality.
- Plasma liver function tests (LFTs), triglycerides.
- Consider adrenal and thyroid function tests.

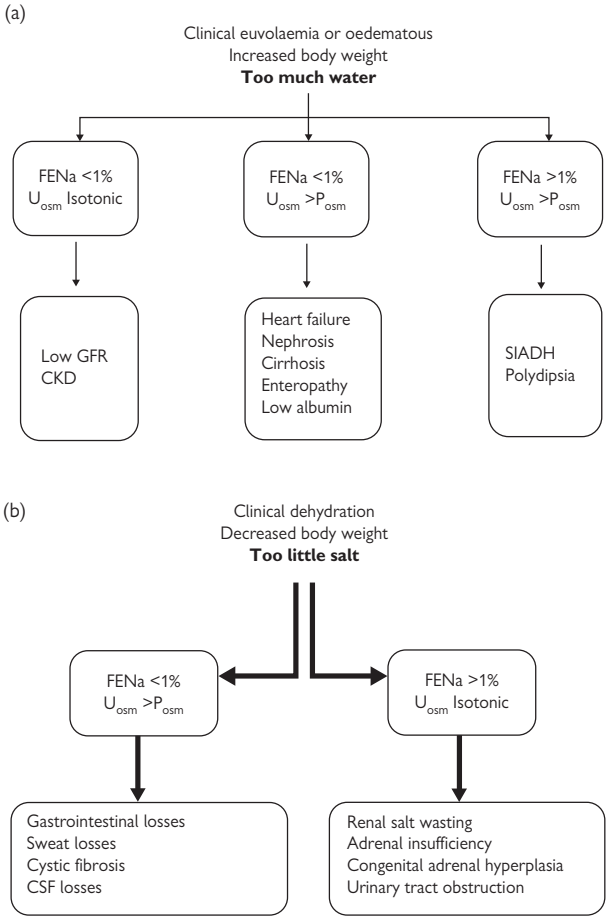

Fig. 6.2 (a) A diagnostic algorithm for hyponatraemia due to an excess of water. (b) A diagnostic algorithm for hyponatraemia due to a deficiency of salt.

The limit for FENa of 1% is not absolute. Neonates have higher FENa due to tubular immaturity. In general, the lower the FENa, the better tubular reabsorption.

Syndrome of inappropriate antidiuretic hormone

Diagnosis

- Decreased plasma osmolality (<280mosm/kg).
- Inappropriately high urine osmolality (higher than plasma).
- No evidence of volume depletion.
- Absence of other conditions that cause retention of free water, e.g. renal, hepatic or cardiac failure, or adrenal, pituitary, or thyroid dysfunction.
- Decrease in haematocrit, plasma albumin, urea, uric acid, and creatinine concentrations as a consequence of increased ECF volume are indicative of SIADH.

Note: As a consequence of the increased ECF volume from water retention in SIADH, the kidneys increase urinary Na excretion, leading to urine Na concentrations typically around 20–70mmol/L and even higher, if salt is supplemented. This often leads to confusion with salt wasting states. The latter have evidence of volume depletion.

Causes of SIADH

- Pain, stress.
- *CNS disease:* meningitis, head injury.
- *Lung disease:* pneumonia, tumours.
- *Drugs:* SIADH often occurs several days after certain drugs. Exogenous vasopressin, vincristine, nicotine, chlorpropamide, carbamazepine, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), thioridazine, cyclophosphamide, clofibrate, bromocriptine, haloperidol, thiothixene, monoamine oxidase inhibitors.
- *Inherited:* gain-of-function mutation in the vasopressin receptor AVPR2 (R137C or R137L). See 🕮 'Nephrogenic syndrome of inappropriate antidiuresis', p.159.

Emergency management

- The main concern of rapid correction of hyponatraemia is the development of pontine myelinolysis with permanent neurological sequelae. However, in an acutely symptomatic child (e.g. having seizures) with hyponatraemia, hypertonic saline is used to achieve a rapid increase in plasma Na to a level usually considered 'safe', which is 125mmol/L.
- A bolus of 2–3ml/kg of 3% saline can be given. The rate of administration should be slowed as soon as symptoms improve, so that the total increase in plasma Na does not exceed 10mmol/day. The bolus may need to be repeated if symptoms persist.

Non-emergency management

With water excess

- Restriction of water intake.
- Careful fluid balance, and monitoring of weight and electrolytes necessary, as water output must exceed water intake to achieve net water removal. This can be especially difficult in SIADH, when the urine is concentrated and thus urine volume low.

- Especially challenging in infants where nutrition is provided in liquid form. Formulas should be maximally concentrated to allow fluid restriction without starving the baby.
- Loop diuretics can be considered, as they impair the urinary concentrating mechanism and thus enhance water excretion. They can be especially helpful in hyponatraemia associated with nephrotic syndrome, and also in SIADH. The recently introduced vasopressin receptor antagonists (e.g. tolvaptan) may provide an alternative in the future.

With salt deficiency

Salt deficiency is usually associated with hypovolaemia. Replacement of the volume deficit and ongoing losses with normal saline is a reasonable first treatment. Again, close monitoring of the patient is necessary to avoid too rapid correction.

Disorders of potassium: basic principles

- More than 98% of body potassium (K) is intracellular, yet we measure extracellular K concentration. The plasma K level is therefore only a poor representation of total body K and levels can change because of a shift of K between compartments, as well as from changes in total K.
- In general, acute changes reflect shifts between compartments and chronic changes reflect total K. Since the ratio of extra- and intracellular K is the major determinant for the membrane potential of excitable cells, such as in heart or the neuromuscular system, acute changes in K can be life-threatening. A good indicator for the physiological relevance of a given K level is the height of the T wave in the electrocardiogram (ECG): hypokalaemia is associated with ST-depression, a flat T-wave and emergence of a U-wave, whereas hyperkalaemia leads to peaked T-waves. If these changes are not present, the K level is unlikely to represent an emergency.
- Distribution of K between the ICF and ECF is maintained primarily by the Na^+/K^++-ATPase. Compounds that enhance the activity of this pump, such as insulin or adrenergics can cause K alterations and be used for treatment of hyperkalaemia.
- K excretion in the kidney is determined in the collecting duct under the control of aldosterone. Excretion of K needs electrical balancing, typically by exchanging it for Na. Thus, a prerequisite for K excretion is sufficient distal delivery of Na, which is impaired in dehydration.

Disorders of potassium: hyperkalaemia

- *Pseudohyperkalaemia:* artefactually high plasma K caused by movement of K out of cells after blood taking. The commonest cause in paediatrics is a haemolysed blood sample (Fig. 6.3). Other causes include:
  - hereditary spherocytosis and familial pseudohyperkalaemia, caused by excessive tendency of K to leak from red cells as a result of cooling of blood *ex vivo*;
  - leaving the blood for a prolonged period prior to centrifugation and separation of the plasma from the cellular fraction will also cause pseudohyperkalaemia;
  - improper collection or handling of blood sample (e.g. K ethylenediaminetetra-acetic acid (EDTA) contamination);
  - any other cause of *in vitro* haemolysis, e.g. excessive shaking of blood bottle following collection;
  - leucocytosis or thrombocytosis.

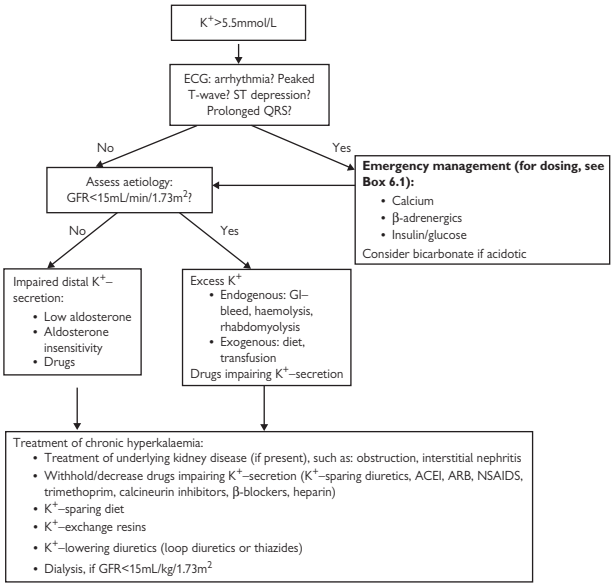

Fig. 6.3 An algorithm for hyperkalaemia.

Causes of true hyperkalaemia

Glomerular filtration rate <15mL/min/1.73m²

Patients with CKD 5 have an intrinsic risk of hyperkalaemia, but this can be compounded by the following:

- *Decreased renal excretion:* AKI, K-sparing diuretics, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDS), trimethoprim, heparin.
- *Increased K load:* Oral/IV supplementation, blood transfusion, endogenous cell breakdown (e.g. tumour lysis syndrome, GI-bleed, rhabdomyolysis, haemolysis, catabolic state).

GFR>15mL/min/1.73m²

The kidneys have a very high capacity to excrete K. Hyperkalaemia thus develops virtually only if other factors are present that impair distal K secretion. This can be estimated using the transtubular K gradient (TTKG):

$$\text{TTKG} = (\text{Urine K}/\text{urine osmolality})/(\text{Plasma K}/\text{plasma osmolality})$$

Normal values of TTKG in children are 4.1–10.5 (median 6.0); for infants the normal range is 4.9–15.5 (median 7.8). A decrease in TTKG suggests aldosterone deficiency or insensitivity. An increase in TTKG suggests dietary excess of K or high aldosterone activity.

Example You are asked to give advice regarding a 10-day-old female neonate on the intensive care unit with the following investigation results. Specifically, you have been asked whether the results may be caused by adrenocortical insufficiency (e.g. congenital adrenal hyperplasia). Na 132mmol/L, K 8.9mmol/L (non-haemolysed), urea 2mmol/L, creatinine 23µmol/L. You request urinary electrolytes, and paired (blood and urine) osmolarity: urine K 10mmol/L, urine osmolarity 151mmol/L, plasma osmolarity 311mosm/L. This gives a TTKG of 2.3. This value would be compatible with aldosterone (mineralocorticoid) deficiency or insensitivity. The differential diagnosis would thus include congenital adrenal hyperplasia or hypoplasia, hypoaldosteronism, or pseudohypoaldosteronism or insufficient distal Na delivery.

Causes for impaired potassium secretion

- Volume depletion/impaired distal Na delivery.
- Obstructive uropathy.
- Interstitial nephritis.
- Drugs, e.g. ciclosporin, tacrolimus, NSAIDs, ACEI, ARB, trimethoprim, K-sparing diuretics.
- Congenital adrenal hyperplasia.
- Primary hypoaldosteronism.
- Pseudohypoaldosteronism type 1 and 2.
- Sickle cell disease.
- Diabetes mellitus.

Rarely, hyperkalaemia is due to redistribution:

- Metabolic/respiratory acidosis.
- Hyperkalaemic periodic paralysis.

- Insulin deficiency (diabetic ketoacidosis: may be hyperkalaemic, but total body K depleted).
- Drugs/toxins.

Clinical features

- Muscle weakness.
- Cardiac arrhythmia.
- Hyperkalaemic renal tubular acidosis.

ECG changes

See Fig. 6.4.

- Peaked T waves ('tenting').
- Loss of P wave.
- Widened QRS.
- ST depression.
- Bradycardia, heart block, ventricular arrhythmia, cardiac arrest (K >10mmol/L).
- See Box 6.1 for emergency treatment.

Box 6.1 Emergency treatment

See also Chapter 17. Seek cause and treat appropriately. The following is a guide:

- Place on cardiac monitor
- Salbutamol nebulizer 2.5–5mg: repeat three times—can be given continuously, *or*
- Salbutamol IV 4 micrograms/kg in 5mL water given over 10–20min
- *Correct acidosis:* Na bicarbonate 1–2mmol/kg IV over 30 min
- *Calcium Resonium*® 1g/kg (to a maximum 60g), then 0.25–1g/kg qds po/pr. If given orally, should give with lactulose 5–10 mL qds
- Ca gluconate 10%: 0.5 mL/kg IV over 10 minutes (note- this does not lower K, but protects the myocardium against arrhythmias)
- Glucose 0.5–1g/kg and insulin 0.1–0.2U/kg as a bolus, or continuous infusion of 10% glucose at 5mL/kg/h (0.5g/kg/h) with insulin 0.1U/kg/h. Monitor glucose at least hourly
- Consider HyperK cocktail (see Table 6.1)
- Dialysis.

Table 6.1 Some constituents of a HyperK cocktail

Constituents	Amount
30% Glucose	500mL
Regular insulin	30U
10% Ca gluconate	30mL
Sodium acetate	100mmol

Infuse at 2mL/kg/h, preferably by central line for the first hour, then 1–2mL/kg/h.

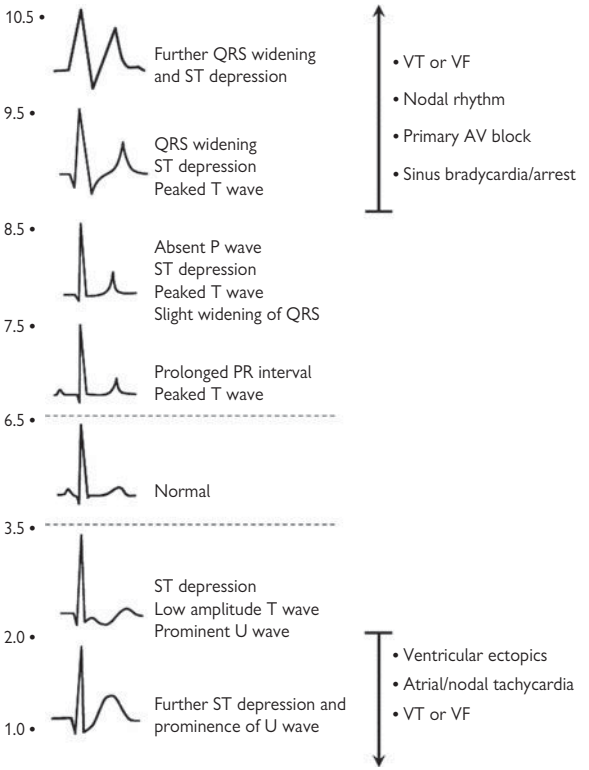

Fig. 6.4 Typical ECG patterns seen with plasma levels of K from 1.0–10.5 mmol/L (indicated on the left).

Disorders of potassium: hypokalaemia

- Hypokalaemia, unless of acute onset, is rarely a clinical emergency.
- Caused by either a shift of K into the ICF or by total body K depletion.

Clinical features

- Muscle weakness, paralysis.
- *Smooth muscle involvement:* intestinal ileus, ureteric dilatation.
- *Cardiac:* myocardial cell necrosis, arrhythmia, and ECG changes (Fig. 6.5).
- Rhabdomyolysis and myoglobinuria.
- Lethargy, confusion, tetany.
- *Autonomic insufficiency:* postural hypotension.
- Renal consequences:
  - *decreased concentrating capacity:* polyuria, polydipsia;
  - increased renal ammonia production;
  - increased proton secretion in distal tubule (to allow Na reabsorption) => maintenance of metabolic alkalosis.

ECG changes

See Fig. 6.4.

- Prolonged QT and QU interval.
- Increased U wave amplitude.
- Prolonged QRS.
- ST depression.
- Decreased T wave amplitude.
- Increased P wave amplitude.
- Increased PR interval.

Investigations

- Careful dietary and fluid intake history, and document extra losses, e.g. diarrhoea or vomiting.
- Careful drug history (diuretics/laxatives/chemotherapy/amphotericin).
- Measure BP (hypertension and hypokalaemia—think about Conn's, Liddle's, and Cushing's syndromes).

Laboratory and radiological investigations guided by clinical suspicion:

- *Plasma chemistry:* look for evidence of tubulopathy (acidosis or alkalosis, dehydration, hypophosphataemia, hypocalcaemia, hypomagnesaemia).
- Blood gas.
- *Urine chemistry:* consider Na, K, Ca, Mg, creatinine, osmolality, pH, and excessive urinary losses of K.
- Plasma glucose and urine glucose/ketones.
- Plasma renin activity, aldosterone.
- Plasma cortisol; (24-h) urine corticosteroid profile.
- Renal US (nephrocalcinosis).
- X-ray knee or wrist for associated rickets.

Assessment (Fig. 6.5)

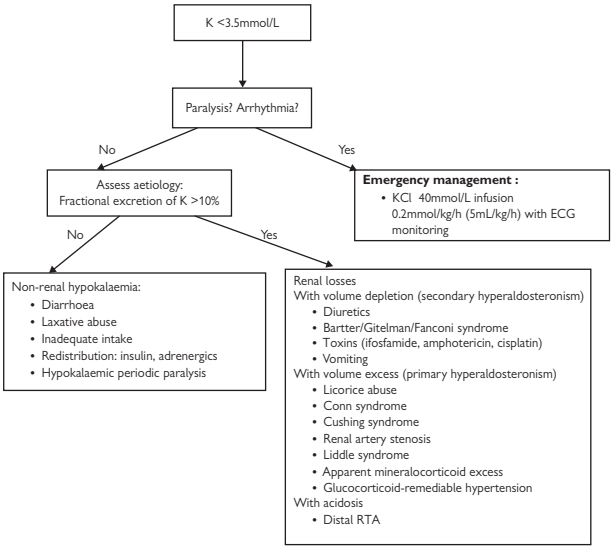

Fig. 6.5 An algorithm for the assessment of hypokalaemia.

Treatment

- *Emergency treatment:* very rarely there is an urgent need to correct severe hypokalaemia (e.g. arrhythmia or paralysis). In most other cases, rapid infusion of K^+ is likely to cause more harm than good. **Excess administration can be fatal!** IV bolus administration should therefore be happening with ECG monitoring, ideally in the intensive care setting. According to British National Formulary for Children (BNF-C), KCl should be diluted to 40mmol/L and given at a rate not exceeding 0.2mmol/kg/h (5mL/kg/h). Some authors set higher limits—0.5mmol/kg in 20mL of 5% glucose over 30min with a concentration not exceeding 80mmol/L. However, the higher the concentration and dose, the more likely even a small error in calculation or infusion speed can be fatal!
- Oral supplementation with K^+ usually suffices. Dose is dependent on cause (see 📖 'Disorders of renal salt handling: proximal tubule', p.144, on renal Fanconi syndrome and tubulopathies). In children with salt-wasting tubulopathies, such as Bartter and Gitelman syndrome, normokalaemia is rarely achieved and excessively high doses of oral supplementation may cause vomiting or diarrhoea and thus worsen the hypokalaemia starting a vicious circle of increasing supplementation, worsening GI-symptoms and lower plasma K^+. A plasma K^+ of 2.5mmol/L or higher is usually acceptable.
- Replacing K^+ in children with renal failure should be carefully considered since hyperkalaemia can easily occur.

Disorders of calcium: basic principles

- Calcium (Ca) is the most abundant mineral in the body with >98% stored in bone.
- Plasma Ca is tightly regulated with a normal range of 2.1–2.6mmol/L. However, normal ranges vary with age and infants typically have higher Ca levels than older children (see 📖 Chapter 18, p.409).
- Approximately 40% of plasma Ca is protein-bound (mainly albumin) and 10% complexed to anions, such as bicarbonate and phosphate. The remaining 50% represents the biologically active ionized or free Ca. Thus, total Ca levels vary with those of the binding partners and the following formula is commonly used to 'correct' total Ca levels for albumin levels:

$$\text{Corrected Ca (mmol/L)} = \text{Measured total Ca (mmol/L)} + 0.02\ (40 - \text{albumin (g/L)})$$

- Each mmol/L Ca is equivalent to 2.5mg/dL.
- Measurement of ionized Ca is a better indicator of physiologically active Ca, but can be acutely altered by technique, such as the use of a tourniquet, which may cause intracellular Ca release and acidosis. The proportion of free Ca varies with pH, as protons compete with Ca for albumin binding sites: thus, alkalosis decreases and acidosis increases free Ca.
- Functions of Ca include:
  - stabilization of cell membranes;
  - intra- and intercellular signalling, e.g. muscle contraction;
  - neurotransmitter release, hormone secretion (PTH);
  - co-factor in enzymatic processes, especially clotting;
  - stabilization of skeletal and dental structure.
- Key organs involved in Ca homoeostasis are:
  - *gut (absorption):* active (transcellular) and passive (paracellular) transport. Active transport is regulated by Vitamin D;
  - *bone (storage):* Ca can be stored in (stimulated by Vitamin D) or released from (stimulated by PTH) bone;
  - *kidney (excretion):* about 65% of filtered Ca is passively reabsorbed in the proximal tubule and another 25% in the thick ascending limb of Henle's loop (see 📖 'Disorders of renal salt handling: basic principles', p.140). The remaining 10% is actively (transcellularly) reabsorbed in the distal convoluted tubule under control of PTH;
  - filtered vitamin D (bound to vitamin D-binding protein) is reabsorbed and 1-α hydroxylated in the proximal tubule;
  - *parathyroid glands (regulation):* the parathyroid glands produce the key regulatory hormone PTH, secretion of which is controlled by direct feedback from Ca levels (via the Ca-sensing receptor), phosphate, and vitamin D (via vitamin D receptor) (see Chapter 18).

Disorders of calcium: hypercalcaemia

Definition

Total Ca (corrected)>2.6mmol/L, ionized Ca >1.3mmol/L. Severe, if total Ca (corrected)>3.0mmol/L, ionized Ca >1.5mmol/L.

Causes

- Hyperparathyroidism (primary, tertiary, not secondary).
- *Inherited loss of function of the Ca sensing receptor (CaSR):* loss of function of one allele (dominant inheritance) causes familial hypocalciuric hypercalcaemia. Hypercalcaemia in this disorder is usually asymptomatic and thus requires no treatment. In contrast, loss of function in both alleles (recessive inheritance) cause neonatal severe hyperparathyroidism, which results in rickets, extraosseous calcifications, and neurodevelopmental delay. Treatment is early parathyroidectomy.
- Idiopathic infantile hypercalcaemia.
- CKD (see Chapter 18):
  - Ca-containing phosphate binders;
  - activated vitamin D supplementation;
  - adynamic bone disease;
  - after transplantation when tertiary hyperparathyroidism present.
- Malignancy associated hypercalcaemia:
  - synthesis of PTH-related peptides by the tumour;
  - calcitriol producing lymphoma.
- Vitamin D intoxication.
- *Extrarenal 1-alpha-hydroxylase activity:* TB, sarcoidosis, lymphoma, cat-scratch fever, and other granulomatous diseases (phosphate usually normal).
- Leprosy.
- Milk-alkali syndrome.
- Vitamin A toxicity.
- *Immobilization:* particularly after fracture.
- After BMT for osteopetrosis (transplanted osteoclasts remove excess bone).
- Subcutaneous fat necrosis.
- *Other endocrine causes:* hyperthyroidism and hypothyroidism, phaeochromocytoma, adrenal insufficiency, islet cell pancreas tumour, VIPoma.
- *Drugs:* aminophylline, oestrogen, thiazide diuretics, prostaglandin E infusion.
- *Syndromic:*
  - William's syndrome (see 🕮 'William's syndrome', p.343);
  - Jansen's syndrome (autosomal dominant—neonates with hypercalcaemia, rickets, metaphyseal dysplasia, low PTH);
  - *hypophosphatasia:* alkaline phosphatase low or absent, hypercalcaemia, hypercalciuria, rickets.

Clinical features

Often asymptomatic, depending on severity and rapidity of onset.

- 'Stones' renal calculi; 'Bones' bone pain; 'Moans' depression; 'Groans' (abdominal) due to constipation.
- Failure to thrive.
- Nephrocalcinosis/lithiasis.
- Decreased GFR.
- Short corrected QT-interval (QTc), arrhythmias.
- Hyporeflexia.
- Polyuria (nephrogenic diabetes insipidus).
- Venous thromboses.
- Metastatic calcification.

Investigation

Investigations to be considered in all cases

- U&Es, creatinine, Ca (total) and phosphate, and venous bicarbonate.
- Liver function tests including albumin and alkaline phosphatase.
- Ionized Ca.
- PTH.
- Daytime spot Uca:Ucr.
- US kidneys for nephrocalcinosis.

Investigations to be considered in select cases

- *Vitamin D levels:* these are expensive and results are often delayed. May be omitted if clear history of vitamin D intoxication.
- *Blood gas:* pH, pCO_2, pO_2, bicarbonate, base excess.
- Thyroid function tests.
- US of parathyroid glands.
- FBC and blood film/bone marrow aspirate and trephine/lymph node biopsy if suspected malignancy.
- Computed tomography (CT) or magnetic resonance imaging (MRI) of abdomen and chest.
- Mantoux test and/or quantiferon test (or similar gamma interferon release assay for *Mycobacterium tuberculosis*).
- Serum ACE.
- C7q FISH for William's syndrome.
- X-ray knee and wrist for rickets.
- X-ray skeletal survey (occult fracture or syndromic skeletal dysplasia, e.g. Jansen's syndrome).
- ECG.
- Serology for cat scratch fever.
- *Endocrine tests:* urine vanillylmandelic acid (VMA)/ homovanillic acid (HVA); plasma and urine adrenaline and noradrenaline; other (e.g VIPOMA- seek expert advice).
- Genetic test for hypocalciuric hypercalcaemia.

Assessment

See Fig. 6.6.

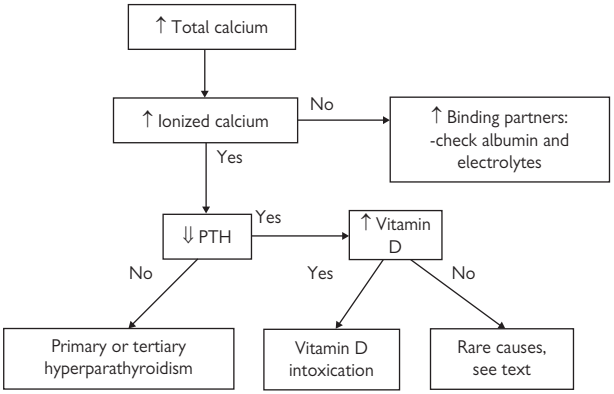

Fig. 6.6 An algorithm for the assessment of hypercalcaemia.

Treatment

In asymptomatic cases, identification and removal of the underlying cause is usually sufficient, e.g. stopping Vitamin D supplementation. In acute symptomatic cases the following can be used:

Hyperhydration (e.g. 3 l/m^2/24h IV 0.9% saline): Ca reabsorption in the proximal tubule passively follows Na reabsorption. As volume expansion diminishes proximal Na reabsorption, urinary Ca excretion will be increased.

In severe hypercalcaemia that does not respond, there is the occasional need for:

- *Loop diuretic* (furosemide 1 mg/kg/IV): 6–8-hourly (may need to replace K and Mg) to minimize Ca reabsorption in Henle's loop.
- *Corticosteroid:* occasionally for chronic hypercalcaemia e.g. in sarcoid.
- *Calcitonin infusion* (salcatonin, derived from salmon): 5–10U/kg IV followed by 4U/kg IV or SC 12–24-hourly.
- *Dialysis:* if concomitant oliguric renal failure.
- *Bisphosphonate* (e.g. pamidronate infusion): usually for hypercalcaemia of malignancy (especially if bone pain) or immobilization:
  - the dose of pamidronate is 1mg/kg/day to a maximum of 60mg, usually on three successive days;
  - dilute pamidronate initially in water, but infuse in saline or 5% glucose;
  - final concentration should not exceed 12mg/100mL of diluent;
  - give infusion over 4h on first occasion; thereafter, pamidronate can be given over 2–4h.

Disorders of calcium: hypocalcaemia

Definition

Total Ca (corrected) <2.1mmol/L, ionized Ca <1.2mmol/L. Severe hypocalcaemia, if total Ca (corrected)<1.75mmol/L, ionized Ca <0.8mmol/L.

Causes

Neonatal

- Birth trauma, perinatal asphyxia.
- Prematurity.
- Respiratory distress syndrome.
- Infants of diabetic mothers.
- *Iatrogenic:* Na bicarbonate therapy; exchange transfusion; increased free fatty acids (intralipid).
- Congenital hypomagnesaemia with secondary hypocalcaemia.
- Transient neonatal hypoparathyroidism:
  - after operation or in severe infection;
  - maternal hyperparathyroidism;
  - maternal osteomalacia;
  - high phosphate intake (cow's milk formula);
  - persistent idiopathic hypoparathyroidism;
  - Di George syndrome;
  - intestinal malabsorption.

Older children

- Lack of PTH effect (hypoparathyroidism, pseudohypoparathyroidism).
- *Vitamin D deficiency:*
  - nutritional rickets, malabsorption syndrome, chronic liver disease, anticonvulsants;
  - renal rickets; AKI;
  - vitamin D dependent rickets/resistant rickets;
  - nephrotic syndrome (increased loss of Vitamin D with binding protein).
- Osteoblastic metastases.
- *Hypomagnesaemia:* magnesium (Mg) is required co-factor for PTH release from parathyroid gland.
- Hypercalciuria: usually compensated by increased Ca absorption in the gut, but will compound nutritional Ca/vitamin D deficiency.
- Hyperphosphataemia.
- Tumour lysis syndrome.
- Rhabdomyolysis.
- Acute pancreatitis.
- *Hungry bones syndrome:* healing of bones when there is an increased requirement for Ca.
- Activating mutations of the Ca sensing receptor (autosomal dominant hypoparathyroidism).

- Drug-induced: phosphate enemas/infusion, laxatives, calcitonin, colchicine, citrate, Ca-free albumin, furosemide, aminoglycosides.
- Alkalosis.
- Massive blood transfusion.
- Acute leukaemia.

Clinical features

- *Neuromuscular:*
  - paraesthesia and tetany;
  - seizures;
  - myopathy;
  - psychosis;
  - dementia;
  - depression;
  - laryngospasm (hypocalcaemic stridor);
  - extrapyramidal disorders;
  - Chvostek sign (twitching of the facial muscles in response to gentle tapping over the facial nerve anterior to the earlobe);
  - Trousseau sign: carpal spasm following inflation of sphygmomanometer over upper arm above systolic BP.
- Skin and ectoderm:
  - dry skin and eczema;
  - hair loss, brittle nails, candidiasis;
  - lenticular cataracts;
  - tooth enamel hypoplasia.
- Hypotension, prolonged QT, heart block, ventricular arrhythmias, congestive cardiac failure (chronic hypocalcaemia).

Assessment

See Fig. 6.7.

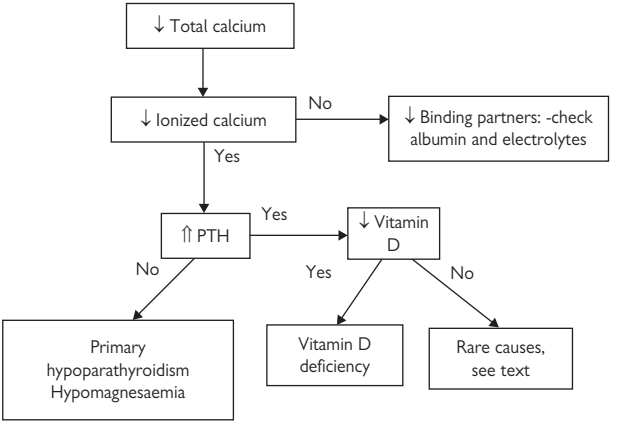

Fig. 6.7 Assessment of hypocalcaemia.

Treatment

Acute symptomatic hypocalcaemia

- 0.3mL/kg 10% Ca gluconate IV over 10–30min (monitor heart rate for bradycardia); can repeat until normal. Ensure good vascular access as extravasation causes severe skin injury.
- Correct hypomagnesaemia if present. 0.2mL/kg of 50% Mg sulphate IV over 30 min; repeat as necessary.
- Consider ongoing replacement therapy after the acute episode, e.g. maintenance infusion of 10% Ca gluconate (0.2–1mmol/kg/day) or oral Ca supplements (50–75mg/kg/day of elemental Ca in four doses).

Chronic hypocalcaemia

- In patients with CKD (see Chapter 18).
- 1,25-dihydroxycholecalciferol (calcitriol) and l-α-hydroxycholecalciferol (alfacalcidol) are used to treat chronic hypocalcaemia resulting from hypoparathyroidism and pseudohypoparathyroidism. Aim to maintain the plasma Ca concentration in the low normal range and monitor Uca:Ucr (risk of hypercalciuria and nephrocalcinosis; see 🕮 'Renal calculi', p.174 stones for normal ranges).
- *Calcitriol:* started at the initial oral dose of 15ng/kg (maximum dose 1.5microgram/day) usually in a split twice daily dose.
- *Alfacalcidol:* initial starting dose of 10–25ng/kg/once daily (maximum dose usually 2microgram/day). Alfacalcidol is usually administered as a single daily dose.

Disorders of magnesium: basic principles

- Mg is the second most abundant cation in the body, localized mainly in bone and intracellular compartments. Less than 1% is present in the ECF, of which about 30% is protein-bound (mainly albumin) and 10% is complexed to other anions (e.g. bicarbonate, phosphate). The rest is in the biologically active, ionized form. Total Mg levels can be corrected for hypoalbuminaemia with the following formula:
  Corrected Mg(mmol/L) = total Mg (mmol/L) + 0.005*(40-albumin(g/L))
- 1mmol/L of Mg is equivalent to 2.5 mg/dL.
- Functions of Mg include:
  - co-factor in many biological processes, including DNA synthesis and translation, provision of cellular fuel in the form of nucleotide triphosphates and metabolism of glucose, fatty acids, and protein;
  - stabilization of cell membrane;
  - intra- and intercellular signalling.
- Necessary co-factor for stimulation of CaSR.
- Magnesium is transported in gut and kidney using both passive (paracellular) and active (transcellular) pathways. A common component of the transcellular pathway in both gut and kidney is TRPM6 (see also 🕮 'Disorders of renal magnesium handling', p.160).

Disorders of magnesium: hypermagnesaemia

The kidneys can increase fractional Mg excretion to almost 100%, thus hypermagnesaemia is exceedingly rare without concomitant renal failure.

Definition

Plasma Mg >1.0mmol/L.

Causes

- *Impaired renal excretion:* CKD; lithium.
- *Increased Mg uptake:* Mg infusions, use of Mg-containing antacids or laxatives.
- *Intracellular release:* cell necrosis.
- *Impaired regulation:* the CaSR is also important in the regulation of Mg and loss-of-function as in familial hypocalciuric hypercalcaemia (see 📖 'Disorders of calcium: hypercalcaemia', p.116) is also associated with hypermagnesaemia.
- *Other:* hypothyroidism, Addison's disease.

Clinical features

Clinical symptoms are usually only seen if the plasma Mg exceeds 2.0mmol/L. These can include:

- Lethargy, drowsiness, nausea, flushing, loss of deep tendon reflexes.
- Ileus, urinary retention.
- ECG changes (prolongation of PR and QT, widening of QRS) and arrhythmia.
- Coma, paralysis, apnoea if levels >5.0mmol/L.

Investigations

- *History:* use of Mg-containing medications.
- U&Es and creatinine to assess kidney function.
- Urine Mg and creatinine to assess fractional excretion of Mg (expect >5% as appropriate renal response).

Disorders of magnesium: hypomagnesaemia

Definition

Plasma Mg <0.7 mmol/L.

Causes

Increased renal excretion

- *Inherited disorders:* see 📖 'Disorders of renal magnesium handling', p.160.
- *Acquired:*
  - *tubular damage:* ATN, tubulointerstitial nephritis, postobstuctive;
  - *drugs:* thiazides, tacrolimus, ciclosporin, loop diuretics, aminoglycosides, amphotericin, cisplatin, foscarnet, pentamidine.

Decreased intestinal absorption

- Inherited disorders: familial hypomagnesaemia with secondary hypocalcaemia (see 📖 'Disorders of renal magnesium handling', p.160); primary intestinal hypomagnesaemia (Paunier disease).
- Malabsorption syndrome.
- Short bowel syndrome.
- Ileostomy.
- Coeliac disease.
- Inflammatory bowel disease.
- Prolonged diarrhoea and laxative use.

Decreased intake

- Prolonged vomiting or nasogastric suction.
- Malnutrition.
- Parenteral nutrition.

Endocrine causes

- Hypoparathyroidism.
- Hyperthyroidism.
- Infant of diabetic mother.
- Hyperaldosteronism.

Miscellaneous

- Hungry bone syndrome. Hypomagnesaemia can occur as a part of the 'hungry bone' syndrome in which there is increased uptake of Mg (and Ca) into bones as a result of bone healing, e.g. following parathyroidectomy or treatment of rickets with Vitamin D.
- Hypercalcaemia.
- Phosphate depletion.
- Volume expansion (mild hypomagnesaemia).
- Intrauterine growth retardation (first 3–5 days of life).

Clinical features

Hypomagnesaemia is usually asymptomatic, unless plasma levels are severely depressed (<0.5mmol/L):

- Weakness, tremors and tetany seizures.
- Positive Chvostek and Trousseau signs.
- ECG changes, ventricular arrhythmias (Torsade De Pointes).
- Hypokalaemia (likely because of common aetiology).
- *Hypocalcaemia:* Mg is required co-factor for PTH release.

Investigations

- History (drugs, kidney disease, family history).
- U&Es with urine Mg, Ca, creatinine. In the presence of hypomagnesaemia a fractional excretion of Mg (FEMg) >4% is consistent with renal Mg wasting. However, with severely decreased plasma levels and thus decreased filtered load of Mg, the FEMg may well be below 4%. In those cases, normalization of plasma levels with IV infusion of Mg may be necessary to establish aetiology.

Treatment

- *Acute symptomatic hypomagnesaemia:* 0.1–0.2mmol/kg of 10% Mg sulphate (i.e. 0.25–0.5mL/kg) IV over 30min; repeat as necessary. Consider ongoing replacement.
- *Chronic asymptomatic hypomagnesaemia:* oral Mg (e.g. Mg glycerophosphate) 0.2mmol/kg/day three times daily In renal Mg wasting, it is usually impossible to achieve normal plasma levels and excessive oral supplementation may cause diarrhea, and thus worsen hypomagnesaemia. Levels above 0.5mmol/kg are usually acceptable. In patients with impaired intestinal absorption, intermittent IV supplementation may need to be considered.

Disorders of phosphate: basic principles

- Each mmol/L of phosphate is equivalent to 3.097mg/dL.
- Phosphate is the most abundant anion in the body, mostly stored in bones and teeth.
- Less than 0.1% of total body phosphate is in plasma, where we measure it.
- Phosphate levels vary with age and are highest in the neonate (see 🕮 Chapter 18, p.409).
- Functions of phosphate include:
  - energy storage (ATP);
  - component of lipids (phospholipids) and nucleic acids;
  - signalling (protein phosphorylation);
  - acid-base buffering.
- Key organs involved in phosphate homoeostasis are:
  - *gut (absorption), mostly duodenum and jejunum:* active (transcellular) and passive (paracellular) transport. Active transport is regulated by Vitamin D, similar to Ca;
  - *Bone (storage):* phosphate can be stored in (stimulated by vitamin D) or released from bone (stimulated by PTH), similar to Ca;
  - *Kidney (excretion):* under normal circumstances, more than 80% of filtered phosphate is actively reabsorbed in the proximal tubule by Na/phosphate co-transporters (NaPi) under control of PTH;
  - Parathyroid glands (regulation): The parathyroid glands produce the key regulatory hormone PTH, which mobilizes Ca-phosphate from bone and enhances renal phosphate excretion.
- A key regulatory factor for phosphate excretion is fibroblast growth factor (FGF23). Other important factors, such as PHEX and Klotho likely work through FGF23 (see 🕮 Chapter 18, p.409).

Disorders of phosphate: hyperphosphataemia

Definition

Plasma phosphate level above the age-appropriate upper limit of normal (2.1mmol/L in infants, decreasing to 1.4mmol/L in adults (see 📖 Chapter 18, p.409).

Causes

Decreased renal excretion

- *Renal impairment:* as renal excretion of phosphate can be highly upregulated, hyperphosphataemia most commonly occurs with a decreased GFR.
- Hypoparathyroidism.
- Pseudohypoparathyroidism.
- Nephrotic syndrome.

Intracellular release

- Tumour lysis, rhabdomyolysis.
- Acidosis.

Increased absorption Phosphate enemas.

Endocrine causes

- Thyrotoxicosis.
- Acromegaly.
- Glucocorticoid deficiency.

Artefactual *In vitro* haemolysis.

Clinical features

- No specific symptoms, unless accompanying hypocalcaemia.
- Chronic hyperphosphataemia may induce ectopic calcifications, including in blood vessels.

Investigations

- *Plasma:* U&Es and creatinine, including Ca, albumin, alkaline phosphatase (ALP), PTH.
- Lactate dehydrogenase (LDH), uric acid, CK in suspected rhabdomyolisis or tumour lysis.
- *Urine:* phosphate and creatinine to calculate tubular reabsorption of phosphate (TRP) = (1 – (urine phosphate/urine creatinine) × (plasma creatinine/plasma phosphate)) × 100. TRP is expected to be <70% as evidence for appropriately increased renal excretion.

Management

- In CKD: see Chapter 18.
- *In acute tumour/rhabdomyolysis:* saline infusion can enhance renal phosphate excretion with an intact GFR. With a decreased GFR consider haemodialysis.

Disorders of phosphate: hypophosphataemia

Definition

Plasma phosphate level below the age-appropriate lower limit of normal (1.2mmol/L in infants, decreasing to 0.8mmol/L in adults).

Causes

Increased renal excretion

- Hyperparathyroidism.
- Vitamin D deficiency.
- *Renal tubular dysfunction:* Fanconi syndrome, TIN.
- *Increased phosphaturic factors:* hypophosphataemic rickets, post-renal transplantation, tumour-related.

Increased intracellular uptake

- Refeeding syndrome (insulin release with feeding of malnourished patients results in intracellular uptake of glucose and phosphate).
- Treatment of diabetic ketoacidosis.
- Alkalosis.

Decreased absorption

- Vitamin D deficiency.
- Malabsorption.
- Phosphate-binding antacids.

Endocrine causes

Glucocorticoid excess.

Clinical features

- No specific symptoms acutely, although severe hypophosphataemia (<0.5mmol/L) may be associated with signs of decreased energy (ATP) availability, including weakness, lethargy, paraesthesia.
- Long-standing hypophosphataemia will result in rickets.

Investigations

- *Plasma:* U&Es and creatinine, including Ca, albumin, ALP, PTH.
- *Urine:*
  - *phosphate and creatinine to calculate tubular reabsorption of phosphate (TRP):* 1-(urine phosphate/urine creatinine)/(plasma phosphate/plasma creatinine). TRP is expected to be >80% as evidence for appropriately increased renal excretion;
  - *Note:* with severely decreased plasma phosphate and/or GFR, the filtered load may be so low that TRP is within the reference range;
  - *A better way is to calculate the threshold for maximum phosphate reabsorption TMP/GFR:* plasma phosphate – ((urine phosphate/urine creatinine) × plasma creatinine).
- Skeletal X-ray in case of suspected rickets.

Management

Depends on the underlying cause:

- Ensure sufficient phosphate supplementation in cases of increased intracellular uptake.
- Normalize PTH by vitamin D supplementation in cases of rickets.
- With a fixed renal leak (e.g. hypophosphataemic rickets) persistent normalization of plasma phosphate is virtually impossible and phosphate supplementation is limited by side-effects such as diarrhoea. Treatment should aim to minimize the associated rickets by Vitamin D supplementation.

Disorders of acid-base balance: basic principles

The pH of plasma is tightly calibrated around 7.4 to enable optimal function of most enzymes in our body. This occurs mainly through regulation of bicarbonate (HCO_3^-) and CO_2 concentrations, which are related via the following equations:

Equation 1: $H_2O + CO_2 \Leftrightarrow H_2CO_3 \Leftrightarrow HCO_3^- + H^+$

Equation 2 (Henderson-Hasselbalch): $pH = pKa + \log (HCO_3^-/CO_2)$

CO_2 is regulated by the lungs and bicarbonate by the kidneys (directly via reabsorption and indirectly via excretion of H^+). Therefore, we separate respiratory (ventilation of CO_2) from metabolic disorders (excretion of bicarbonate and H^+), but the two processes can occur simultaneously (mixed acid-base disorders). The individual contributions can be assessed by plotting pH, CO_2 and bicarbonate on a nomogram (see Fig. 6.8).

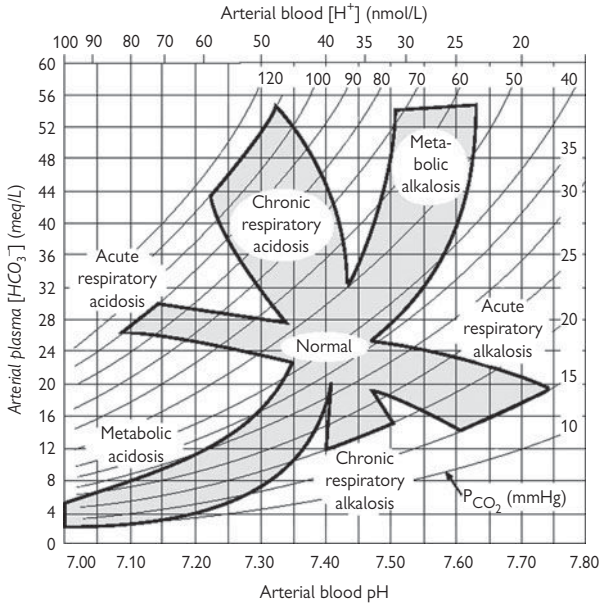

Fig. 6.8 A nomogram for the assessment of mixed acid-base disorders.

Reproduced with permission from Cogan MG (ed.) (1991). *Fluid and Electrolytes: Physiology and Pathophysiology*. Appleton & Lange, Stamford. © The McGraw-Hill Companies, Inc.

- Bicarbonate concentration on a blood gas analysis is calculated, not measured. For most accurate assessment, bicarbonate concentration is best measured in plasma.
- Steady state pH homeostasis is maintained in the kidney by excreting acid in the urine equivalent to the acid load.
- Acid load consists mainly of sulphur-containing amino acids in the diet (methionine, cystine), which are metabolized to sulphuric acid. Animal proteins contain a higher amount of sulphur amino acids compared with plant proteins. Conversely, plant protein contains a higher amount of basic amino acids (lysine, arginine), thus vegetarians have a lower acid load than the average Western diet high in animal protein.

Disorders of acid-base balance: acidosis

Definition

A disorder leading to increased acidity. Because of buffering ability plasma pH can remain normal and the acidosis manifests only in a decreased plasma bicarbonate concentration. A fall of plasma pH below 7.35 is referred to as acidaemia.

- The anion gap (AG) is a useful tool to assess whether a metabolic acidosis is due to loss of bicarbonate (most common) or accumulation of acid. It is calculated by subtracting the 2 main plasma anions from the main cation:

$$\text{Equation3: } AG = [Na^+] - \{[Cl^-] + [HCO_3^-]\}$$

- A normal value for the anion gap is between 8 and 12. This represents the unmeasured anions, which consist mostly of proteins, such as albumin, which have an excess of negative charges. Thus, in hypoproteinaemic states, such as nephrotic syndrome, the usual normal values for anion gap are decreased (anion gap decreases roughly by 2.5 for each 10g/L of serum albumin below 40 g/L).
  - *normal anion gap acidosis (bicarbonate loss):* bicarbonate is lost in either the gastrointestinal (GI) tract (e.g. diarrhoea) or the urine together with a cation, mostly Na, to maintain electroneutrality. Because of this concurrent loss of Na and bicarbonate, the anion gap is unchanged;
  - *increased anion gap acidosis:* excess accumulation of acid (e.g. lactic acid or ketones) leads to a decrease in bicarbonate (to buffer the acid) without changing Na or CL^- concentration, therefore increasing the AG.

Causes of AG acidosis are often memorized with the mnemonic MUDPILES:

- M = metabolic disease, metformin;
- U = uraemia;
- D = diabetic ketoacidosis;
- P = paraldehyde, propylene glycol, phenformin;
- I = isoniazid, iron;
- L = lactic acidosis;
- E = ethanol, ethylene glycol;
- S = starvation, salicylates.

- Common and misleading cause of low plasma bicarbonate is exposure of blood sample to air, for instance when it is obtained by fingerprick.

Example CO_2 diffuses immediately into the air, shifting the equilibrium described in equation 1 to the left, leading to a decrease in both bicarbonate and H^+ concentration. Thus, if both a blood gas and bicarbonate are determined, this falsely low bicarbonate concentration is recognized by the simultaneous presence of elevated pH (low H^+ concentration). However, if only bicarbonate was determined in the context of an electrolyte panel, a low bicarbonate concentration with increased anion gap (Na and Cl^- concentrations are unaffected by CO_2 diffusion) in the absence of an obvious cause (MUDPILES), should raise suspicion of this artefact.

- It is important, that blood samples for pH and bicarbonate are analysed promptly, as they otherwise decrease due to ongoing metabolic activity of the blood cells.
- Similar problems occur in the assessment of urine pH, as exposure of the sample to air will artificially increase urine pH, so it is best determined by dipstix immediately after obtaining the sample. Ideally, urine is collected under oil, which in clinical practice is difficult, especially from non-toilet trained children. Samples obtained by urine bag or cotton balls in the nappy are unreliable for pH determination.

Diagnosis

A diagnostic algorithm for the assessment of a metabolic acidosis is shown in Fig. 6.9, based on the key diagnostic information provided by history, and plasma and urine biochemistry

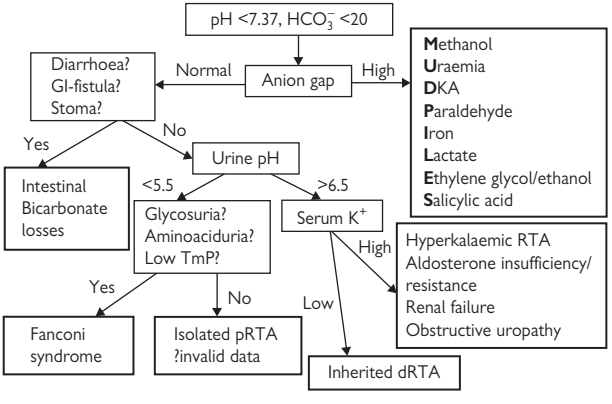

Fig. 6.9 A diagnostic algorithm for the diagnosis of renal tubular acidosis.

Treatment

- Diagnose and treat underlying cause (e.g. give oxygen, correct shock with volume replacement, treat sepsis) and avoid lactate-containing replacement fluids.
- Role of acute alkali replacement is controversial—potential harmful effects include:
  - worsening of intracellular acidosis despite improvement of extracellular acidosis due to diffusion of CO_2 into cells (bicarbonate administration shifts the equilibrium in equation 1 to the left with increased formation of CO_2, which is membrane permeable);
  - volume overload;
  - hypernatraemia;
  - hypercapnia (especially in patients with respiratory insufficiency).

- In acidosis due to chronic bicarbonate loss (e.g. CKD, renal Fanconi syndrome, chronic diarrhoea, GI-stoma), bicarbonate obviously needs to be replaced (see also 📖 'Distal renal tubular acidosis', p.135).
- In cases of severe intractable acidosis, dialysis, or haemofiltration may be indicated.

Clinical features

- Failure to thrive, vomiting, anorexia, and variable degrees of muscle weakness are common to all renal tubular acidosis.
- Since bone is a major buffer of acid, chronic metabolic acidosis (from any cause) can have a major impact on the developing skeleton, and poor growth is an important consequence of acidosis. Correction of the acidosis is thus important to restore growth.
- Buffering of acid by the bone leaches Ca from the bone, which needs to be excreted by the kidney with consequent nephrocalcinosis and possibly stones.
- Signs of Fanconi syndrome (polyuria, polydipsia, dehydration, rickets, glycosuria, hypophosphataemia, aminoaciduria) in proximal RTA.
- Some forms of distal RTA are associated with sensorineural deafness.

Renal tubular acidosis

Historically, RTA has been classified into four subtypes, numbered according to the chronological sequence of the descriptions:

- Classical (hypokalaemic) distal RTA.
- Proximal RTA.
- Mixed proximal distal RTA.
- Hyperkalaemic RTA.

For practical purposes, we will only separate proximal from distal RTA, as the mixed form is extremely rare and easily recognizable due to its association with osteopetrosis (see Table 6.2); hyperkalaemic RTA is primarily a disorder of distal salt reabsorption with secondary acidosis.

Table 6.2 Recognized genetic causes of primary renal tubular acidosis

Gene	Function	Inheritance	Type	Extrarenal manifestation
SLC4A4 (NBC1)	Basolateral Na-bicarbonate cotransporter	AR	Proximal	Eye and teeth abnormalities, short stature, developmental delay
CA2	Carbonic anhydrase	AR	Mixed	Osteopetrosis
SLC4A1 (AE1)	Basolateral Cl-bicarbonate exchanger	AD or AR	Distal	Red cell disorder (in some)
ATP6V1B1	Apical proton pump subunit	AR	Distal	Sensorineural deafness (infantile onset)
ATP6V0A4	Apical proton pump subunit	AR	Distal	Sensorineural deafness (in some)

Proximal renal tubular acidosis

Proximal RTA (pRTA) is caused by an impaired ability to reabsorb bicarbonate in the proximal tubule, resulting in urinary bicarbonate wasting. Isolated proximal bicarbonate wasting is extremely rare (see Table 6.2). Instead, pRTA occurs in the context of generalized proximal tubular dysfunction, also called renal Fanconi syndrome, characterized by glycosuria, phosphaturia, amino aciduria, organic aciduria and low-molecular weight proteinuria. The consequent biochemical abnormalities (see also Table 6.2 and Fig. 6.9) establish the diagnosis of pRTA. Because distal urinary acidification is intact, urinary pH can be below 5.5.

Distal renal tubular acidosis

This form of RTA is caused by an impaired ability to secrete protons in the collecting duct. As can be seen in Fig. 6.10, Na (and thus volume), K, and acid-base homoeostasis are linked together: Na is reabsorbed in the collecting duct in exchange for either protons or K to maintain electroneutrality. Thus, with proton secretion impaired in distal RTA (dRTA), more K needs to be secreted to allow a similar amount of Na reabsorption, resulting in hypokalaemia. In dRTA, urine pH is always above 5.5, because of the impaired distal acidification.

dRTA may develop as a secondary complication of other diseases.

- Disorders affecting salt reabsorption in the collecting duct (see Chapter 7). Because salt reabsorption through the epithelial Na channel ENaC (see Fig. 6.10) provides the favourable electrical gradient for proton and K secretion, impairment of this pathway results in hyperkalaemic acidosis (type 4RTA).
- CKD (see Chapter 18).
- Autoimmune diseases.
- Toxins/drugs involving the distal tubule and collecting duct.

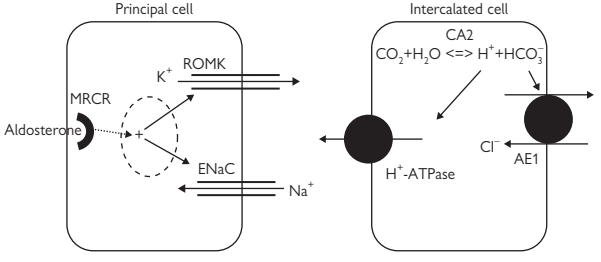

Fig. 6.10 The molecular basis of distal RTA. Shown are a principal and intercalated cell.

Salt reabsorption via the epithelial Na channel ENaC in the principal cell creates a favourable electrical gradient for proton secretion from the intercalated cell via the H-ATPase. Protons are generated by the action of the carbonic anhydrase 2 (CA2) and the remaining bicarbonate re-enters the blood stream via the basolateral anion exchanger AE1.

Genetics of renal tubular acidosis

For pRTA see also 📖 'Disorders of renal salt handling: proximal tubule', p.144.

Treatment of dRTA

Despite the often severe symptoms at presentation, the acidosis of dRTA is easily treatable:

- Correction of the acidosis allows normal growth and development and prevents worsening of the nephrocalcinosis, but does not correct extrarenal manifestations, such as deafness.
- Treatment consists of administration of alkali, equal in amount to the acid load (usually l–3mmol/kg/day), such as bicarbonate or citrate, ideally as a mixed K/Na salt (e.g. polycitra or tricitrate). This allows supplementation of both alkali and K.
- Citrate may also alleviate the nephrocalcinosis.
- 1mmol of citrate is converted in the liver to 2mmol of bicarbonate, thus half the amount of citrate is necessary for correction of alkalosis compared with bicarbonate.
- Patients with dRTA need to have regular clinical and biochemical monitoring for adjustment of their supplementation. In the beginning, more frequent visits are necessary; once established, longer intervals (every 6 months) are usually sufficient.
- Plasma pH and bicarbonate can vary quickly, e.g. depending on the time of the last dosage.
- In contrast, urinary Ca, as a reflection of acid-buffering by the bone, is a good long-term indicator of acidosis control.

Disorders of acid-base balance: alkalosis

Definition

- A primary elevation of plasma bicarbonate (>28mmol/L) with rise in arterial pH (>7.40).
- *Note:* normal range for bicarbonate is lower in infants.

Causes

As seen in Fig. 6.10, Na reabsorption in the collecting duct (under the control of aldosterone) is molecularly linked with K and acid-base homoeostasis. To maintain electroneutrality, Na is reabsorbed in exchange for K or protons. Thus, with enhanced distal Na reabsorption there will be increased K and proton secretion, resulting in a hypokalaemic metabolic alkalosis, the classical electrolyte pattern seen with aldosterone activation.

There are many potential causes for enhanced distal Na reabsorption:

- *With volume contraction:*
  - GI losses, including laxative use and congenital Cl^- losing diarrhoea;
  - loop diuretics and thiazides;
  - Bartter and Gitelman syndrome;
  - cystic fibrosis due to excess of chloride loss in the sweat.
- *With excess volume:*
  - renal artery stenosis;
  - mineralocorticoid excess (e.g. Conn syndrome);
  - pseudo-mineralocorticoid excess (liquorice, Liddle syndrome, 11-beta-hydroxysteroid dehydrogenase deficiency; high dose glucocorticoids).
- Acid loss (usually from the stomach—if losses of fluid are not replaced, alkalosis will be further compounded by aldosterone activation):
  - vomiting, e.g. pyloric stenosis;
  - gastric suction.
- Excess alkali administration.

This page intentionally left blank

Chapter 7

Tubular disease

Disorders of renal salt handling: basic principles

- The adult kidneys filter on average 150 L of plasma per day containing 22.5mol of sodium (Na), the equivalent of roughly 1.25 kg of salt (NaCl). Since Na constitutes the major ion in extracellular fluid (ECF), Na homoeostasis determines volume homoeostasis and all recognized causes of BP dysregulation affect renal Na handling.
- Thus, disorders in Na handling affect blood pressure (BP): Na loosing disorders lead to lowered BP and, conversely, disorders of increased Na reabsorption to increased BP.
- The kidneys have no sensor for Na concentration. This is regulated by osmoreceptors in the brain via anti-diuretic hormone (ADH) and renal water handling. Thus, disorders of renal salt handling typically have normal plasma Na concentration.
- Usually, more than 99% of filtered Na is reabsorbed, so that the final excretion is <1% and equivalent to salt intake (1–10 g, depending on diet). Approximately 80% of salt reabsorption occurs in the proximal tubule, ~10–15% in the thick ascending limb of Henle's loop (TAL), ~5–10% in the distal convoluted tubule (DCT) and the remaining ~5% in the collecting duct (see Fig. 7.1). The driving force is created by the basolateral Na^+/K^+-ATPase, present in all cells, which generates a favourable electrochemical gradient for Na entry into the cell. This gradient also enables co-transport of other substances (such as glucose, amino acids, phosphate (P)) into the cell or counter-transport (such as Na–hydrogen (H) exchange).
- Since Na is the main determinant of intravascular volume, fractional excretion of Na is normal in almost all renal salt wasting disorders (<1%). This is due to activation of compensatory mechanisms, such as up-regulation of the renin-angiotensin axis (hyperaldosteronism), which enhances distal Na reabsorption in exchange for K and protons. However, if this compensatory mechanism is impaired, as in pseudohypoaldosteronism type 1, fractional excretion of Na is elevated and the disorder is life-threatening because of volume depletion.
- An overview of clinical and molecular features of inherited disorders of renal salt handling is given in Table 7.1.

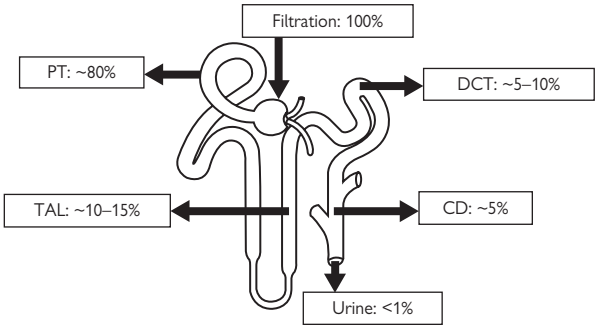

Fig. 7.1 Na reabsoprtion along the nephron.

PT: proximal tubule; TAL: thick ascending limb of Henle's loop; DCT: distal convoluted tubule; CD: collecting duct.

Table 7.1 Clinical and molecular characteristics of renal salt handling disorders

	Locus	Gene	Mode	Protein	renin	aldo	K^+	Cl^-	HCO_3^-	Other features/comments
Fanconi	*	*	*	*	⇑	⇑	⇓	⇑	⇓	*
Type I Bartter	15q15–21	SLC12A1	AR	NKCC2 co-transporter (furosemide-sensitive)	⇑	⇑	⇓	⇓	⇑	Nephrocalcinosis, often pre- or neonatal onset
Type II Bartter	11q24–25	KCNJ1	AR	K channel ROMK	⇑	⇑	⇓	⇓	⇑	Nephrocalcinosis, often pre- or neonatal onset
Type III Bartter	1p36	CLCNKB	AR	Cl channel ClCKNB	⇑	⇑	⇓	⇓	⇑	Often hypomagnesaemia Mostly childhood onset
Type IV Bartter	1p31	BSND	AR	Barttin	⇑	⇑	⇓	⇓	⇑	Often hypomagnesaemia deafness. Usually neonatal onset
Gitelman	16q13	SLC12A3	AR	NCC (thiazide-sensitive)	⇑	⇑	⇓	⇓	⇑	Hypomagnesaemia, hypocalciuria Mostly childhood onset
EAST/SeSAME	1q23	KCNJ10	AR	KCNJ10/Kir4.1	⇑	⇑	⇓	⇓	⇑	Epilepsy, ataxia, sensorineural deafness, tubulopathy with hypomagnesaemia, hypocalciuria
CAH type I	6p21	CYP21A2 CYP21 CYP21B	AR	Subunits of 21-hydroxylase	⇑	⇓	⇑	⇑	⇓	Virilization

CAH type II	1p13	HSD3B2	AR	3-β-hydroxysteroid dehydrogenase	⇑	⇓	⇑	⇑	⇓	Hypospadias, male pseudohermaphroditism
PHA1	12p13	SCNN1A	AR	EnaC sodium channel subunits A,B,G	⇑	⇓	⇑	⇑	⇓	Symptoms are severe in recessive form, milder in dominant form
	16p13	SCNN1B	AR							
	16p13	SCNN1G	AR	Mineralocorticoid receptor						
	4q31	NR3C2	AD							
PHA2	12p13	WNK1	AD	WNK-kinases	⇓	⇑	⇑	⇑	⇓	
	17q21	WNK4	AD							
Liddle	16p13	SCNN1B	AD	EnaC sodium channel subunits B,G	⇓	⇓	⇓	⇓	⇑	
	16p13	SCNN1G	AD							
AME	16q22	HSD11B2	AR	11-β-hydroxysteroid dehydrogenase	⇓	⇓	⇓	⇓	⇑	Intrauterine growth retardation
GRA	8q21	CYP11B1	AD	11-β-hydroxylases	⇓	⇑	⇓	⇓	⇑	
		CYP11B2								
CAH type IV	8q21	CYP11B1	AR	11-β-hydroxylase	⇓	⇓	⇓	⇓	⇑	Virilization
CAH type V	10q24	CYP17A1	AR	17-alpha-hydroxylase	⇓	⇓	⇓	⇓	⇑	Ambiguous genitalia

Listed are disorders of tubular salt handling. The upper 10 rows (white) list disorders of salt wasting (hypovolaemia/low blood pressure), whereas the lower 6 rows (shaded) list disorders of salt retention (hypervolaemia/hypertension). aldo:aldosterone. AR: autosomal recessive, AD: autosomal dominant
(* for details of disorders in the proximal tubule see 📖 'Disorders of renal salt handling: proximal tubule', p.144).

Disorders of renal salt handling: proximal tubule

- Renal Fanconi syndrome is a collective term used for dysfunction of the proximal tubule, of which there are many causes, both congenital and acquired.
- Substances reabsorbed by the proximal tubule include: water, Na, K, Ca, P, bicarbonate (proximal renal tubular acidosis (RTA) in children is almost always associated with a renal Fanconi syndrome), urate, glucose, amino acids, and low molecular weight proteins.
- In classical renal Fanconi syndrome all of these substances are wasted, while in some disorders, such as Lowe Syndrome and Dent Disease only selective proximal reabsorption pathways are affected. Causes of renal Fanconi syndrome are listed in Table 7.2.

Presentation

- Presentation in the first year of life is usually with non-specific symptoms, such as irritability, poor feeding, vomiting, and failure to thrive as the classical symptoms of polydipsia and polyuria can be difficult to detect at this age.
- Polydipsia and polyuria are the classical symptoms. However, most children with histories of 'always being thirsty' do not have a tubular disorder—on the whole this is a behavioural phenotype of young children. It is useful to ask whether the child would still drink excessively if only water is offered, and in the older child, whether they wake at night for a drink.
- The selective proximal tubular dysfunction seen in Dent disease usually does not result in failure-to-thrive and polyuria. Therefore, presentation is typically in later child- or adulthood with rickets and/or stones.
- Clinical signs of rickets.
- Poor growth.
- Constipation due to dehydration.
- Nephrocalcinosis/stones (especially Dent disease).
- Extrarenal manifestations, such as cataracts, cryptorchidism, and developmental delay (Lowe syndrome).

Investigations

- *Plasma:* Na, K, bicarbonate, Cl, Ca, P, urate, pH, creatinine, urea, alkaline phosphatase, parathyroid hormone (PTH). The typical constellation of results is listed in Table 7.3. PTH and alkaline phosphatase may be elevated secondary to urinary Ca/vitamin D loss or CKD.
- *Urine:* Na, K, Cl, Ca, P, urate, pH, glucose, amino acids, low-molecular weight proteins (e.g. retinol-binding protein, β-2-microglobulin).
- *Fractional excretion of Na:* usually normal (<1%), because of the importance for volume homoeostasis and compensation from more distal Na transporters. Fractional excretion of K is usually elevated (>15%), as is that of Ca (>1%) and P (>20%). In cases of very low plasma P and thus low amounts of filtered P, the tubular reabsorption of P may be falsely normal. Calculation of the transport maximum for

P (TmP/GFR) is more accurate to determine renal P wasting (see 📖 'Disorders of phosphate: hypophosphataemia', p.128).
- The most sensitive indicator for proximal tubular dysfunction is low-molecular weight proteinuria, such as retinol-binding protein or beta-2-microglobulin.
- An US for renal size and echogenicity, and to look for the presence of nephrocalcinosis, which may be present due to hypercalciuria.
- Bone X-rays for changes of rickets.
- White cell cystine and formal ophthalmology review (for corneal cystine crystals) for all cases of suspected renal Fanconi syndrome as cystinosis is the commonest cause (see 📖 'Cystinosis', p.271).

Treatment

- Treatment specific to the cause (see Table 7.2 for differential diagnosis).
- Replacement of electrolyte losses orally. It can be very difficult to replace these adequately, and very large doses of Na Cl, K, P, and bicarbonate may be required. IV rehydration with normal saline and added electrolytes (e.g. K, P, etc.) is often needed, both at diagnosis and during intercurrent illness to correct biochemical disturbance.
- Activated vitamin D (1-alfacalcidol, or calcitriol if liver dysfunction).
- Free access to water.

Acquired causes of Fanconi syndrome

Drugs/toxins

- Aminoglycosides.
- Ifosfamide.
- Outdated tetracyclines.
- Na valproate.
- 6-mercaptopurine.
- Heavy metal poisoning.
- Toluene.
- Paraquat.

Renal causes

- Post-renal transplant.
- Recovery phase of acute tubular necrosis.
- Tubulointerstitial nephritis.
- Nephrotic syndrome (FSGS).

Fig. 7.2 represents an epithelial cell in the proximal tubule. Na is reabsorbed either in exchange with substances that need to be secreted (such as protons via the Na–H exchanger (NHE3)) or in co-transport with substances that need to be reabsorbed (such as P or glucose). The epithelial cells in the proximal tubule (PT) all express the water channel AQP1, so that solutes are reabsorbed isotonically with water.

Table 7.2 Genetic causes of Fanconi syndrome

Onset	Disorder	Gene	Features	Diagnostic test
Neonatal	Galactosaemia	*GALT*	Liver dysfunction, encephalopathy, sepsis	Red cell galactose-1-phophate uridyl transferase
	Mitochondrial cytopathy	Various mitochondrial and nuclear genes	Multi-systemic: 'illegitimate associations'	Mitochondrial DNA (blood); muscle enzymology
	Tyrosinaemia	*FAH*	Poor growth, hepatomegaly, and hepatic dysfunction	Plasma amino acids, urine organic acids (succinyl acetone)
Infancy	Fructosaemia	*ALDOB*	Rapid onset after fructose given—vomiting, hypoglycaemia, hepatomegaly	Hepatic fructose-1-P aldolase B
	Cystinosis	*CTNS*	Poor growth, rickets, corneal cystine crystals	White cell cystine; mutational analysis
	Fanconi–Bickel syndrome	*GLUT2*	Failure to thrive, hepatomegaly, hypoglycaemia, rickets, severe glycosuria, galactosuria	Mutational analysis
	Lowe's syndrome	*OCRL*	Males (X-linked), cataracts, hypotonia, developmental delay	Mutational analysis
Childhood	Cystinosis	*CTNS*	As cystinosis in infancy	As cystinosis in infancy
	Dent's disease	*CLCN5*	Males (X-linked), nephrocalcinosis, hypercalciuria	Molecular diagnosis
	Wilson's disease	*ATP7B*	Hepatic and neurological disease, Kayser-Fleischer rings	Plasma copper, caeruloplasmin

Adapted with permission from van't Hoff W. (2003). Renal tubular disorders. In Webb N and Postlethwaite R (eds) *Clinical Paediatric Nephrology*. Oxford University Press, Oxford, 103–12.

Table 7.3 Typical constellation of biochemistries in proximal tubular dysfunction

Parameter/disease	Renal Fanconi	Lowe	Dent
Plasma: Na	→	→	→
K	↓	↓→	→
Cl	↑	↑→	→
HCO_3	↓	↓→	→↓
PO_4	↓	↓→	→↓
Urine			
TmP/GFR	↓	↓→	→↓
Ca/Cr	↑	↑	↑
FEK	↑	↑→	→
low-molecular weight proteinuria	↑↑↑	↑↑↑	↑↑↑
Glucose	↑	↑→	→

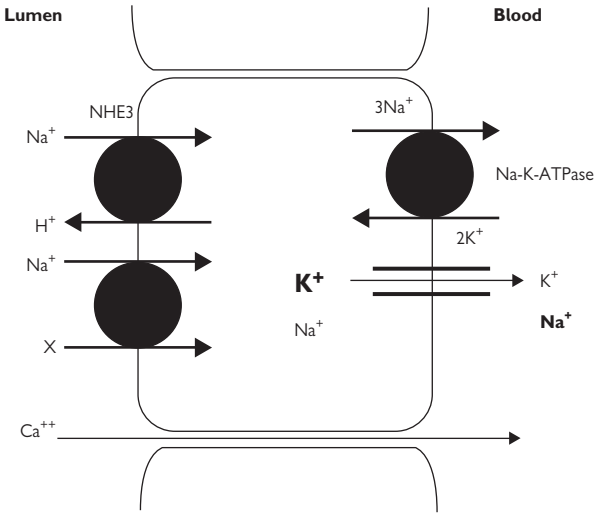

Fig. 7.2 Diagram of a PT cell.

Disorders of renal salt handling: thick ascending limb

- Salt reabsorption in the thick ascending limb of Henle's loop (TAL) is mediated by the furosemide-sensitive Na co-transporter NKCC2 (Fig. 7.3). In Bartter syndrome the function of this transporter is either directly or indirectly compromised, and thus its symptoms are best compared with the effects of loop-diuretics, such as furosemide.
- Four genes underlying Bartter syndrome have been identified so far and more are expected (Table 7.1). In addition, isolated patients with autosomal dominant (AD) hypocalcaemia can also have Bartter-like symptoms.

Clinical features

Key symptoms

- Hypokalaemic, hypochloraemic metabolic alkalosis with elevated renin and aldosterone levels, and normal to low BP.
- Polyuria, polydipsia, and salt-craving to replace renal losses.

Additional symptoms

- Salt reabsorption in the thick ascending limb (TAL) is a critical step in the renal concentration/dilution system. Therefore, patients with Bartter syndrome have impaired urinary concentration (hypo- to isosthenuria). Because of this, patients with Bartter syndrome have high renal water losses and are prone to hypernatraemic dehydration.
- The combined actions of the NKCC2 co-transporter and subsequent 'recycling' of K back in the tubular lumen through the K channel ROMK provide the driving force for reabsorption of Ca and magnesium (Mg) in the TAL (Fig. 7.3). Therefore, patients with mutations in the genes encoding NKCC2 or ROMK typically have hypercalciuria, hypermagnesuria, and nephrocalcinosis. Conversely, patients with mutations affecting the chloride (Cl) channel CLCKNB or its subunit Barttin typically have normocalciuria and no nephrocalcinosis.
- The Barttin subunit is also expressed in inner ear and patients with Barttin mutations have Bartter syndrome associated with sensorineural deafness (very rare).
- The Cl channel CLCKNB is also expressed in the DCT and patients with mutations in the encoding gene may have an overlap of Bartter and Gitelman (see 📖 'Disorders of renal salt handling: distal convoluted tubule', p.151) features.
- Spectrum of severity can vary widely in Bartter syndrome with the most severe cases showing an antenatal presentation with polyhydramnios, premature delivery, severe and life-threatening dehydration, failure to thrive (neonatal Bartter syndrome). These patients also have highly elevated levels of urinary prostaglandins, especially PGE_2. Many of these patients also experience progression to CKD over time. Other patients with Bartter syndrome are identified in adulthood during a routine blood test and have no other apparent symptoms.

Investigation

- *Urine:* Na, K (FE > 15%), Cl (FE > 1%), Ca (variable), Mg (high, FE > 4% in some forms), creatinine (to calculate fractional excretions).
- *Plasma:* Na (variable), K, Cl (both low), Mg (normal or low), Ca (usually normal), bicarbonate (high), urea, creatinine, albumin (as indicators of renal function and hydration).
- Renal US for nephrocalcinosis.
- Genetic analysis.

Diagnosis

- *Extrarenal salt and water losses ('pseudo-Bartter'):* distinguished by low urinary Cl concentration (FE < 1%). This can be difficult in Cl losing diarrhoea as the stool may be so watery it is indistinguishable from urine.
- *Hypomagnesaemia-hypercalciuria-nephrocalcinosis syndrome:* in this condition there is marked hypercalciuria, nephrocalcinosis, calculi, and progression to CKD 5 (see 📖 'Disorders of magnesium: hypomagnesaemia', p.124).
- Surreptitious diuretic use (history and toxicology).
- *Aldosterone excess (primary or secondary):* patients have increased vascular volume and hypertension.
- Some patients have marked hyposthenuria and have been misdiagnosed as primary nephrogenic diabetes insipidus.

Treatment

- Treatment of Bartter syndrome involves replacement of fluid and electrolyte losses followed by administration of indometacin, which reduces renal losses.
- Severely affected children may initially require IV saline rehydration, milder cases can simply be started on K and or NaCl ideally divided into 3–4 doses per day.
- It is usually very difficult to achieve adequate K supplementation to restore the K level to the normal range, and most patients tolerate hypokalaemia of 2.5mmol/L with no obvious ill effect.
- There may be a role for spironolactone in some cases, but beware that this inhibits the physiological compensatory mechanisms and may lead to severe hypotension.
- Indometacin is usually given at a dose of 0.5–1mg/kg/day, divided into four doses, with stepwise increases to a maximum of 2–4mg/kg/day.
  - should be given with food (or milk) and parents counselled regarding gastrointestinal (GI) side effects including ulceration, and benign intracranial hypertension;
  - some authorities have concerns about chronic usage of indometacin in the neonatal period because of the risk of necrotizing enterocolitis;
  - consider concurrent use of a gastric acid inhibitor, such as ranitidine.
- Other prostaglandin inhibitors, such as Ibuprofen and COX-2 inhibitors have also been used.

Fig. 7.3 represents an epithelial cell in the TAL of Henle's loop. Fontsize represents relative concentration for K and Na (not to scale) and (+) and (–) signs represent electric charges (not to scale).

Na is reabsorbed via NKCC2 (defect in Bartter type 1), together with 1 K and 2 Cl ions. The transporter can only function with all 4 ions bound and K binding is the rate-limiting step. Therefore, K is recycled through the K channel ROMK (defect in Bartter type 2) to ensure an adequate supply of K. This also leads to a relative excess of positive charges in the tubular lumen, providing the driving force for paracellular absorption of Ca and Mg.

Na can exit the cell on the basolateral (blood side) via the Na/K-ATPase, while Cl exits through the Cl channel CLCKNB (defect in Bartter type 3). CLCKNB requires Barttin (defect in Bartter type 4) for proper membrane localization.

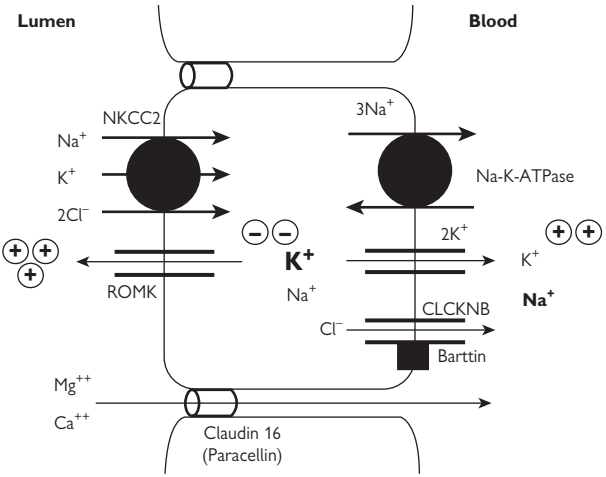

Fig. 7.3 Diagram of a TAL cell.

Disorders of renal salt handling: distal convoluted tubule

Salt reabsorption in the distal convoluted tubule (DCT) is mediated by the thiazide-sensitive NaCl-co-transporter NCC (Fig. 7.4). Hence, symptoms in Gitelman and EAST (also called SeSAME) syndrome are best compared with the effects of thiazide diuretics. The electrolyte constellation in these two disorders is characterized by the secondary hyperaldosteronism, i.e. a hypokalaemic hypochloraemic metabolic alkalosis, as in Bartter syndrome.

Clinical features

Gitelman syndrome

- Gitelman syndrome is usually diagnosed during adolescence or later.
- Hypomagnesaemia is due to an increased urinary Mg excretion (*syn* 'familial hypomagnesaemia') and the likely cause for many of the neurological symptoms seen, including seizures, tetany, muscle weakness, or cramps.
- Other symptoms include hypotension and dizziness, joint pains, and nocturnal enuresis.
- Systemic calcifications, such as chondrocalcinosis are unusual in childhood.
- Prolongation of the QT interval on ECG occurs in 10% of patients.
- The prognosis is generally excellent.

EAST syndrome

- Patients typically present in infancy because of the neurological manifestations (seizures, ataxia, developmental delay).
- Sensorineural deafness.

Treatment

Gitelman syndrome

- Supplementation of K, Cl, and Mg to control electrolyte and acid-base balance. This should be lifelong therapy to prevent neurological symptoms. Patients are encouraged to maintain a high-salt diet.
- Spironolactone and amiloride have been used to correct severe hypokalaemia, but may lead to severe hypotension.

Pseudohypoaldosteronism type 2

Pseudohypoaldosteronism type 2 (PHA2) is a rare dominantly inherited disorder. Not to be confused with PHA1, which is a salt wasting disorder (see 📖 'Disorders of renal salt handling: collecting duct', p.153), PHA2 is a disorder of Na retention, due to mutations in the genes *WNK1* or *WNK4*. They encode kinases, which regulate salt reabsorption in the distal tubule and the mutations lead to an over-activity of the thiazide-sensitive Na transporter. Consequently, the symptoms are the mirror image of Gitelman syndrome: patients have hypertension, hyperkalaemic, hyperchloraemic metabolic acidosis, and hypercalciuria. The hypertension often develops during adolescence and thus may not be apparent in younger children. The treatment consists of thiazide diuretics, which completely reverses the symptoms.

Fig. 7.4 represents an epithelial cell in the DCT. Na is reabsorbed via NCC and can exit towards the blood side via the Na-K-ATPase, while Cl can pass through the Cl channel CLCKNB. NCC is regulated by the WNK-kinases WNK1 and WNK4. KCNJ10 is necessary to supply sufficient K to the Na-K-ATPase and build up a voltage gradient over the basolateral membrane that promotes Cl reabsorption.

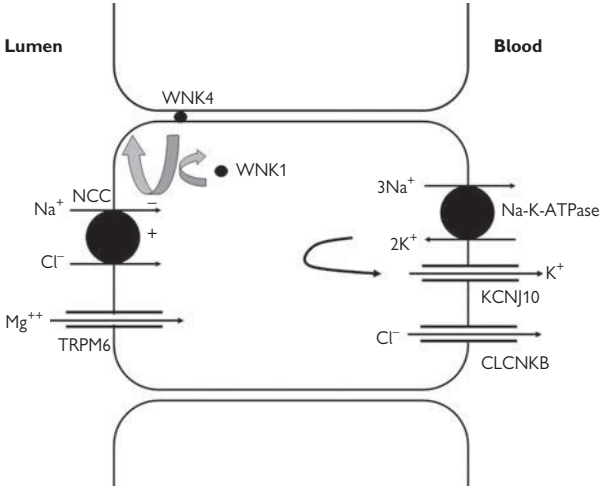

Fig. 7.4 Diagram of a DCT cell.

Disorders of renal salt handling: collecting duct

- Salt handling disorders of the collecting duct all affect salt reabsorption through the Na channel ENaC, present in the apical membrane of principal cells, which consists of different subunits, encoded by three different genes (Table 7.1 and Fig. 7.4).
- ENaC is blocked by amiloride and regulated by the mineralocorticoid receptor (MCR), which is blocked by spironolactone.
- The MCR is activated by aldosterone and cortisol, which has a ~1000-fold higher plasma concentration than aldosterone. However, cortisol is usually metabolized in the principal cell to cortisone (which cannot activate MCR) by 11-β-hydroxysteroid dehydrogenase.
- In GRA, an unequal crossover in meiosis creates a fusion gene from the highly homologous genes *CYP11B1* and *CYP11B2*, which are adjacent on chromosome 8 and encode key enzymes in glucocorticoid (CYP11B1) and aldosterone (CYP11B 2) synthesis. In the fusion gene, the *CYP11B1* promoter is fused to the coding sequence of *CYP11B2*, so that ACTH now drives aldosterone, rather than glucocorticoid synthesis.
- In CAH the effect on renal salt handling depends on the localization of the defect: if aldosterone synthesis is impaired, patients develop salt wasting, if metabolites with mineralocorticoid activity accumulate, patients have salt retention, otherwise salt handling is unaffected.
- Impaired ENaC channel activity (PHA1) results in hypovolaemia, hyponatraemia, and a hyperkalaemic, hyperchloraemic acidosis, which especially in the recessive form is life-threatening.
- Conversely, increased channel activity results in hypertension with a hypokalaemic, hypochloraemic alkalosis (AME, Liddle syndrome).

Diagnosis

Based on the specific clinical findings (Table 7.1) and confirmed by genetic testing.

Treatment

Pseudohypoaldosteronism type 1

Na and bicarbonate supplementation (10–20mmol/kg/day not unusual in the recessive form). These patients often require a central line for reliable emergency access. Na-exchange resins (such as Kay-exelate) provide a good form for sustained Na administration and K removal.

Liddle syndrome and AME

These disorders respond well to ENaC blockade through amiloride. Patients with AME may also benefit from MCR blockade by spironolactone, but require high doses (up to 10mg/kg/day), as spironolactone in this disorder competes for MCR binding with cortisol, which is present in much higher concentration than aldosterone (see third bullet point at the start of this section).

GRA and CAH

Amiloride, spironolactone and/or glucocorticoid supplementation provides effective treatment.

Fig. 7.5 represents a principal cell in the collecting duct. Na is reabsorbed via the epithelial Na channel ENaC. Na entry provides the electrical driving force for K secretion through the K channel ROMK or proton secretion (from the intercalated cell, not shown).

ENaC activity is regulated by the mineralocorticoid receptor. The enzyme HSD11B2 is necessary to metabolize cortisol to cortisone to prevent receptor activation from cortisol.

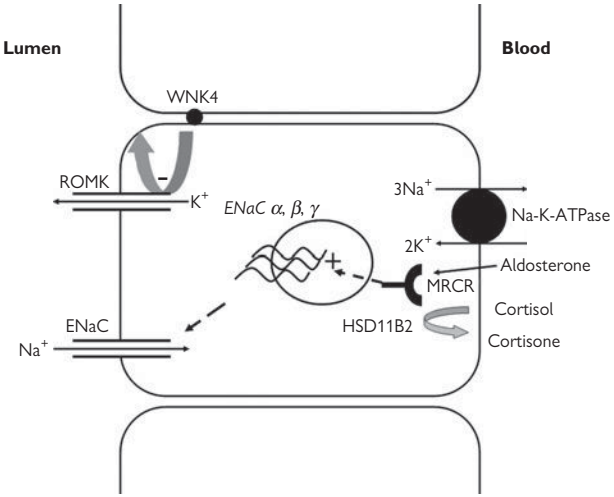

Fig. 7.5 Diagram of a principal cell.

Disorders of renal water handling

Basic principles

- The kidneys in an adult filter about 150 L of plasma per day. About 80% of this is passively reabsorbed in the proximal tubule (PT), which is water permeable due the presence of water channels (AQP1) in both apical and basolateral membranes. Thus, as solutes such as Na, bicarbonate, and P are reabsorbed in the PT, water follows passively.
- Final urine osmolality and thus water excretion is determined by the water permeability of the collecting duct:
  - urine is diluted in the preceding water-impermeable nephron segments, the thick ascending limb of Henle's loop (TAL) and the distal convoluted tubule (DCT);
  - salt reabsorption in TAL (by the furosemide-sensitive NKCC2) not only dilutes the urine, but also generates the medullary interstitial concentration gradient;
  - when the dilute urine enters the medullary collecting duct, a concentration gradient between urine (osmolality of ~50mosm/kg) and interstitium (up to 1200mosm/kg) exists;
  - the osmotic force is enormous (19.2mmHg/mOsm/L) and water will move out of the tubule, if water channels are provided.
- The availability of water channels is regulated by AVP, which binds to its receptor (AVPR2), located in the principal cells of the collecting duct. When activated by binding of vasopressin, AVPR2 causes an increase in cAMP, which in turn causes movement of intracellular vesicles containing water channels (AQP2) to the apical membrane, thereby increasing water permeability.

Nephrogenic diabetes insipidus

- Nephrogenic diabetes insipidus (NDI) is a renal disorder characterized by tubular unresponsiveness to antidiuretic hormone (AVP) resulting in the excretion of an increased volume of dilute urine. Congenital (usually severe) and acquired (usually milder) forms are recognized.
- In complete and untreated NDI, the urine osmolality is typically 50–100mosm/kg. The total volume excreted depends on the osmotic load (osmotically active substances in the diet) that needs to be excreted by the kidney. A typical western diet presents about 500mosm/day to the kidney. With a urine osmolality of 50mosm/kg, this will require 10L water to be excreted. An extra gram of salt (≅ 18mmol of Na and Cl each ≅ 36mosm) in the diet would increase urine output by approximately 700mL.
- A simple, but often confused point is the difference between osmolarity and osmolality: these are numerically similar, although osmolarity is expressed as number of osmotically active substances per volume of analysed fluid (mosm/L), while osmolality is per weight (mosm/kg).

Genetics of nephrogenic diabetes insipidus

- The gene for *AVPR2* is located on the X-chromosome and accounts for about 90% of inherited cases of NDI, while *AQP2* is located on chromosome 12. Mutations in *AQP2* cause autosomal recessive NDI. Some very rare mutations in *AQP2* can also cause autosomal dominant NDI.

- Some mutations disrupt function completely, while others only decrease affinity of the receptor to AVP, resulting in a milder phenotype (partial NDI).
- Female carriers of an AVPR2 mutation are generally asymptomatic, but skewed X-inactivation may cause various degrees of symptoms.
- In addition to genetic forms of NDI, there are many causes of secondary NDI (see 📖 'Acquired (secondary) nephrogenic diabetes insipidus', p.158).

Clinical features (primary, X-linked genetic nephrogenic diabetes insipidus)

Males

- Present in infancy (no prenatal symptoms, no polyhydramnions).
- Polyuria and polydipsia with episodes of hypernatraemic dehydration.
- Episodes of pyrexia, irritability, and vomiting.
- Failure to thrive (patients are only interested in drinking, but not eating).

Females

Usually present at a later age with milder symptoms or are asymptomatic. Rarely more prominent symptoms are encountered (depending on X-inactivation).

Complications include:

- Developmental delay/learning problems (due to repeated episodes of hypertonic dehydration).
- Renal cortical necrosis during episodes of severe dehydration.
- Hydronephrosis and dilatation of the lower urinary tract (due to high urine volume, especially with urinary withholding).

Investigations

- Basic biochemistry and haematological screen: urea & electrolytes (U&Es), creatinine, Ca, PO_4, liver function tests (LFTs), full blood count (FBC) (increased haematocrit as a sign of intravascular water depletion).
- *Paired urine/plasma osmolarity:* inappropriately dilute urine (Uosm<Posm) in the presence of elevated plasma osmolarity establishes a diagnosis of diabetes insipidus (DI). To differentiate central DI from nephrogenic DI, a DDAVP® test is performed (see 📖 Appendix, 'DDAVP® test', p.604).
- US kidneys and bladder (gross dilatation of urinary tract, altered echogenicity or nephrocalcinosis suggest secondary NDI due to underlying nephropathy, (see 📖 'Acquired (secondary) nephrogenic diabetes insipidus', p.158).

Water deprivation test and DDAVP® test

- Never undertake a water deprivation test in the presence of hypernatraemia and/or increased plasma osmolarity. In this situation, paired plasma and urine osmolarities are sufficient. Thus, children presenting with hypernatraemia do not need another water deprivation test, if Uosm had been measured at presentation.
- In normonatraemic children suspected of having DI, a first morning Uosm is often sufficient as an informal water deprivation test, unless the child gets up at night to drink. A Uosm > Posm rules out a severe form of DI.

- A formal water deprivation test, if needed, should be carried out in the early morning. The patient is weighed, and plasma and urine osmolarities measured. The test is stopped if >3% of body weight is lost or if Posm > 300msom/kg. If the plasma osmolality is 300mosm/kg or higher, and the urine is dilute (<Posm), then the diagnosis of DI is confirmed. If the urine concentration is >800mosm/kg (or >600mosm/kg in infants), a normal urinary concentrating ability is established and DI has been ruled out. If the Uosm is <800mosm/kg (<600mosm/kg infants), DDAVP® (desmopressin) should be given to further assess renal concentrating ability.
- *DDAVP® test:* various protocols, using oral, nasal, im, or IV administration of DDAVP® exist. The main risk of a DDAVP® test is hyponatraemia. This can only occur in patients who respond to desmopressin, but continue drinking water or who ingested a large bolus of water immediately prior to the test. In patients with intact thirst mechanism, the risk of dysnatraemias is very low (as they will stop drinking), but patients with suspected psychogenic polydipsia (or Munchhausen by proxy) are at risk. It is paramount that patients do not drink an hour before desmopressin and are closely observed so that fluid intake during the test does not exceed urine output. The half-life of desmopressin depends on the mode of administration. The shortest is after IV administration, where only a 2-h observation period is required. This mode also eliminates questions about incomplete absorption, which is possible with oral or nasal doses.
- A well-established protocol (see 📖 Appendix, 'DDAVP® test', p.604) uses 0.3 microgram/kg desmopressin (max 15 microgram) dissolved in 1mL/kg (max 50mL) of 0.9% saline as an IV bolus (this is the same dose given to patients with von Willebrand disease to promote platelet aggregation). The bladder should be emptied before the administration of desmopressin to avoid admixture of urine. As many aliquots of urine as possible should be obtained during the 2-h test and individually sent for urine osmolality. Paired plasma and urine sample are obtained at the beginning and the end of the test.
- In central DI, the urine will concentrate to over 800mosm/kg (>600mosm/kg in infants) following desmopressin; in complete NDI the urinary concentration will be unchanged (<Posm) or mildly increased (300–600mosm/kg) in partial NDI.

Management of primary (genetic) nephrogenic diabetes insipidus

Diet

The mainstay of treatment is to reduce the osmotic load, which mainly consists of salts and protein (as it is metabolized to urea):

- Salt is restricted as much as possible, but enough protein must be given to allow proper growth. This is most challenging during infancy, when caloric and fluid intake is coupled and the input of an experienced dietician is very important.
- The general aim is to provide adequate nutrition to meet recommended intakes, but this limits the osmotic load to 15mosm/kg/day.
- As a general rule, each g of protein provides 4mosm and each mmol of Na or K provide 2mosm (because of the accompanying anion).
- Fat and carbohydrates provide calories, but no osmotic load.

Example The importance of osmotic load reduction becomes apparent when you consider an adolescent NDI patient, who enjoys a 500g steak (containing ~200g protein) seasoned with 2g of salt: the total osmotic load from the steak is 800mosm (200 × 4) and from the salt ~70mosm (each g of salt contains ~35 mmol of Na and Cl each). With an average urine osmolality of 100mosm/kg, the patient will need to drink almost 9L of water in order to be able to excrete the osmotic load provided by this meal.

- The child needs free access to water and infants should be offered fluid frequently (every 1–2h).

Drug therapy

Chlorothiazide 1–2 mg/kg/day or other thiazide diuretic:

- The administration of a diuretic in a polyuric disorder is counterintuitive but effective.
- Thiazides impair the urinary diluting mechanism in the distal tubule. Moreover, they increase urinary Na excretion, which leads to intravascular volume depletion.
- This enhances Na (and thus water) reabsorption in the proximal tubule. Less water is then presented to the defective portion of the tubule.
- Watch for hypokalemia and use K supplements if needed (however, these will present an additional osmotic load). Amiloride can sometimes be used in combination with chlorothiazide to achieve K sparing.
- *Indometacin 0.75–2mg/kg/day (divided into 2–3 doses):* inhibitor of prostaglandin synthesis. Helpful in the management of infants, but often not necessary in older children. Counsel patients regarding GI bleeding. The mechanisms of action are unclear, but probably include reduction of GFR and stimulation of proximal Na (and thus water) reabsorption.

Management of NDI during intercurrent illness, and perioperatively

During intercurrent infection or for elective surgery, children with NDI may require IV fluids. Unlike the usual paediatric situation this should be given as 5% glucose without saline. The inclusion of saline will increase the solute load and thus worsen hypernatraemia. Patients should be closely monitored with a strict input/output balance, daily weights and for the development of dysnatraemias with adjustment of IV fluids accordingly.

Acquired (secondary) nephrogenic diabetes insipidus

Inherited NDI is a rare disease, and secondary forms occur more commonly (and often have only moderately impaired urinary concentrating ability-isosthenuria):

- Amyloidosis.
- Analgesic nephropathy.
- CKD (particularly renal dysplasia and nephronophthisis).
- Drug induced:
  - lithium;
  - tetracycline.
- Hypercalcaemia/hypercalciuria.

- Chronic hypokalaemia.
- Post-obstructive uropathy.
- Bartter syndrome.
- Apparent mineralocorticoid excess.
- Sarcoidosis.
- Sickle cell anaemia.

Nephrogenic syndrome of inappropriate antidiuresis

- Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is the mirror image of NDI: in NDI water is lost, whereas in NSIAD water is inappropriately retained. Thus, NSIAD is a genetic form of the syndrome of inappropriate anti-diuresis (SIADH).
- NSIAD is caused by gain-of-function mutations in AVPR2 (loss-of-function of which cause NDI, see 🕮 'Nephrogenic diabetes insipidus', p.155). Accordingly, NSIAD is an X-linked dominant disorder, with men typically more severely affected than women.
- Only 2 mutations have so far been isolated in NSIAD, both affecting the same amino acid, arginine 137: R137C and R137L. Interestingly, mutation of this residue to histidine (R137H) results in NDI.
- Affected patients present with hyponatraemia, with no evidence of hypovolaemia and inappropriately high urine osmolality (Uosm > Posm).
- NSIAD can be differentiated from SIADH by the presence of a family history (usually), and very low or absent levels of anti-diuretic hormone.
- Treatment is similar to that in SIADH and consists of water restriction:
  - older patients will refrain from drinking automatically, but in infants this is more difficult, as fluid and calorie intake are coupled;
  - feeds should be concentrated as much as possible and solids introduced early;
  - urea supplementation (to increase osmotic load) and furosemide (to impair urinary concentration) have been described, but no clear data exist.

Disorders of renal magnesium handling

Basic principles

While most other ions are predominantly reabsorbed in the proximal tubule, the key sites for Mg reabsorption are the thick ascending limb of Henle's loop (TAL) and distal convoluted tubule (DCT) (Fig. 7.6a,b). Consequently, all disorders associated with abnormal renal Mg handling affect transport in these two segments (Table 7.4). Clinically, they can be separated into three groups, based on urinary Ca excretion (Table 7.4).

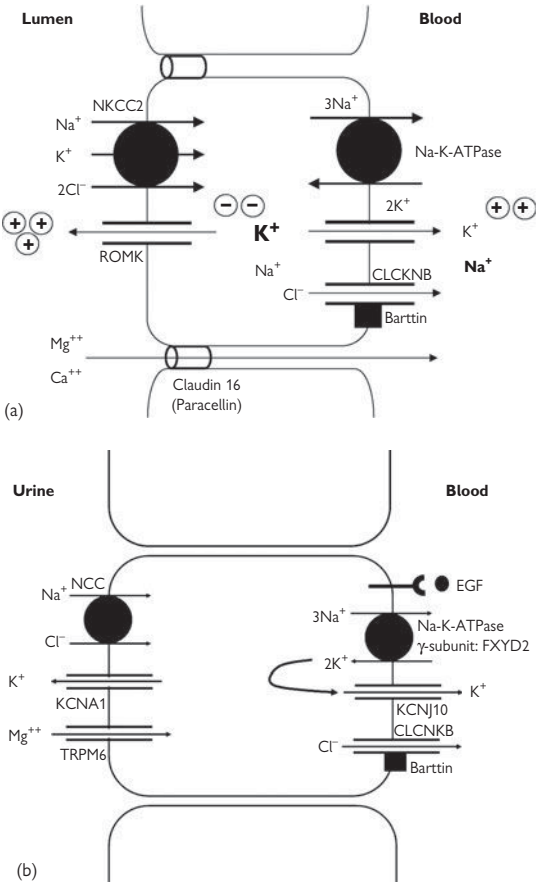

Fig. 7.6 (a) Schematic of salt transport in TAL. (b) Schematic of salt transport in DCT.

Disorders in TAL are associated with hypercalciuria

The molecular pathway for Mg reabsorption in TAL includes Claudin 16 and 19, and is shared with Ca. The voltage gradient driving absorption is generated by the combined actions of NKCC2 and ROMK (mutations that cause Bartter syndrome). Therefore, loss-of-function in any of these four proteins leads to waste of both Mg and Ca. In Bartter syndrome there is additional salt wasting with consequent hypokalaemic hypochloraemic metabolic alkalosis.

- *Inherited causes:*
  - familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (autosomal recessive (AR) mutations in CLDN16 or 19);
  - Bartter syndrome type 1 or 2 (AR mutations in NKCC2 or ROMK).
- *Acquired causes:*
  - loop diuretics;
  - amphotericin, cisplatin, foscarnet, pentamidine (usually associated with more generalized tubular dysfunction).

Disorders in the distal convoluted tubule affecting magnesium reabsorption only are associated with normocalciuria

The key entry step for Mg into the cell is through the ion channel TRPM6. Disorders that directly or indirectly impair this entry step affect renal Mg excretion only. The excretion of other salts, such as Ca, Na, Cl^-, and K is unaffected.

- *Inherited causes:*
  - familial hypomagnesaemia with secondary hypocalcaemia (AR mutations in TRPM6);
  - hypomagnesaemia HOMG (AD mutations in KCNA1);
  - hypomagnesaemia HOMG4 (AD mutations in EGF).
- *Acquired causes:* tacrolimus, ciclosporin, proton-pump inhibitors.

Disorders in the distal convoluted tubule primarily affecting sodium reabsorption are associated with hypocalciuria

Impaired Na reabsorption in DCT indirectly affects Mg reabsorption. Thus, disorders of Na reabsorption (e.g. Gitelman and EAST syndrome) are associated with renal Mg wasting. The resulting volume loss from impaired Na reabsorption leads to up-regulation of proximal Na transport, which is paralleled by Ca reabsorption. Thus, these disorders are associated with hypocalciuria.

- *Inherited causes:*
  - Gitelman syndrome (AR mutations in NCC);
  - Bartter syndrome type 3 and 4 (AR mutations in CLCKNB or Barttin);
  - EAST/SeSAME syndrome (AR mutations in KCNJ10);
  - HOMG2 (AD mutations in FXYD2);
  - Renal cysts and diabetes syndrome (AD mutations in HNF1B).
- *Acquired causes:* thiazides.

Since the active, transcellular transport in the kidney requires energy, renal Mg wasting can also be seen in mitochondrial cytopathies. Since these disorders can affect any other transport pathway, the associated abnormalities can be highly variable. Since aminoglycosides affect mitochondrial function, they also can cause hypomagnesaemia.

Investigations and treatment

See 🕮 ‘Disorders of magnesium: basic principles’, p.122.

Table 7.4 Inherited disorders and genes associated with renal Mg wasting

Gene	Protein	Phenotype								Disease
		Plasma					Urine		Extrarenal	
		Mg	Ca	K	Cl	HCO_3	Ca	K		
SLC12A1	NKCC2	↔↓	↔	↓	↓	↑	↑	↑		Bartter 1
KCNJ1	ROMK	↔↓	↔	↓	↓	↑	↑	↑		Bartter 2
CLDN16	Claudin16	↓	↔	↔	↔	↔	↑	↔		FHHNC, HOMG3
CLDN19	Claudin19	↓	↔	↔	↔	↔	↑	↔	Eye problems	FHHNC, HOMG5
CLCKNB	CLCKNB	↓↔	↔	↓	↓	↑	↓↔	↑		Bartter 3
BSND	Barttin	↓↔	↔	↓	↓	↑	↓↔	↑	Deafness	Bartter 4
TRPM6	TRPM6	↓↓	↓	↔	↔	↔	↔	↔	Epilepsy, DD	HSH, HOMG1
EGF	EGF	↓↓	↔	↔	↔	↔	↔	↔	DD	HOMG4
KCNA1	KV1.1	↓↓	↔	↔	↔	↔	↔	↔	Episodic ataxia, myokymia	HOMG
FXYD2	Na^+/K^+-ATPase, γ-subunit	↓↓	↔	↔	↔	↔	↓	↔		HOMG2

HNF1B	*HNF1B*	↓↓	↔	↔↓	↔↓	↔↑	↓	↔↑	Renal malformation, MODY	RCD
SLC12A3	NCC	↓	↔	↓	↓	↑	↓	↑		Gitelman
KCNJ10	Kir4.1	↓	↔	↓	↓	↑	↓	↑	Epilepsy, ataxia, deafness, DD	EAST/SeSAME
MTTI	tRNA	↓	↔	↔↓	↑↔↓	↓↔↑	↓↔↑	↔↑	Syndrome X	Mitochondrial

Listed are known inherited disorders of renal Mg handling. The darkly shaded first 4 rows contain disorders of Mg-handling in TAL, the lightly shaded next 2 rows contain disorders of Mg-handling in TAL and DCT. The next 3 unshaded rows are disorders of Mg-handling in DCT. The last 4 boxed rows are disorders of renal Na handling in DCT with secondary renal Mg wasting.

DD: developmental delay; FHHNC: familial hypomagnesaemia with hypercalciuria and nephrocalcinosis; HSH: hypomagnesaemia with secondary hypocalcaemia; HOMG: hypomagnesaemia, renal; RCD: renal cysts and diabetes syndrome; MODY: maturity onset diabetes in the young.

Rickets

General principles

- Rickets refers to impaired mineralization at the epiphyseal growth plate, with deformity and impaired linear growth.
- Rickets occurs due to a deficiency in one of the two key components of bone: Ca and/or P. This deficiency can be primary or secondary.
- Broadly speaking the rickets syndromes can be classified in:
  - deficiency of vitamin D (with secondary deficiency of Ca and P;
  - nutritional deficiency of Ca;
  - renal P wasting (hypophosphataemic rickets);
  - CKD (see 📖 Chapter 18, p.409).
- Occasionally, more generalized proximal tubular dysfunction (e.g. glyco-, aminoaciduria, acidosis, low-molecular weight proteinuria) can be seen in vitamin D deficiency or Ca deficiency rickets. These findings thus do not always indicate a primary renal tubular problem such as renal Fanconi syndrome and should be reassessed when rickets is controlled.
- Glycosuria can also be seen with hypophosphataemic rickets.
- Table 7.5 summarizes the major clinical and biochemical features of the rickets syndromes, including therapy.
- PTH and ALP are elevated in all forms of rickets, reflecting the body's attempts to normalize plasma Ca and P levels by mobilization from the bone. These two parameters can thus be used as markers of rickets activity and treatment should aim at normalization of them.
- At presentation, it may be difficult to distinguish between vitamin D deficient and hypophosphataemic rickets (unless plasma levels of vitamin D are available), as the elevated PTH induces renal P wasting. The initial treatment goal thus is to normalize PTH by vitamin D supplementation. Persistent renal P wasting with normal PTH argues for a primary renal defect in P transport.
- Attempts at normalization of plasma P levels in states of primary renal P wasting are usually futile: the more P is supplemented, the more is lost in the urine. Occasionally, plasma levels may return to normal, if obtained shortly after intake of P supplement.
- To avoid large swings in plasma P levels, supplementation should be spread throughout the day in four or more doses. It may be helpful to dissolve the daily dose of P supplement in a bottle of water and advise the patient to drink from this throughout the day.
- Table 7.6 lists P preparations available in the UK. At high doses all P supplements can cause diarrhoea.
- Vitamin D supplementation with the goal of normalizing PTH and ALP in hypophosphataemic rickets is in our experience key to optimizing growth and minimize skeletal deformities. However, about 50% of patients develop nephrocalcinosis. A good fluid intake should be encouraged to minimize urine Ca concentration.

Table 7.5 Rickets: causes and biochemical findings

Type	Cause	Biochemistry						Treatment
Vitamin D related		Ca	PO_4	PTH	ALP	25 (OH) Vit D	1, 25 (OH) Vit D	
Nutritional/deprivational	Lack of dietary vitamin D and/or lack of sunlight	↓→	↓→	↑	↑	↓	↓	Vitamin D2 or D3 at 1500–3000iu/day (RDA in health is 7–10micrograms/day or 280–400iu/day) for 6–8 weeks, followed by prophylactic doses of 300–400iu/day
Malabsorption	Malabsorption of vitamin D and/or calcium	↓→	↓→	↑	↑	↓	↓	Treat underlying cause. Vitamin D supplements may be required
Pseudovitamin D deficiency (PDDR, VDDR type 1)	Mutations in 25-hydroxyvitamin D-1-alpha-hydroxylase genes.	↓→	↓→	↑	↑	→	↓	1-alpha calcidol or calcitriol
Hypocalcaemic vitamin D resistant (HDRR, VDDR type II)	Mutations in the vitamin D receptor (*VDR*) gene. Inability of cells to respond to 1,25 (OH)2 D.	↓→	↓→	↑	↑	→	↑	No satisfactory treatment. Nocturnal intravenous calcium infusions?
Calcium deficiency	Lack of calcium in diet	↓	↓→	↑	↑	→	→	Calcium supplement.

(Continued)

Table 7.5 (*Contd.*)

Type	Cause	Biochemistry						Treatment
Hypophosphataemic								
Renal Fanconi syndrome	Loss of phosphate in urine	→	↓	↑	↑	→	↓→	As per X-linked (see 'X-Linked dominant', this table)
Oncogenic	Tumour production of FGF23	→	↓	↑	↑	→	↓→	Treat tumour
Inherited hypophosphataemic								
X-Linked dominant	Mutations in the *PHEX* gene causing phosphaturia plus inadequate synthesis of 1,25 (OH)2 D	→	↓	↑	↑	→	→	1-alphacalcidol at 25–50ng/kg/day (maximum 2micrograms/day) once daily. Oral phosphate supplements: neutral phosphate at 1–4g/day (30–120mmol/day) divided into 4–6 doses.
Autosomal dominant	Mutation of the *FGF23* gene	→	↓	↑	↑	→	↓→	Phosphate supplementation
Autosomal hypercalciuric hypophosphataemic rickets	Recessive mutations in *SLC34A3* (NaPi-IIc). Also reported with dominant mutations in *SLC34A1* (NaPi-IIa).	→	↓→	↑	↑	→	↑→	Phosphate supplementation

Table 7.6 Phosphate supplements

Preparation	P	K	Na
Phosphate-Sandoz® (also contains 800mg per tablet of citrate), UK licensed	16.1mmol	3.1mmol	20.4mmol
Na acid (di-hydrogen) phosphate, unlicensed special (special products)	1mmol/mL	None	1mmol/mL
K acid (di-hydrogen) phosphate, unlicensed special (special products)	1mmol/mL	1mmol/mL	None
K-Phos® neutral, film-coated tablet, 250mg (Beach US) import	8mmol	1.1mmol	13mmol
Neutra-Phos® powder sachets (makes solution), Baker Norton US	7.125mmol	7.125mmol	7.125mmol
Neutra-Phos® K, powder sachets (makes solution), Baker Norton US	7.125mmol	14.25mmol	None
K-Phos original, (Na free) tabs, Beach US	4mmol	3.7mmol	None
K-Phos MF tablet, Beach US	4mmol	1.1mmol	2.9mmol
K-Phos No. 2, tablet Beach US	8mmol	2.3mmol	5.8mmol

Tubulointerstitial nephritis

Basic principles

- In contrast to glomerular disorders, which typically present with oliguria, fluid retention and hypertension, tubulointerstitial disorders usually maintain good, even increased urine output with low-normal BP and thus the possibility of kidney disease may not be considered initially.
- Presenting symptoms are often non-specific, such as malaise, fatigue, and polyuria.
- Clinical features are very similar to nephronophthisis (see 📖 'Nephronophthisis', p.329) which is an important differential diagnosis.
- Renal dysfunction is revealed by severe uraemia. The reasons for the secondary decrease in glomerular filtration are complex and probably include tubuloglomerular feedback to limit fluid and electrolyte losses.
- Tubulointerstitial nephritis (TIN) in children is usually acute (history of weeks to months), but chronic TIN (history of months to years) can be seen typically in the context of systemic diseases (see 📖 'Causes of chronic tubulointerstitial nephritis', p.169).
- Acute TIN accounts for approximately 7% of AKI in children.
- In adults, about 70% of all cases of TIN are due to drug reactions and another 15% infection-associated. No good epidemiological data exist for children. In our own experience, idiopathic (presumed autoimmune) TIN, often associated with uveitis (TINU) is the most common aetiology of biopsy-proven TIN. Thus, the clinical experience from adult cases has limited relevance for paediatric patients.

Clinical features of acute tubulointerstitial nephritis

- Non-oliguric or polyuric.
- Oliguria may develop in more severe forms.
- Acute and progressive rise in plasma urea and creatinine.
- Laboratory parameters can reflect the whole spectrum of tubular dysfunction, including glycosuria, tubular proteinuria, acidosis, isosthenuria.
- Normochromic normocytic anaemia may be observed in long-standing TIN affecting the erythropoietin-producing peri-tubular cells.
- Haemolytic anaemia can accompany acute TIN caused by drugs.
- Uveitis is a common associated problem (TINU), which may be asymptomatic or show only minor symptoms, such as light sensitivity. In some children uveitis precedes the TIN, in others uveitis may develop later.
- Rarely, sensorineural deafness is observed as part of the TINU spectrum, which may respond to corticosteroid/immunosuppressant therapy.

Causes of acute tubulointerstitial nephritis

- *Idiopathic:* typically associated with uveitis and thought to be due to an autoimmune reaction against a common antigen in eye and kidney.
- *Drugs:*
  - rifampicin;

  - meticillin;
  - phenytoin;
  - ciclosporin;
  - intravenous immunoglobin;
  - NSAIDs;
  - omeprazole;
  - herbal medicines;
  - *toxins:* heavy metals;
  - *NB:* anti-TBM antibodies can occur in drug-induced TIN (see 🕮 'Causes of chronic tubulointerstitial nephritis', p.169).
- *Infection:*
  - viral (including HIV), bacterial (including TB), protozoal (including malaria);
  - acute pyelonephritis.
- *Autoimmune disease:*
  - complicating glomerulonephritides, e.g. systemic lupus erythematous (SLE), IgAN;
  - *vasculitis:* including Kawasaki disease (feature of the disease or complication of IVIG therapy);
  - Henloch –Schönlein purpura (HSP);
  - juvenile idiopathic arthritis;
  - sarcoidosis.
- *Malignancy:* lymphoma.

Causes of chronic tubulointerstitial nephritis

- Idiopathic.
- Autoimmune: see 'Autoimmune disease' bullet in 🕮 'Causes of acute tubulointerstitial nephritis', p.168; may also be associated with antitubular basement membrane antibodies (anti-TBM), sometimes in association with autoimmune enteropathy.
- Urate nephropathy: must examine renal biopsy under polarized light to detect urate crystals.
- Associated with cholestatic liver disease.
- Obstructive uropathy.
- Balkan nephropathy (non-inflammatory, chronic, slowly progressive interstitial kidney disease, frequently associated with urinary tract tumours in endemic areas).

Laboratory features

Blood

- Elevated urea and creatinine.
- Hyperchloraemic metabolic acidosis (normal anion gap).
- Hyperkalaemia (with severe uraemia); but hypokalaemia (due to renal wasting) is more commonly observed.
- Hypernatraemia.
- Hyperphosphataemia (with severe uraemia) or more typically hypophosphataemia.
- Hyperuricaemia.
- Elevated IgE.
- Eosinophilia.
- Anaemia.
- Leucocytosis, high ESR, high CRP.

Urine

- Proteinuria (tubular): e.g. retinal-binding protein (RBP):creat ratio.
- Microscopic haematuria.
- Elevated white cells in urine (eosinophiluria = >1% of all white cells in urine). Request Wright stain of urine to assess eosinophiluria.
- Isosthenuria.
- Glycosuria.
- Phosphaturia and decreased tubular re-uptake of P (TRP): measure plasma and urine P simultaneously for this test.
- Bicarbonaturia.
- Aminoaciduria.

Renal ultrasound

- Increased renal size with loss of cortico-medullary differentiation (acute TIN).
- Small kidneys in chronic TIN.

Ophthalmology review

- In view of the recognized association of TIN with uveitis (TINU), screening for uveitis is recommended for all children with biopsy-proven TIN, since uveitis may be asymptomatic until blindness occurs.
- This assessment is also important to screen for tapetoretinal degeneration, which can be observed as part of nephronophthisis.
- Since uveitis can develop after TIN, patients should be told to watch out for symptoms of light sensitivity or visual problems and ophthalmological follow-up for at least a year after presentation with TIN is recommended, even if no uveitis was present.

Renal biopsy

- Light microscopy in both acute and chronic TIN shows the presence of diffuse or patchy interstitial deposits consisting of activated lymphocytes, macrophages, plasma cells, polymorphonuclear leukocytes, and eosinophils in acute TIN and mainly lymphocytes in chronic TIN.
- Cortical tubules separated by expanded interstitium (oedema) in acute TIN.
- Interstitial fibrosis in chronic TIN.
- Tubular epithelial injury varying from degeneration to necrosis and focal loss of tubular basement membrane may be present in acute TIN. Tubular lumen may contain casts made of desquamated cells or blood.
- In chronic TIN, tubular atrophy and thickening of the tubular basement membrane are prominent.
- If high intratubular pressure is present (as in obstruction), renal tubules may be dilated.
- Generally kidneys are enlarged in acute TIN; contracted and scarred in chronic TIN.
- Blood vessels and glomeruli are normal in acute TIN and in the early stages of chronic TIN, but periglomerular fibrosis and sclerosis develop during the course of chronic TIN.
- Immunofluorescence studies are generally negative for immune deposits.

Treatment of tubulointerstitial nephritis

- Supportive.
- Remove offending agent if possible (stop all drugs, ask about herbal medicines).
- Idiopathic TIN(U) typically responds well to treatment with corticosteroids. Typical dose—2mg/kg prednisolone (max 60mg) daily for 4–8 weeks, tapering over subsequent months once symptoms have improved.
  - if no clinical improvement with corticosteroids over 1–2 months, this should be discontinued and the differential diagnosis (especially nephronophthisis) revisited;
  - immunosuppressants such as azathioprine (2mg/kg/od) have been used for TINU in combination with corticosteroids. Associated uveitis may require topical steroids +/– systemic therapy: seek ophthalmology advice.

Prognosis of tubulointerstitial nephritis

- The degree of interstitial fibrosis has been correlated with outcome in some studies, but in other studies there is no such relationship. These conflicting observations may be due to patchy nature of the disease and the random sampling on renal biopsy.
- Prognosis is usually excellent for acute TIN.
- The prognosis for chronic TIN is guarded, with risk of progression to CKD 5.

Further reading

Jahnukainen T, Ala-Houhala M, Karikoski R, et al. (2011). Clinical outcome and occurrence of uveitis in children with idiopathic tubulointerstitial nephritis. *Pediatr Nephrol* **26**:291–9.

This page intentionally left blank

Chapter 8

Renal calculi and nephrocalcinosis

Renal calculi

Causes

Types of calculi

- *Metabolic:* supersaturation of stone forming ions (Ca, phosphate, urate, oxalate, cystine) due to increased excretion, increased urinary concentration, alteration of ion solubility due to urine pH or lack of normally-produced inhibitors of crystal formation.
- *Infective:* may occur in association with structural abnormalities of the urinary tract that cause stasis of urine; or with urease producing organisms (particularly *Proteus* spp.) that break down urea to ammonia, resulting in an alkaline urine, and the precipitation of Ca phosphate and magnesium ammonium phosphate (struvite).
- Both metabolic and infective.

There is often a family history. Occasionally, children are given 'over the counter' vitamin and Ca supplements (see Table 8.1).

Presentation

- Urinary tract infection (UTI).
- Ureteric colic.
- Macroscopic or microscopic haematuria.
- Chronic ill health and anaemia.
- Dysuria or strangury (slow and painful micturition) due to bladder calculi, which may occur in augmented bladders. They are also relatively common in the Middle East, principally due to diet.
- Incidental finding causing no symptoms.

Metabolic disorders that cause calculi

- *Hypercalciuria:* the commonest cause.
  - idiopathic;
  - hypercalcaemic;
  - associated with renal tubular dysfunction (e.g. renal tubular acidosis, Dent's disease, Bartter syndrome, familial hypomagnesaemia with hypercacluria).
- *Hyperoxaluria:* see 🕮 'Specific causes of calculi: investigation and management', p.178.
  - primary types 1 or 2 (the association of nephrocalcinosis and renal/ureteric calculi is highly suggestive of primary hyperoxaluria type 1).
  - enteric;
  - idiopathic.
- Cystinuria.
- *Disorders of purine metabolism:*
  - uric acid over-production, e.g. following chemotherapy;
  - familial juvenile hyperuricaemic nephropathy;
  - xanthinuria;
  - 2,8-dihydroxyadenine calculi.

Table 8.1 Drugs/intoxications associated with stones

Drugs/intoxications associated with stones	Mechanism
Ampicillin	Precipitation of drug/metabolite in the urine
Triamterene	
Sulfonamides	
Aciclovir	
Indinavir, lopinavir	
Ceftriaxone	
Furosemide	Increase in urinary Ca
Calcium	
Vitamin D	
Glucocorticoids	
Ethylene glycol	Metabolization to oxalate
Vitamin C	
Probenecid	Increasing urinary uric acid
Acetazolamide and other carbanhydrase inhibitors	Altering urinary pH

Environmental factors facilitating stone formation

- Low fluid intake.
- Diet (high salt, high protein).

Investigations for all causes of calculi

Radiological

- *US:* acoustic shadowing is present.
- *CT (helical, non-contrast):* best modality to detect stones, but high radiation burden.
- *Abdominal X-ray (purine stones are radiolucent):* include the penis if history and findings are suggestive of bladder outlet obstruction.
- *Dimercaptosuccinic acid* (DMSA) in order to determine the extent of renal involvement.
- *Intravenous pyelogram* (IVP) prior to intervention in order to define the position of the stones within the calyces if lithotripsy is planned. Mostly replaced by CT.

Stone/gravel

This is the most important tool to discover the underlying cause—the composition of the stone will give strong clues towards the aetiology (e.g. oxalate vs. struvite). Any fragment excreted should be sent for analysis and patients may need to strain their urine for a while to enhance the chances of stone recovery.

Urine

If no underlying disorder is known and if no stone analysis was done, a full metabolic screen should be performed; otherwise only selected tests will be necessary. The metabolic screen is best done via a 24-h urine collection. A concurrent urine creatinine should always be performed to assess completeness of collection (expected creatinine excretion 0.1–0.2 mmol/kg/day, depending on muscle mass).

- Microscopy and culture (spot sample) to assess for infective aetiology.
- Calcium (normal <0.1 mmol/kg/day): for incomplete collections, the Ca/creatinine ratio can be used, which varies with age (Table 8.2).
- Oxalate (normal 100-460 μmol/d/1.73m^2). Alternatively the oxalate/creatinine ratio can be used for a spot urine (Table 8.3).
- Urate (normal <0.1 mmol/kg/d)/creatinine ratio (Table 8.4).
- Urine amino acids (assess for cystinuria—increased excretion of dibasic amino acids).
- Citrate normal range for all ages: Female—0.11–0.55 mmol/mmol crea. Male—0.04–0.33 mmol/mmol crea.

Table 8.2 Age-dependent normal values for urine Ca:Cr ratios

Age (years)	Ca:Cr (mmol/mmol)	Ca:Cr (mg/mg)
<1	0.09–2.2	0.03–0.78
1–2	0.07–1.5	0.02–0.53
2–3	0.06–1.4	0.02–0.50
3–5	0.05–1.1	0.02–0.39
5–7	0.04–0.8	0.01–0.28
7–17	0.04–0.7	0.01–0.25

Table 8.3 Age-dependent normal values for urine oxalate:Cr ratios

Age (years)	Oxalate:Cr (μmol/mmol)
<1 year	4–98
1–4 years	4–72
5–12 years	3–71
>12 years	1–38

Table 8.4 Age-dependent normal values for urine urate:Cr ratios

Age	Urate:Cr (mmol/mmol)
0–7 days	0.12–1.96
7 days–2 years	0.42–1.53
2–6 years	0.57–1.35
6–10 years	0.39–0.85
10–18 years	0.15–0.67

Blood

- Urea & electrolytes (U&Es), creatinine.
- Calcium, magnesium, phosphate, albumin.
- TCO_2 (or bicarbonate).
- Urate.
- Parathyroid hormone (PTH).

Treatment for all causes of calculi

Medical

- High fluid intake.
- Low salt intake (to reduce urinary Ca).
- Potassium supplements (see next bullet point) reduce urinary Ca excretion.
- Citrate forms soluble complexes with Ca. Give 1mmol/kg/day of potassium citrate.
- Bicarbonate supplementation increases urinary citrate.
- Treatment of specific metabolic disorder.

Surgical

- Small stones that are not causing any symptoms may not require intervention as they may pass spontaneously.
- Percutaneous nephrostomy may be needed as a temporary measure if there is obstruction to urine flow.
- *Extracorporeal shock wave lithotripsy:* not good for cystine stones, which are hard. Fragments may cause obstruction. Careful consideration needs to be given to its use with severe nephrocalcinosis, which may predispose to damage to the renal parenchyma.
- *Percutaneous nephrolithotomy:* particularly for very large stones.
- *Ureteroscopy:* for ureteric stones.
- *Open surgery:* particularly if associated with pelviuteric junction (PUJ) obstruction.

Further reading

Cochat P, Pichault V, Bacchetta J, et al. (2010). Nephrolithiasis related to inborn metabolic diseases. *Pediat. Nephrol.* **25**: 415–24.

Specific causes of calculi: investigation and management

Hyperoxaluria

Primary hyperoxalurias are inherited metabolic disorders with increased production of oxalate (see 📖 'Renal calculi', p.174 and 'Nephrocalcinosis', p.180).

Secondary hyperoxaluria is due to increased enteric oxalate absorption. Oxalate absorption is increased if there is not enough Ca to bind oxalate in the gut. It occurs in:

- Malabsorption syndromes (e.g. inflammatory bowel disease, cystic fibrosis).
- Low Ca diets.

Specific treatment

A low oxalate diet, oral citrate, and bicarbonate.

Cystinuria

- Autosomal recessive disorder causing around 10% of childhood stones.
- Typical hexagonal crystals are present in the urine sediment.
- Diagnosis is by measurement of urinary cystine >100 mcmol/mmol creatinine (mornal <30).
- Can be caused by two genes, *SLC3A1* (rBAT, encoding a necessary transporter subunit) and *SCL7A9* (encoding the actual transporter).
- Categorized in 3 types:
  - *A:* recessive mutations in SLC3A1 (45% of patients, heterozygotes unaffected);
  - *B:* recessive mutations in SLC7A9 (>50%: heterozygotes have moderately increased cystine excretion);
  - *AB:* heterozygote mutations in both SLC3A1 and SLC7A9 (2%).
- Often presents with bladder stones, these should always prompt this diagnostic consideration.
- Impaired transport of cystine, ornithine, lysine, and arginine is due to a defective subunit of the proximal renal tubular transport molecule.
- Cystine is poorly soluble at a pH between 5 and 7 and stones form at concentrations over ~1 mmol/L.

Specific treatment

- At pH >8, solubility increases 3- fold so treatment is by alkalinization of the urine.
- Cleavage of the disulphide bond of cystine to cysteine by chelating agents is another approach to treatment, particularly if cystine excretion exceeds 3mmol/day. Cysteine does not form stones at physiological pH.
- Chelating agents are D-penicillamine (DP) and ∝-mercaptoproprionyl-glycine (MPG). Dose is 20–40mg/kg given in 2 doses/day. Pyridoxine supplementation is required with DP.

Purine stones

- High urate levels may occur due to rapid cell turnover in leukaemia or lymphoma, particularly after commencement of chemotherapy (see 📖 'Tumour lysis syndrome', p.406).
- Familial juvenile hyperuricaemic nephropathy is an autosomal dominant (AD) disorder characterized by abnormal tubular handling of urate, gouty arthritis and late development of chronic interstitial nephritis leading to CKD.
- Lesch–Nyhan syndrome is an autosomal recessive (AR) disorder due to deficiency of hypoxanthine-guanine phosphoribosyltransferase. Presentation may be with choreoathetosis, self-mutilation, uric acid calculi, and CKD.
- Glycogen storage disease type 1 may increase uric acid excretion.
- Xanthinuria is an AR disorder due to deficiency of xanthine oxidase, which converts xanthine to uric acid. There is, therefore, hypouricaemia and xanthine stones.
- Adenine phosphoribosyltransferase deficiency (AR disorder) results in 2,8-dihydroxyadenine rather than adenine. 2,8-dihydroxyadenine is relatively insoluble, resulting in calculi formation.

Specific treatment

Allopurinol is used alongside usual medical therapy.

Hypercalcuria

- The commonest metabolic abnormality found in paediatric stone formers.
- Calcium excretion is affected by Na intake: Ca reabsorption in the proximal tubule (PT) parallels Na reabsorption. Consequently, changes that lead to an expansion of the extracellular volume, such as a high Na intake, will decrease Na and thus Ca reabsorption in PT and vice versa. This is used for therapeutic purpose, when thiazide diuretics are prescribed (see 📖 'Specific treatment', p.179): the resulting volume depletion enhances Na, and thus Ca reabsorption in the PT.
- For causes see 📖 'Nephrocalcinosis', p.180).

Specific treatment

- Thiazide diuretics increase tubular Ca reabsorption.
- Dietary Ca restriction is only useful if the hypercalciuria is due to increased intestinal absorption of Ca, such as in idiopathic infantile hypercalcaemia. Otherwise, Ca restriction can actually be harmful—in the gut, Ca complexes with other lithogenic substances, such as oxalate, preventing their absorption. Thus, dietary Ca restriction enhances the absorption of oxalate and thus increases the risk of stones. Moreover, as plasma Ca is maintained constant by vitamin D and PTH, patients with a renal Ca leak may increase Ca mobilization from the bone if intake is restricted.

Further reading

Cochat P, Pichault V, Bacchetta J, et al. (2010). Nephrolithiasis related to inborn metabolic diseases. *Pediat. Nephrol.* **25:** 415–24.

Nephrocalcinosis

An increase in the Ca content of the cortex or medulla. It can be due to any cause of hypercalcaemia, hypercalciuria, or hyperoxaluria. US shows a typical pattern of hyperechoic medullae, which can be graded according to severity. If there is doubt, a single-slice computed tomography (CT) scan can confirm that this is due to Ca.

Causes of medullary nephrocalcinosis

- Adrenal insufficiency.
- Bartter's syndrome.
- Cushing syndrome.
- Dent's disease.
- Distal renal tubular acidosis (RTA).
- Familial hypomagnesaemia-hypercalciuria.
- Hyperparathyroidism.
- Hyper- and hypothyroidism.
- Idiopathic hypercalcuria.
- Immobilization.
- Lesch–Nyhan syndrome.
- Lowe's syndrome.
- Malignant neoplasm.
- *Medications:* frusemide, dexamethasone, thus very commonly seen in premature babies.
- Medullary sponge kidney.
- *Nutrition:* parenteral vitamins A, C, or D intoxication.
- Prematurity.
- Tyrosinaemia.
- Sarcoidosis and other granulomatous diseases.
- William's syndrome.
- Wilson's disease.
- Enamel–renal syndrome (amelogenesis imperfecta and nephrocalcinosis; inherited dental disorder associated with hypocalciuria, yet patients develop nephrocalcinosis).

Causes of cortical nephrocalcinosis

Cortical necrosis.

Causes of both cortical and medullary nephrocalcinosis

- Hyperoxaluria:
  - primary types 1,2 or 3 (the association of nephrocalcinosis and renal/ureteric calculi is highly suggestive of primary hyperoxaluria type 1);
  - enteric;
  - idiopathic.
- Hypercalcaemia.
- Lipoid (fat) necrosis.
- Sickle cell disease.

Chapter 9

Glomerular disease

Overview of inherited glomerular diseases

Basic principles

The glomerular barrier consists of three layers:

- *Endothelium:* formed by vascular endothelial cells. No inherited kidney disease has yet been localized to this layer.
- *Basement membrane:* defects in this layer are typically associated with haematuria (e.g. Alport syndrome), except Pierson syndrome, a form of congenital nephrotic syndrome due to mutations in the basement membrane protein laminin-β2.
- *Epithelium:* formed by podocytes. Inherited diseases affecting podocyte function result in proteinuria/nephrotic syndrome (see 📖 'Nephrotic syndromes: definitions', p.192).

Nephrotic syndrome

- Genetic studies have identified several genes implicated in the pathogenesis of rare inherited forms of steroid-resistant nephrotic syndrome (SRNS; see Table 9.1).
- Nephrotic syndrome can occur in the context of mitochondrial cytopathies and these should always be considered as they are potentially treatable, e.g. in cases of co-enzyme Q10 (ubiquinone) deficiencies.
- There are currently no genes known to cause steroid-sensitive nephrotic syndrome (SSNS).

The identification of a genetic cause should prompt careful consideration of further management:

- A biopsy is unlikely to provide important information.
- There are no data to support the use of aggressive immunosuppression such as high-dose methylprednisolone or cyclophosphamide.
- There are some reports of patients with SRNS due to mutations in NPHS2 and WT1, who experienced partial remission with ciclosporin, which may be due to effects beyond immunosuppression.
- Use of an immunosuppressive drug in patients with WT1 mutations must be carefully considered, however, as it would likely increase the already high cancer risk.

Mutations in NPHS1 are the most common cause of congenital nephrotic syndrome and the clinical course is usually severe. However, there appears to be some genotype–phenotype correlation: a few patients homozygous for the R1160X mutation have the initial severe presentation, but then spontaneous improvement and even resolution of the nephrotic syndrome later in childhood. This needs to be considered before embarking on aggressive therapy in infancy, such as nephrectomies. Moreover, some cases of childhood-onset SRNS are due to NPHS1 mutations and these patients have at least one 'milder' mutation with presumed residual nephrin function.

Table 9.1 Known disease genes in steroid-resistant nephrotic syndrome

Gene	OMIM	Inheritance	Onset	Disease
NPHS1	602716	AR	Infant/child	SRNS only
NPHS2	604766	AR	Infant to adult	SRNS only
PLCE1	608414	AR	Infant	SRNS only
CD2AP	604241	AD (AR)	Adult/(infant)	SRNS only
TRPC6	603652	AD	Adult/child	SRNS only
ACTN4	604638	AD	Adult	SRNS only
INF2	610982	AD	Adult/child	SRNS only
Syndromes				
WT1	607102	AD	Infant	Denys–Drash, Frasier
Lamb2	150325	AR	Infant	Pierson syndrome
ITGB4	147557	AR	Infant	Epidermolysis bullosa
LMX1B	602575	AD	Child to adult	Nail-patella syndrome
SCARB2	602257	AR	Child	Action-myoclonus renal failure syndrome
SMARCAL1	606622	AR	Child	Schimke immuno-osseous dysplasia
Mitochondrial cytopathies				
COQ2	609825	AR	Infant	COQ10 deficiency
PDSS2	610564	AR	Infant	COQ10 deficiency
MTTL1	590050	mitochondrial	Infant	MELAS

AR, autosomal recessive; AD, autosomal dominant; NS, nephrotic syndrome; MELAS, myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.

Alport syndrome and thin basement membrane nephropathy

Definition

- *Alport syndrome (AS):* multi-system disorder including nephritis, sensorineural deafness and often eye abnormalities. The severity of the individual symptoms is variable. Classical Alport syndrome is due to mutations in type IV collagen (see Table 9.2). In addition, mutations in MYH9 can cause familial nephritis indistinguishable from AS by biopsy, as well as sensorineural deafness (see Table 9.2).
- Thin basement membrane nephropathy (TBMN) is a histological diagnosis, defined by attenuation of the basement membrane. It is often equated with benign familial haematuria, but there is overlap with AS: some patients with AS initially have a picture of TBMN.

Genetics

- AS and TBMN are due to structural abnormalities of the basement membrane:
  - a key component of the basement membrane is type IV collagen, which in itself is a composite of so-called α-chains;
  - there are 6 genes encoding these α-chains, *COL4A1* to *COL4A6*, and chains come together to form a trimer, which then assembles with another trimer to form type IV collagen;
  - these chains have specific assembly partners, as well as tissue and developmental expression;
  - mutations in three of these chains are associated with AS (Table 9.2).

Table 9.2 Genes underlying Alport-like syndromes

Gene	OMIM	Inheritance	Extrarenal symptoms
COL4A5	301050	X	Eye, ear
COL4A3	120070	AR (AD)	Eye, ear
COL4A4	120131	AR (AD)	Eye, ear
MYH9	160775	AD	Ear, platelets, leukocytes

X, X-linked; AR, autosomal recessive; AD, autosomal dominant; heterozygous mutations in *COL4A3, 4*, and *5* can be associated with both Alport syndrome and TBMN

- The most common underlying gene (~80%) is *COL4A5*, which is located on the X-chromosome and thus affected patients are almost exclusively males.
- Heterozygous mutations in the *COL4A* genes are associated with TBMN. However, in about 5% of patients with AS, only heterozygous mutations in *COL4A3* or *COL4A4* are found (autosomal dominant AS). Females, carrying *COL4A5* mutations can have a broad spectrum of severity, presumably due to random X-inactivation.

- In about half of all cases with TBMN, the genetic aetiology is unclear.
- A different form of hereditary nephritis and deafness is due to mutations in *MYH9*, a gene encoding a myosin heavy chain and is further associated with macrothrombocytes (Epstein syndrome) and leukocyte inclusions (Fechtner syndrome).

Histology

- Light microscopic changes are only seen in advanced stages of AS. The characteristic changes are seen on electron microscopy—thickening of the capillary wall and lamellation of the basement membrane ('basket weave pattern') in AS and only thinning if the basement membrane in TBMN. However, there is no clear distinction between these two entities.
- The diagnostic role of the biopsy is increasingly being replaced by genetic testing.

Clinical features

- A child presenting with haematuria, particularly if intermittent macroscopic and persistent microscopic, should be assessed for symptoms associated with AS, particular if there is a family history:
  - sensorineural deafness (with *COL4A* mutations);
  - eye abnormalities (with *COL4A* mutations): anterior lenticonus, dot-fleck retinopathy, recurrent corneal erosions;
  - leiomyomatosis (appears to be restricted to individuals carrying an X-chromosomal deletion involving *COL4A5* and *COL4A6*);
  - giant platelets and leukocyte inclusions (with *MYH9* mutations).
- 100% of males and approximately 95% of female carriers of *COL4A5* mutations have microscopic haematuria, often with intermittent gross haematuria.
- Proteinuria in AS is a later feature, typically occurring in late childhood.
- CKD 5 occurs in virtually all males with X-linked AS, typically between 20 and 60 years of age.
- There is emerging clinical data suggesting that angiotensin-converting enzyme inhibitor (ACEI) may delay the progression of CKD in AS, even before the onset of proteinuria.
- TBMN has an excellent prognosis, but patients should be monitored every 1–2 years for proteinuria and hypertension because of the overlap with AS, unless there is a clear family history of benign haematuria.
- Transplantation in AS can be complicated by anti-glomerular basement membrane (GBM) disease, caused by antibodies against type 4 collagen, typically the $\alpha 3$ chain. This causes a crescentic nephritis, which is associated with a very high incidence of graft loss. Prognosis is very poor for recurrence after a second transplant.
- Live donors from the family must have AS excluded. Female carriers of a *COL4A5* mutation (e.g. the mother of a patient) should be discouraged from donation if they have any symptoms.

Acute nephritis

Definition

Acute glomerular injury with:

- Acute kidney injury (AKI) (oliguria, uraemia, elevated creatinine).
- Hypertension (salt and water retention).
- Haematuria (microscopic or macroscopic) with red cell casts on microscopy.
- Peripheral and/or pulmonary oedema.
- Proteinuria, which can reach nephrotic range (>200mg/mmol; 'nephritic-nephrotic syndrome').

Causes in children

- Post-infectious: usually post-Streptococcal, accounting for approximately 80% of cases.
- Other post-infectious causes include:
  - bacteria: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Escherichia coli*, *Yersinia*, *Campylobacter*, *Salmonella*, *Syphilis*, TB;
  - viruses: Epstein–Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), parvovirus B19, hepatitis B and C;
  - Rickettsiae: Rocky Mountain spotted fever, Q fever (*Coxiella burnetii*), *Legionella pneumophila*;
  - fungi: Candida, Aspergillus, histoplasmosis, cryptococcoccus, Pneumocystis carinii, Nocardia;
  - parasites: malaria, schistosomiasis, leishmaniasis, trypanosomiasis, filariasis, trichinosis, echinococcus, toxoplasmosis.
- Henoch–Schönlein purpura (HSP).
- IgA nephropathy (IgAN).
- Systemic lupus erythematous (SLE).
- AS.
- Membranoproliferative glomerulonephritis (MPGN, primary types 1, 2, and 3; secondary types have many causes, see 📖 'Membranoproliferative (mesangiocapillary) glomerulonephritis (MPGN)', p.218).
- Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome, renal limited vasculitis).
- Ventriculo-atrial shunt nephritis.
- Haemolytic uraemic syndrome.
- Thrombotic thrombocytopenic purpura.

Post-Streptococcal glomerulonephritis

This is the commonest cause of acute GN:

- May follow 1–2 weeks after infection of the throat or up to 6 weeks after infection of the skin (typically in the child with eczema) with group A ß haemolytic *Streptococcus*.
- Presentation is with haematuria (urine tea or coca cola coloured), proteinuria, oliguria, hypertension, and oedema.
- Antistreptolysin O titre (ASOT) is raised in the majority of pharyngeal infections, but may not be post-skin infection. It may be positive in up to 20% of healthy children.

- The streptozyme assay detects antibodies to other Streptococcal antigens (e.g. DNAse B), improving the chance of detecting infection.
- C3 is low and deposits can be seen in the glomeruli as 'humps' in the subepithelium (see 📖 'Renal histology', p.23). This leads to an inflammatory infiltrate ('exudative' GN).
- C4 is usually normal (unlike MPGN, SLE, endocarditis, shunt nephritis).
- C3 returns to normal by 6–8 weeks so if a low level persists, consider MPGN or SLE.
- Treatment with penicillin is necessary to prevent spread to contacts, but will not help the nephritis.
- Hypertension may respond to furosemide as it is principally due to fluid overload.
- Severity and duration of nephritis is variable, but mostly resolves within 2–3 weeks.
- Renal biopsy is indicated in the acute phase if there is nephrotic syndrome and a rapidly rising creatinine, which is suggestive of a rapidly progressive (crescentic) glomerulonephritis (RPGN—see Fig. 11.2).
- Renal biopsy, for prognosis and to ensure that the diagnosis is correct, is indicated with:
  - abnormal creatinine at 6 weeks;
  - low C3 >3 months;
  - proteinuria >6 months.
- Microscopic haematuria alone may persist for 1–2 years and is of no long-term relevance.
- Immunosuppression is only to be considered if there is crescentic nephritis on biopsy, although its use is controversial. There are well-documented descriptions of patients with very significant crescentic changes who have been treated conservatively (without corticosteroids) with good renal outcome; there are also reports of patients who have been given pulsed IV methylprednisolone in this situation.
- Based on the overall excellent prognosis of children with post-infectious GN (less than 1% will develop CKD), the vast majority will be treated with supportive care, and antibiotics to eradicate the offending organism where appropriate. Occasionally, where there is RPGN and severe crescentic change, steroids may have a role, but such cases should be considered individually.

Causes of hypocomplementaemic nephritis

- Post-infectious GN.
- SLE.
- Shunt nephritis:
  - nephritis due to infection of vascular access and ventriculo-atrial shunts and infective endocarditis;
  - commonest bacterium is *Staphylococcus*;
  - may all present with fever, arthralgia, hepatosplenomegaly, lethargy;
  - C3 and C4 are usually low;
  - treat with antibiotics and removal of the infected shunt or line.
- Other immune complex mediated nephritis, e.g. hepatitis B, C.
- primary and secondary MPGN.

Investigation of acute nephritis

Generic investigations for all patients

- Full blood count (FBC), blood film, erythrocyte sedimentation rate (ESR).
- C-reactive protein.
- Blood culture.
- Urea & electrolytes (U&Es), creatinine, albumin, bicarbonate, liver function tests (LFTs), calcium, phosphate, glucose.
- ASOT, anti-DNase B.
- Urine culture, microscopy for casts, Ua:Ucr.
- Throat swab.
- C3/C4, antinuclear antibodies (ANA), double-stranded DNA (ds-DNA), ANCA.
- Renal US.

Specific tests for certain patients

- Blood film if suspect haemolytic uraemic syndrome (HUS).
- Direct Coomb's test and T-antigen (if available) if suspect pneumococcal HUS.
- Stool culture and *Escherichia coli* 0157:H7 serology if suspect diarrhoea positive HUS.
- Blood cultures if suspect sepsis.
- Chest X-ray (CXR) if suspect pulmonary oedema or sepsis.
- C3 nephritic factor (C3NeF) if C3 low and MPGN suspected.
- Immunoglobins (particularly IgA), if post-infectious causes excluded and IgA nephropathy could be a cause (see 📖 'Ig A nephropathy', p.190).
- Anti-GBM antibodies if haemoptysis and Goodpasture's syndrome (GS) suspected:
  - GS is one of the 'pulmonary-renal syndromes' characterized by pulmonary haemorrhage (usually alveolar haemorrhage) and crescentic nephritis; other causes of pulmonary-renal syndromes include: SLE, Wegener's granulomatosis, microscopic polyangiitis, and HSP;
  - GS is an autoimmune immune complex mediated disease—GN and pulmonary haemorrhage occur with little or no involvement of other systems;
  - the presence of anti-GBM antibodies in peripheral blood confirms the diagnosis;
  - treatment comprises early corticosteroids, cyclophosphamide, and plasmapheresis;
  - the prognosis appears to be good if treatment is started early, although published data relating to long-term outcomes in children are lacking;
  - anti-GBM antibodies can also form following renal transplantation for Alport's syndrome, and are a cause of graft loss in this context (see 📖 'Alport syndrome and thin basement membrane nephropathy', p.184).

Indications for renal biopsy

- *RPGN:* defined as glomerular disease (proteinuria, haematuria, and red cell casts) accompanied by rapid loss of renal function with rising creatinine over days to weeks.
- C3 depressed for longer than 3 months since in post-infectious stage the C3 will have returned to normal by then.
- Nephrotic range proteinuria (spot Ua:Ucr of >200mg/mmol).
- Immunology suggestive of cause other than post-infectious, e.g. SLE, ANCA-associated vasculitis.
- Family history of glomerular disease.
- Age under 4 years and consider if older than 15 years.
- Recurrent nephritis.
- Moderate proteinuria persisting >6 months.
- Microscopic haematuria persisting >12 months (optional).
- Extra-renal symptoms.

Management

See also 🕮 Chapter 17, p.377.

The management outlined here concentrates on the emergency renal management of the child with acute nephritic syndrome, but does not describe the detailed management of the individual and varied causes of nephritis. The reader is referred to the individual chapters for these entities.

- As discussed (🕮 'Indications for renal biopsy', p.189), the indication for immunosuppression in management of post-infectious GN is controversial, and usually not warranted.
- Since the prognosis of children with post-infectious GN is usually excellent (less than 1% will develop CKD) the vast majority will be treated with supportive care and antibiotics to eradicate the offending organism where appropriate. In rare case, where there is RPGN and severe crescentic change, steroids may have a role, but such cases should be considered individually.

General management

- *Assess fluid balance:* is the patient oliguric because of pre-renal failure or established renal failure?
- *Fluid restriction:* insensible fluid losses (200–400mL/m^2/24h; or 20–40mL/kg/24h) plus previous hour's urine output, plus any additional losses (vomitus, diarrhoea). Usually given as 0.45% saline/2.5% dextrose; 0.45% saline/5–10% dextrose in infants.
- *Consider diuretic challenge if severe fluid overload:* furosemide 2–5mg/kg IV by slow (10min for bigger doses) infusion/injection, usually give 2mg/kg first then if no response after 1–2h give 4mg/kg. Provide calories (reduces catabolism and improves acidosis and hyperkalaemia)—this can be achieved in acutely unwell children by giving enteral Maxijul® (10–20%) via nasogastric tube.
- For management of acute kidney injury see 🕮 Chapter 17, p.377.

IgA nephropathy

Background

- Male preponderance, mainly presenting in second and third decades.
- Adult studies show differing geographical incidences. IgAN accounts for 18–40% of all GN in Japan, France, Italy and Australia, but only 2–10 % of GN in the UK and USA. This is likely due to a combination of environmental and genetic factors, and to differing rates of pickup related to screening for haematuria in different countries.
- Familial in around 10% of cases.

Aetiology

- IgA is produced in two forms, IgA1 and IgA2, and is secreted from mucosal surfaces, with very little reaching the systemic circulation.
- Increased levels of circulating IgA immune complexes have been documented in some patients but do not correlate with disease activity.
- It has been proposed that there is a defect in glycosylation of the IgA1 hinge region leading to mesangial deposition.

Clinical and laboratory findings

Five main presentations:

- Macroscopic haematuria.
- Asymptomatic microscopic haematuria with or without proteinuria.
- Acute nephritis (haematuria, proteinuria, renal insufficiency, hypertension).
- Nephrotic syndrome (<10%).
- Mixed nephritic/nephrotic state.

The commonest mode of presentation is macroscopic haematuria following an upper respiratory tract infection. The time interval between infection and haematuria is 1–2 days, in contrast to post-infectious GN where the time interval is typically 10–14 days post-pharyngitis or 3–6 weeks following skin infection.

- Diagnosis can only be made by renal biopsy—deposits of IgA are found in the glomerular mesangium. C3 is also usually present and IgG and IgM are seen in approximately 50% of biopsies.
- <20% of children will have elevated serum IgA.
- Serum complement levels are normal.

Up to 20% of pediatric patients progress eventually to CKD 5, but the rate of progression is usually very slow. Features associated with CKD progression are:

- Proteinuria.
- Hypertension.
- Decreased glomerular filtration rate (GFR) at biopsy.
- Biopsy findings of glomerulosclerosis, fibrous crescents, tubular atrophy and interstitial fibrosis.

Treatment

Depends on the severity of the disease and its likelihood of progression.

- *Microscopic haematuria and/or recurrent macroscopic haematuria:* are not of clinical significance. Tonsillectomy has been recommended by some investigators. Some reports suggest that vitamin E may be effective.
- *Proteinuria:* Patients may benefit from ACEIs or angiotensin receptor blockers (ARBs).
- *Children with adverse risk factors:* first line of treatment is for hypertension and proteinuria. Immunosuppressive regimens have been used, including steroids, azathioprine, cyclophosphamide, mycophenylate mofenil (MMF) and mizoribine. Although some studies suggest a benefit, there is no conclusive evidence, so most would recommend starting with anti-hypertensives and anti-proteinurics, moving on to immunosuppression if there is no benefit.
  Example IV methylprednisolone 600mg/m^2/day for 3 consecutive days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5mg/kg on alternate days for 6 months.
- *Crescentic nephritis:* see 🕮 'The standard treatment of childhood vasculitis', p.282.

Omega 3 fatty acids may be of benefit. Available preparations are:

- Omacor®, 1 capsule (1g) contains 460mg eicosapentaenoic acid (EPA) and 380mg docosahexaenoic acid (DHA).
- Maxepa® 1 capsule (1g) and liquid (1.1mL) contains 170mg EPA and 115mg DHA.

Omacor® is more highly processed to minimize contamination with heavy metals, and contains no vitamin A or D. It should thus be the preferred treatment option. Children unable to swallow the capsules can be given the liquid preparation of Maxepa®.

Doses

- 920mg EPA and 760mg DHA bd for children >50kg.
- 460mg EPA and 380mg DHA bd for children <50kg.

In practice children may not adhere to therapy with fish oil; side effects include halitosis.

Further reading

Hogg RJ (2010). Idiopathic immunoglobulin A nephropathy in children and adolescents. *Pediatr Nephrol* **25**: 823–9.

Nephrotic syndromes: definitions

- *Nephrotic syndrome*: triad of heavy proteinuria (protein/creatinine ratio >200mg/mmol), hypoalbuminaemia (<25g/L) and generalized oedema.
- *Congenital nephrotic syndrome (CNS)*: presentation of nephrotic syndrome during the first 3 months of life (often present before or at birth).
- *Infantile nephrotic syndrome*: presentation of nephrotic syndrome between 3 and 12 months of age.
- *Idiopathic nephrotic syndrome*: nephrotic syndrome in the absence of other glomerular pathology mediated by systemic disease (e.g. SLE), structural glomerular changes (e.g. Alport syndrome), vasculitis, immune complex deposition (e.g. post-infectious GN).
- *Urinary remission*: urine Albustix® negative or trace for three consecutive days.
- *Relapse*: urine Albustix® ++ or more for three consecutive days.
- *Frequently relapsing nephrotic syndrome:* children who relapse two or more times in the first 6 months after presentation or four or more times within any 12-month period.
- *Steroid-dependent nephrotic syndrome*: children who relapse whilst on steroid therapy or within 14 days of discontinuation of steroid therapy. These children will almost invariably also have frequently relapsing nephrotic syndrome, though the additional presence of steroid dependency marks the presence of a more significant tendency to relapse.
- *Steroid-resistant nephrotic syndrome*: failure of proteinuria to resolve following at least 28 days of prednisone at a dose of 60mg/m^2/day. There is some variety in this definition:
  - the International Study of Kidney Disease in Children (ISKDC) defined non-responders as those children who failed to achieve remission following 8 weeks of the standard ISKDC oral prednisone regimen (60mg/m^2 daily for 4 weeks followed by 40mg/m^2 on alternate days for 4 weeks);
  - other reported definitions include failure to achieve remission following 4 weeks of daily oral prednisone at a dose of 60mg/m^2 and 4 weeks of daily oral prednisone at a dose of 60mg/m^2 followed by three doses of IV methylprednisolone.
- The terms *minimal change disease/nephrotic syndrome* and *steroid sensitive/responsive nephrotic syndrome* are often used interchangeably. This is not strictly correct, as a small proportion of cases of minimal change disease will not exhibit steroid sensitivity and around 20% of cases of focal segmental glomerulosclerosis (FSGS) will respond to steroids.

Congenital and infantile nephrotic syndrome

Definitions

- *Congenital nephrotic syndrome (CNS)*: children presenting with nephrotic syndrome during the first 3 months of life (often present before or at birth).
- *Infantile nephrotic syndrome:* refers to those presenting between 3 and 12 months of age.

In contrast to idiopathic nephrotic syndrome presenting in older childhood, the outcome of CNS is generally poor with the majority developing CKD 5, although the age at which this develops can be variable. An exception is when CNS is of infectious aetiology; here proteinuria generally resolves with the treatment of the causative infection.

Primary causes

- Finnish-type CNS.
- Diffuse mesangial sclerosis.
- Focal segmental glomerulosclerosis.
- Minimal change disease.
- Membranous nephropathy.

Secondary causes

- Infectious:
  - Congenital CMV;
  - Hepatitis B and C;
  - Human immune deficiency virus (HIV);
  - Congenital syphilis;
  - Congential toxoplasmosis;
  - Congenital Rubella;
  - Malaria.
- Syndrome-associated:
  - Denys–Drash syndrome (DDS);
  - Nail-patella syndrome;
  - Lowe syndrome;
  - Galloway–Mowatt syndrome;
  - Frasier syndrome;
  - Pierson syndrome (microria and CNS).
- Other:
  - SLE;
  - HUS;
  - Nephroblastoma;
  - Drug reaction;
  - Mercury toxicity.

Finnish type congenital nephrotic syndrome

- Commonest form of CNS.
- Inherited in an autosomal recessive manner.

- Occurs worldwide, although increased incidence in Finland (1 in 8200 births).
- Almost always results in the development of CKD 5.
- Most patients of Finnish origin have mutations in the *NPHS1* gene (Finn major and Finn minor mutations), which encodes the protein nephrin.
- Over 70 different mutations have been detected.
- The disease also occurs, though more rarely, in other races.
- *NPHS2* mutations have been reported in addition to *NPHS1*.

Clinical features

- Raised alpha fetoprotein (AFP) in pregnancy in blood and amniotic fluid (secondary to proteinuria).
- Low birth weight.
- Large placenta (>25% mass of newborn).
- Widely spaced fontanelles and cranial sutures.
- Postural elbow and knee deformities.
- Heavy proteinuria with rapidly developing hypoalbuminaemia and oedema.

Renal biopsy

- Light microscopy may be normal in early life.
- Cardinal histological feature is tubular dilatation resulting in diffuse microcystic change (cysts of 0.1–0.5mm).
- Progressive glomerular sclerosis and interstitial fibrosis develop by 6–12 months of age.

Diffuse mesangial sclerosis

- Characteristic histological changes on light microscopy include thickened GBM and increased mesangial matrix without hypercellularity. Capillary loops are usually collapsed and dilated Bowman's spaces are seen.
- Early onset hypertension and CKD develop.
- May be isolated renal disease or as part of DDS:
  - an association of male pseudohermaphroditism, early onset nephrotic syndrome secondary to diffuse mesangial sclerosis and mutations in the *WT-1* gene, which predispose the child to an increased risk of Wilms' tumour and 'prophylactic' nephrectomy should be considered;
  - all phenotypic females presenting with diffuse mesangial sclerosis (DMS) should undergo chromosomal analysis to ensure that they are not male with severe pseudohermaphroditism;
  - DMS does not appear to recur post-transplantation;
  - DMS has also been associated with mutations in *PLCE1*.

Frasier syndrome

- Characterized by the association of male pseudohermaphroditism (so as for DDS, chromosomes should be checked in the phenotypic female) and progressive glomerular disease.
- Proteinuria generally presents between 2 and 6 years of age, although may occur in infancy.
- There is a slow decline in renal function to CKD 5, which is unresponsive to therapy.

- Similar to DDS, Frasier is associated with *WT-1* gene mutations, although the mutations are different and result in normal protein production; as such the risk of Wilms' tumour does not appear to be increased.
- The characteristic renal histological changes are those of FSGS.
- There is a high risk of gonadoblastoma so consideration should be given to the removal of the abnormal gonads.

Minimal change disease and focal segmental glomerulosclerosis

- Minimal change disease rarely presents in infancy and may be steroid responsive as in cases presenting during later childhood.
- Both familial and sporadic forms of idiopathic FSGS may present during infancy. A number of these cases will be associated with *NPHS2* mutations.

Management of Finnish-type congenital nephrotic syndrome

The aim of treatment is to enable growth and development. Various approaches are possible:

Reduction of urinary protein losses

Nephrectomy:

- The Helsinki group advocate insertion of a peritoneal dialysis (PD) catheter at around 4 months of age, with bilateral nephrectomies at around 5 months of age, following confirmation of catheter function. The ultimate goal is transplantation once the child has reached approximately 9–10kg.
- Alternatively, perform early unilateral nephrectomy at around 3 months of age in conjunction with medical therapy (see 📖 'Angiotensin-converting enzyme and prostaglandin inhibitors', p.195), with the second nephrectomy and subsequent transplantation being performed at 3–4 years of age when the child is significantly larger and the incidence of early graft loss is reduced.

Angiotensin-converting enzyme and prostaglandin inhibitors

- For example, in ACEI, captopril up to 5mg/kg divided into three doses, and prostaglandin inhibitors, e.g. indometacin up to 4mg/kg divided into three doses, will reduce GFR and thus protein loss:
  - experience from Helsinki suggests that this strategy is not effective in children with Finn major mutations who have very heavy proteinuria;
  - there are many reports of the successful use of ACEI/ARBs in other patients with CNS.

Replacement of albumin

- Regular 20% albumin infusions until bilateral nephrectomy is performed (around 4g/kg daily initially, although frequency will be reduced as GFR falls). This is initially divided into 3–4 doses/day, then slowly changed so that the entire dose is given as a single daily infusion.
- A central venous catheter is usually required to provide long-term access.
- Albumin requirements are smaller in children who are receiving medical therapy or who have undergone unilateral nephrectomy.

Symptom treatment

- Intensive treatment as proposed by the Helsinki group involves a strong commitment from families and carers—patients are typically hospitalized for most of their first year of life, have multiple interventions (central venous line placements, dialysis access, nephrectomies) and a high risk of infectious complications.
- Despite the intensive treatment mortality is high (10–20%).
- If the child does not receive a transplant early on, dialysis access can become a serious problem due to infectious complications and thrombosis of central veins.
- Some families feel that such intensive treatment is too great a burden for the child and the family, especially, if there are siblings needing care and attention.
- An alternative for these families is symptomatic treatment—the child is cared for at home to receive medical treatment with admission to hospital only for acute illnesses.
- There are no published mortality figures for symptomatic treatment in nephrotic syndrome, but it is probably much higher than with intensive treatment.

Transplantation

Transplantation following bilateral nephrectomies remains the definitive treatment:

- The child needs to be of adequate size to undergo transplantation (9–10kg).
- The high risk of thrombosis in this condition mandates that the major abdominal vessels are assessed pre-transplant (ultrasound or magnetic resonance angiography (MRA)) to ensure patency.
- Following transplantation recurrent nephrotic syndrome may occur in up to 25% of children with Finnish type CNS:
  - related to the production of anti-nephrin antibodies following exposure to normal nephrin in the transplanted kidney;
  - more common in those with the Finn major *NPHS1* mutation;
  - may respond to treatment with cyclophosphamide +/– plasma exchange;
  - up to 50% graft loss may occur due to recurrence.

Other important factors

- Diuretics, e.g. furosemide to reduce oedema (alone and or in conjunction with albumin infusions).
- If there is neonatal hyperbilirubinaemia the risk of kernicterus is increased due to the low plasma albumin. More aggressive therapy is therefore warranted.
- Close attention to nutrition and growth—high calorie and high protein diet (4mg/kg/day).
- Children with heavy proteinuria are hypercoagulable and at significant increased risk of arterial and venous thrombosis:
  - prevent by the use of formal anticoagulation with warfarin;
  - warfarin must be stopped 4 days before surgery and antithrombin given;
  - aspirin may have a role.

- Infection is a significant problem in the nephrotic child:
  - low threshold for empiric aggressive treatment of suspected infection;
  - the Helsinki group have found that the use of prophylactic antibiotics and IV immunoglobulin do not reduce the infection risk, and have abandoned this practice.
- Thyroxine is necessary from birth.
- Administration of childhood vaccines:
  - should be completed prior to transplantation;
  - efficacy is increased if performed after nephrectomy when the child is no longer heavily proteinuric, but it is preferable to progress normally through immunizations (checking for an antibody response) so that transplantation is not delayed.

Management of other forms of congenital nephrotic syndrome

- Where nephrotic syndrome has occurred secondary to congenital infection, then treatment of the specific infection, where possible, leads to resolution of proteinuria.
- Children presenting with minimal change disease or FSGS in infancy should be treated with steroids in an identical manner to older children.
- There are no specific therapies for DMS or the FSGS associated with Frasier syndrome.
- Children with DDS should undergo bilateral nephrectomy to avoid the development of Wilms' tumour, and children with Frasier syndrome should be considered for bilateral orchidectomy to reduce the risk of the development of gonadoblastoma.

Transient neonatal nephrosis

- Induced by circulating maternal antibodies that cross the placenta.
- Caused by maternal deficiency of a podocyte antigen, which is present in the developing fetus.
- A history of transient neonatal nephrosis in successive pregnancies is suggestive.

Steroid sensitive nephrotic syndrome: presenting episode

Introduction

Nephrotic syndrome describes the clinical triad of:

- Heavy proteinuria (protein/creatinine ratio >200mg/mmol).
- Hypoalbuminaemia (<25g/L).
- Generalized oedema.

Around 80% of cases have minimal change disease (MCD) on histological examination (no abnormality seen at light microscopy (LM) level).

Key points about minimal change disease

- Commonest glomerular disorder of childhood.
- Median age of presentation 2–3 years.
- More common in boys (2:1).
- Incidence 2–4/100,000 child population in the UK.
- Six times more common in the UK Asian population.
- Over 90% will respond to corticosteroid therapy.
- Over 70% of those who respond to corticosteroids will subsequently develop a relapsing course.
- 80% will enter long-term remission during childhood; the remainder will continue to have relapses into adulthood, although the frequency of these tends to decrease and a substantial proportion will enter long-term remission in early adult life.
- Steroid responsiveness is the most important factor in determining prognosis: where the presenting episode of nephrotic syndrome responds to steroids and the disease remains steroid sensitive, there is an extremely low risk of developing CKD. This very rare outcome is linked to the development of late (secondary) steroid resistance.
- Published series report mortality rates of 1–7.2% (sepsis and vascular thrombosis), though the current rate is thought to be much lower.
- A small number (<1–2%) of cases are familial.

The remaining 20% of cases have a variety of histological diagnoses, including FSGS and membranoproliferative (mesangiocapillary) glomerulonephritis (MPGN/MCGN). These pathologies tend to present in older children and the majority of cases do not respond to oral steroid therapy alone. Their prognosis is correspondingly poorer. The likelihood of an alternative histological diagnosis increases with increasing age of the child as illustrated in Fig. 9.1.

Investigations at first presentation

- Urine dipstick analysis (protein, blood).
- Early morning Up:Uc or Ua:Uc to quantify proteinuria.
- Urine microscopy and culture as there is an increased rate of UTI.
- Urinary Na (see 🕮 Chapter 18, 'Management: fluid and electrolytes', p.418), particularly if there are symptoms and signs of intravascular depletion (hypo- or hypertension, abdominal pain, decreased capillary refill, increased toe-core temperature gap by >2°C).
- Plasma albumin, creatinine, and electrolytes.

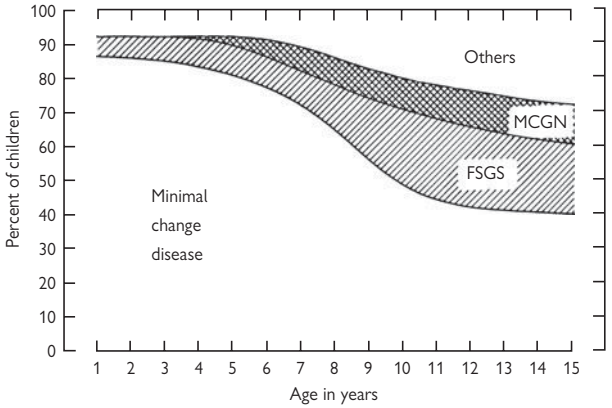

Fig. 9.1 'Smoothed' representation of the distribution of major causes of childhood nephrotic syndrome by age. Based on pooled data from the ISKDC and patients investigated at Guy's Hospital, London (n = 566).

- FBC.
- Complement C3 and C4 levels.
- Varicella zoster serology to determine immune status.
- Hepatitis B and C serology.
- ASOT, anti-DNAase B, and lupus antibody serology (ANA, extractable nuclear antibodies (ENA), and ds-DNA) in older children, and those with atypical presenting features (see 📖 'Renal biopsy requirements', p.199).

Renal biopsy requirements

- As over 90% of children with MCD and an additional 20% of those with FSGS will respond to steroid therapy; the large majority of children are given an empirical course of such therapy without a renal biopsy.
- Children with atypical presenting features should be referred for specialist paediatric nephrology opinion, including, in most cases, a renal biopsy. These features include:
  - Age <12 months or >12 years;
  - Persistent hypertension or impaired renal function;
  - Gross haematuria;
  - Low plasma C3;
  - Hepatitis B or C positive.

Up to 25% of children with MCD may have microscopic haematuria or transient hypertension (which may be paradoxically related to intravascular volume depletion resulting in peripheral vasoconstriction) at presentation: neither should be a contraindication to empirical steroid therapy, but hypertension should prompt the clinician to consider intravascular depletion.

Management

The large majority of children with a presenting episode of nephrotic syndrome should be admitted to hospital to ensure adequate monitoring of their clinical status, and to allow the parents to undergo an education programme about the disease and its treatment, and the importance and practicalities of home urine monitoring.

Steroids

- *ISKDC regimen:* prednisolone (60mg/m^2 (maximum dose 80mg) once daily for 28 days, followed by 40mg/m^2 (maximum dose 60mg) given on alternate days for a further 28 days.
- Meta-analysis has shown a longer duration of steroid therapy (12 weeks or more) at first presentation to reduce the subsequent rate of relapse. Standard regimens in Germany and France incorporate 12 weeks or more of initial steroid therapy. Some studies have shown that the reduction in rate of relapse with intensified steroid treatment is only observed in younger children and is associated with an increased rate of adverse effects. A UK randomized controlled trial is currently further investigating these issues 🔗 http://www.bctu.bham.ac.uk/prednos
- A response to steroid therapy is indicated by the resolution of proteinuria, urinary remission being defined as three consecutive days of zero or trace proteinuria on Albustix®.
- Of those children who respond to steroids, approximately 80% will have entered remission within 14 days using this protocol.
- A clinical diagnosis of steroid sensitive nephrotic syndrome is used in children who enter remission during the first 28 days of therapy and such steroid sensitivity is associated with a good long-term prognosis in the very large majority.
- Conversely, those who fail to respond to steroid treatment require a renal biopsy to obtain a histological diagnosis to guide further therapy and have a poorer long-term prognosis. This is discussed elsewhere (see 📖 'Steroid-resistant nephrotic syndrome', p.210).

Infection

- Children are at increased risk of bacterial infection because of urinary losses of immunoglobulins and complement components.
- Peritonitis, septicaemia, and cellulitis are significant causes of morbidity and mortality.
- *Streptococcus pneumoniae* and Gram negative organisms are the commonest infective pathogens. Broad spectrum antibiotics should be used in suspected infection until the results of bacterial cultures are available.
- Prophylactic penicillin V 12.5mg/kg bd (against *Streptococcus pneumoniae*) should be given whilst the child is oedematous and there should be a low threshold for investigating and adequately treating infection should this be suspected.

- Children with no previous exposure to varicella zoster virus (VZV) should receive Varicella zoster (VZ) immunoglobulin if exposed to the virus.
- If varicella infection occurs, this should be treated aggressively with IV acyclovir if the child is immunosuppressed at the time.
- Children should be immunized against VZV when off immunosuppressive therapy.
- Children with nephrotic syndrome should receive all of the routine childhood immunizations. Live vaccines should only be administered when the child is off all immunosuppressive therapy, remembering that immunosuppression may continue for some time after drug discontinuation; a period of 3 months following discontinuation of steroids or ciclosporin and 6 months following discontinuation of cyclophosphamide is likely to be safe. Children should additionally receive pneumococcal vaccine and an annual influenza/H1N1 vaccine.

Fluid balance, hypovolaemia, and blood pressure

- Children with only mild peripheral oedema do not require fluid restriction, although where significant oedema is present, mild fluid restriction (70% of maintenance requirements) will help prevent further oedema formation. A low salt diet is crucial to control thirst and minimize oedema.
- Where this measure alone is unsuccessful, the subsequent addition of diuretics (furosemide and spironolactone) will help resolve oedema.
- It must be stressed that the child with overt nephrotic syndrome who is being fluid restricted with or without additional diuretic therapy should be kept under very close review to ensure that hypovolaemia (intravascular volume depletion) is avoided.
- The oedematous nephrotic child is at significant risk of hypovolaemia. This increases the risk of pre-renal failure, thrombosis, and other complications.
- Generalized abdominal pain is a common presenting feature of hypovolaemia. Risk factors for the development of hypovolaemia include diarrhoea, vomiting, sepsis, and the injudicious use of diuretic therapy.
- The child should undergo regular clinical assessment of peripheral temperature and capillary refill time, JVP, BP, pulse, and weight during the presenting illness.

Clinical assessment of the intravascular compartment of the oedematous child is difficult:

- *Hypovolaemia:*
  - increased capillary refill time (>3°C core peripheral temperature gap);
  - JVP not raised (may be difficult to see in the oedematous child);
  - normal BP usually, although the BP may be increased due to the vasoconstriction.

- *Hypervolaemia:*
  - normal capillary refill time;
  - BP normal or high;
  - JVP high.
- Urinary sodium must be interpreted with caution in nephrotic states as urinary sodium levels may be low (<10mmol/L) in both hypo and hypervolaemia:
  - in hypovolaemia, levels will be low due to avid salt and water retention by the kidney;
  - in hypervolaemia, however, levels may be low too. This is because there is good evidence for primary sodium retention in nephrotic syndrome due to pathologically filtered proteases, such as plasmin, activating the sodium channel epithelial sodium channel (ENaC);
  - moreover, nephrotic syndrome is associated with a deficiency in certain proteases, such as corin, needed to activate natriuretic peptides.
- Urinary sodium levels are uninterpretable when loop diuretics, e.g. furosemide have been administered.
- An elevated haemoglobin level is suggestive of haemoconcentration, i.e. hypovolaemia.
- Hypovolaemia should be promptly corrected with the use of 10–20ml/kg of 4.5% albumin solution or another colloid and diuretics should be stopped or avoided in this setting.
- Crystalloids, such as 0.9% saline should not be used due to the high salt load resulting in worsening oedema.
- The increased risk of vascular thrombosis in this condition is further enhanced by hypovolaemia.
- 20% (salt poor) albumin should be used in combination with diuretics to relieve symptomatic oedema refractory to diuretics and fluid restriction, particularly where skin is compromised:
  - up to1g/kg (up to 5mL/kg 20% albumin) should be infused slowly over 2–4h with furosemide 1–2mg/kg being given IV during the second half of the infusion;
  - there are a number of reports of intravascular volume overload with the development of pulmonary oedema associated with such therapy. The dose of albumin should not exceed 1g/kg and the infusion time should not be shorter than 4h to avoid this occurring—strict monitoring of vital signs should take place, and this should be given during routine hours where possible;
  - there is no indication to use 20% albumin to correct hypoalbuminaemia alone.
- Remission is heralded by an increased urine output: this should prompt relaxation of any fluid restriction and diuretic therapy should be stopped.
- BP may be temporarily elevated in the acute phase, particularly if there is clinical hypovolaemia—persistent hypertension is an unusual feature of MCD and should prompt discussion with a nephrologist as alternative diagnoses should be considered.

Diet

- No evidence exists to support any alteration in dietary protein content.
- A no-added salt diet is a sensible measure in view of generalized oedema (salt and water overload) and the use of steroids.

Hypercoagulability

- Children will become hypercoagulable whilst nephrotic (see 📖 'Steroid-resistant nephrotic syndrome', p.210 for further details):
  - given that the presenting episode is generally short-lived, systemic anticoagulation is not indicated;
  - bed-rest during the presenting episode may increase the risk of venous thrombosis; this practice has therefore been abandoned.

Information

- Families should be provided with written information about nephrotic syndrome:
  - a variety of written and on-line information is available in a variety of European and other languages e.g. 🖱 http://www.kidney.org.uk or 🖱 http://www.gosh.nhs.uk/gosh_families/information_sheets;
  - families need to be taught urinalysis to allow home urine testing and the early detection of relapses prior to the development of oedema.
- Many centres provide families with a diary in which to enter results of urine tests and medications given. This should be brought to all clinic appointments.

Steroid sensitive nephrotic syndrome: relapsing disease

Over 70% of children with steroid sensitive nephrotic syndrome (SSNS) will develop disease relapses necessitating further courses of immunosuppressive therapy and around 50% will develop frequently relapsing or steroid dependent disease. A suggested outline to the management of relapsing disease is shown in Fig. 9.2.

Management of initial relapses

- Relapses (three consecutive days of 2+ or more proteinuria on Albustix®), are generally detected through routine home urinalysis, allowing the early commencement of treatment at home prior to the development of generalized oedema with its attendant complications.
- It is not uncommon to have such a degree of proteinuria during an intercurrent infection, and there may be a case for observing the child for a little longer prior to commencing steroids provided that there is no evidence of peripheral oedema.
- A recent RCT performed in children receiving alternate day steroid therapy has shown that changing from alternate day to daily steroid therapy at the same dose (e.g. 10mg alternate days to 10mg daily) at the time of a febrile illness significantly reduces the rate of subsequent relapse. Further similar studies are warranted.
- *ISKDC relapse regimen:* prednisolone 60mg/m^2 (maximum dose 80mg) daily until urinary remission (3 days of zero or trace proteinuria), followed by 40mg/m^2 (maximum dose 60mg) on alternate days for 14 doses over a 28-day period.
- Intensification of the relapse regimen has not been shown to be of long-term clinical benefit.

Infrequently relapsing disease

- Children experiencing less than three relapses per year can be managed with repeated courses of the ISKDC relapse regimen, see 📖 'Management of initial relapses', p.204.
- Should side-effects of steroids develop, then alternative therapy should be considered.

Management of frequently relapsing and steroid-dependent SSNS

See 📖 'Nephrotic syndromes: definitions', p.192).

- At least 50% of patients will follow a frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) course.
- More than two relapses in the first 6 months after initial steroid response predicts for high risk of FRNS or SDNS.
- These patients should generally be managed by or in consultation with a paediatric nephrologist.
- See Fig. 9.2 for treatment algorithm.

Relapse

Prednisolone 60mg/m^2/24h (maximum 80mg/kg/24h) until remission followed by prednisolone 40mg/m^2/48h for 28 days

↓

Frequent relapses

Following treatment of relapse, commence maintenance prednisolone 0.1–0.5mg/kg/48h for 6 months, then taper

↓

Relapses on prednisolone

Consider addition of levamisole 2.5mg/kg/alternate days for 6–12 months and/or the use of a marginally higher alternate daily steroid dose if this is well tolerated. Thereafter prednisolone can be tapered and levamisole could be continued for 2–3 years.

↓

Relapses on levamisole/prednisolone or prednisolone alone at >0.5mg/kg/48h or the presence of steroid side effects

Cyclophosphamide 3mg/kg/day for 8 weeks

↓

Post-cyclophosphamide relapses

As 1 and 2 above

↓

Relapse on prednisolone >0.5mg/kg/alternate day

Ciclosporin 6mg/kg/day in two doses for 1–3 years +/– alternate day steroids

↓

Relapse on ciclospsorin +/– alternate day prednisolone

↓

Individual treatment

Options include the use of a higher alternate day prednisolone dose in conjunction with ciclosporin, a second course of cyclophosphamide or a course of chlorambucil or the use of tacrolimus, mycophenolate mofetil, or rituximab.

Fig. 9.2 Treatment of relapsing SSNS.

Notes on drug therapy

Long-term low dose maintenance steroid therapy

- The side-effects of steroids are reduced by the use of the drug in a single alternate daily morning dose at a level that prevents disease relapse.
- Prednisolone dose is gradually tapered, aiming for an initial dose in the range 0.1–0.5mg/kg on alternate days.
- After around 6 months of therapy the dose should be tapered so that the smallest dose possible that maintains remission is used.
- Those with steroid dependency generally require higher maintenance doses that those with frequently relapsing disease.
- Where relapses occur, the subsequent maintenance dose should be targeted just above the dose at which relapse occurred.
- Close monitoring for the well-known adverse effects of steroids is mandatory:
  - posterior subcapsular cataract occurs in 10–38% of children;

  - normal growth has been reported in pre-pubertal children on long term alternate day steroids, though appears to fall off after 10 years of age, particularly in boys, in whom there is also some evidence of pubertal delay;
  - bone mineral density may be reduced by prolonged steroid therapy.
- If the child cannot be maintained in stable remission on an acceptably low dose of alternate day steroids, particularly where steroid side-effects have developed, the use of alternative agents should be considered.

Levamisole

- Immunomodulatory properties not completely understood—appears to stimulate T-cell function.
- Dose 2.5mg/kg on alternate days. This allows the tapering and possible discontinuation of concomitant alternate-day steroids.
- Efficacy of levamisole is dependent upon its continuous administration.
- If remission can be successfully maintained, levamisole is typically continued for a period of up to 2–3 years, though many children have safely received in excess of 5 years of treatment.
- Very low incidence of adverse-effects: neutropenia (reversible upon drug discontinuation), gastrointestinal upset and rash.
- Blood count should be performed regularly (6–8 weekly initially then up to 4 monthly after 6 months) and if neutropenia develops, drug should be discontinued.

Alkylating agents: cyclophosphamide and chlorambucil

- The alkylating agents bind to purine bases and impair normal DNA transcription.
- Cyclophosphamide is the most widely used agent, though chlorambucil may also be used.
- Both agents have been shown to induce a period of steroid-free remission, 2-year relapse free rates following cyclophosphamide therapy being approximately 70% in FRNS and 25% in SDNS.
- Cyclophosphamide dose is 3mg/kg for a total of 8 weeks (total dose 168mg/kg).
- No benefit has been shown by prolongation of this course to 12 weeks and shorter courses have been shown to be less efficacious.
- Chlorambucil dose 0.2mg/kg daily for 8 weeks.
- Prednisolone 40mg/m^2 for the first 4 weeks of therapy, then 20mg/m^2 for the second 4 weeks with subsequent taper so that steroids are discontinued shortly after completion of cyclophosphamide/chlorambucil.
- Short-term adverse effects and their incidence (where available) are shown in Table 9.3.
- Blood count should be performed weekly throughout therapy and if neutropenia develops, the dose should be halved (neutrophil count 1.0–1.5 × 10^9/L) or discontinued (<1x10^9/L): cyclophosphamide or chlorambucil can be recommenced at a lower dose once the neutrophil count recovers, with prolongation of the course so that a total dose of 168mg/kg (cyclophosphamide) or 11.2mg/kg (chlorambucil) is administered.
- Prompt medical advice should be sought if febrile illness develops.

Table 9.3 Short-term adverse effects of cyclophosphamide and their incidence

Short-term adverse effects Incidence and 95% CI	**Infection 1% (0.1–3.5%)**
Myelosuppression	leucopenia (<5000/mm3) 32% (26–39%)
leucopenia necessitating drug cessation 9% (6–15%)	thrombocytopenia 2% (0.4–5.7%)
Nausea (ondansetron responsive) and gastrointestinal upset	Temporary alopecia 14% (9–19%)
Haemorrhagic cystitis 4% (1.5–7.5%).	

Data from Hodson EM, Willis NS, and Craig JC. (2008). Non-corticosteroid treatment for nephrotic syndrome in children. *Cochrane Database System. Rev.* Issue 1.

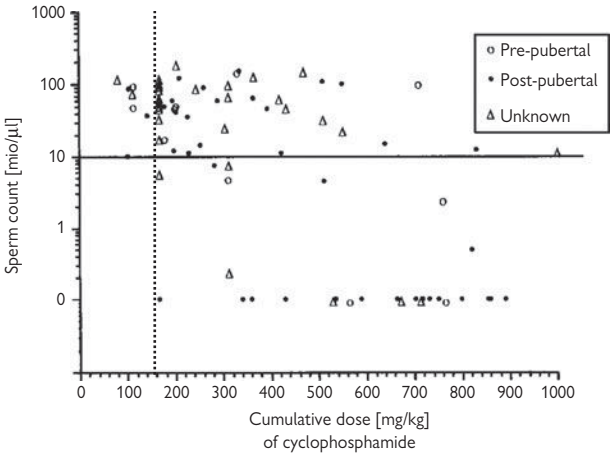

Fig. 9.3 Relationship between cumulative dose of cyclophosphamide and sperm count in adult life.

Vertical dotted line indicates total dose administered during an eight week course of cyclophosphamide at 3mg/kg/day. Modified from Latta k, von Schnakenburg C, Ehrich JH (2001). A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatr. Nephrol.* **16:** 271–82. With kind permission from Springer Science + Business Media.

- *Longer-term adverse-effects:*
  - risk of azoospermia with multiple courses of therapy, though a single 8-week course is not thought to have a significant effect. Fig. 9.3 shows the relationship between the cumulative dose of cyclophosphamide received and the sperm count;
  - the ovary is more resistant than the testis to effects of these drugs;
  - the theoretical risk of malignancy remains unproven.
- Up to three courses of therapy may be administered during childhood, although if the drug has not worked the first time it is unlikely to work during a second course. Long-term adverse effect risk increases with the cumulative dose administered.

Ciclosporin

- Modifies T-cell function, inhibiting IL-2 production by activated T-cells.
- Response to ciclosporin depends upon its continuous administration, with a high rate of relapse occurring upon its discontinuation.
- Often used after a previous course of cyclophosphamide, although it may be used earlier in preference to cyclophosphamide, for example, in peri-pubertal boys possibly at increased risk of cyclophosphamide-related gonadal toxicity.
- Dose 6mg/kg/day divided into two doses.
- Whilst monitoring of trough ciclosporin levels is recommended to ensure compliance and to avoid toxicity, there is no evidence to support any specific target range. Most centres will aim for trough blood levels of 50–125micrograms/L, but successful management with lower doses or once daily dosing has been reported. Thus, if remission is stably maintained on ciclosporin, dosage may be tapered to minimize adverse effects.
- Alternate-day steroid therapy may be tapered or discontinued.
- Short-term adverse-effects with incidence and 95% CI where available are shown in Table 9.4.

Table 9.4 Short-term adverse-effects of ciclosporin and their incidence

Short-term adverse-effects	Incidence and 95% CI
Hypertrichosis	34% (22–48%)
Gingival overgrowth (improved by better dental hygiene +/– azithromycin)	28% (33–60%)
Hypertension	4% (0.4–12%)
Tremor	
Rise in plasma creatinine mediated by glomerular vasoconstriction*	9% (3–20%)

*Where this occurs the dose of ciclosporin should be reduced.

Longer-term adverse effects:

- *Chronic ciclosporin-induced nephrotoxicity:*
  - check for microalbuminuria (Ua:Ucr) on an early morning urine at each clinic visit;

- it is widely accepted practice to perform a renal biopsy after 18–24 months of therapy or if there is microalbuminuria;
- ciclosporin may be continued beyond two years in those patients with no histological evidence of chronic nephrotoxicity, though an annual biopsy is recommended.

Other agents

- Tacrolimus has a similar mode of action to ciclosporin and there are an increasing number of reports of efficacy in patients who relapse on ciclosporin therapy. Dose 0.2–0.3mg/kg/day in two doses. Target levels are unknown but most will aim for 5–8micrograms/L. Two small case series have reported that tacrolimus is probably as effective as ciclosporin.
- Mycophenolate mofetil (MMF) has similarly been shown to be efficacious. Dose 600–1200mg/m2/day divided into two doses. Blood count monitoring is mandatory as with renal transplant patients:
  - the initial open label study of MMF in SSNS reported 24 of 32 patients (predominantly SSNS without SDNS) remained in remission during the 6-month study period;
  - one single RCT compared this agent with ciclosporin. Only 24 patients were recruited so no significant difference in the rate of relapse was detected, however, there was a tendency for more MMF treated patients to relapse.
- The successful use of mizoribine, an imidazole nucleotide originally isolated from *Eupenicillium brefeldianum* has been reported in Japanese patients. Whilst the published data suggests that this agent may hold promise, it is not available in the large majority of Western nations.
- *Rituximab:*
  - the use of this chimeric anti-CD20 monoclonal antibody has risen significantly in recent years (there are many single case reports and small series of the use of this agent in SDNS);
  - a dose of 375mg/m2 has been used, though the number of doses required (1–4) remains uncertain (French registry data suggest that one or two doses are probably as effective as four);
  - fatal pulmonary interstitial fibrosis has been reported, as has progressive multifocal leucoencephalopathy in patients with lupus;
  - there are no data regarding the long-term safety of this agent in children with renal disease;
  - appropriately powered randomized controlled trials of the use of agent are urgently required; a small number are currently ongoing in the UK and elsewhere.

Secondary steroid resistance

- Up to 4.5% of SSNS patients will develop a steroid-resistant pattern of illness in a subsequent relapse.
- The majority will regain corticosteroid responsiveness following further immunosuppressive therapy.
- A small percentage will remain corticosteroid resistant and develop progressive CKD leading to dialysis and transplantation. These children almost invariably have FSGS on histological examination.

Steroid-resistant nephrotic syndrome

Primary steroid-resistant nephrotic syndrome

Introduction

- *Definition:* failure of proteinuria to resolve following at least 28 days of prednisolone at a dose of 60mg/m^2/day.
- There is some heterogeneity in this definition; the ISKDC defined non-responders as those children who failed to achieve remission following 8 weeks of the standard ISKDC oral prednisone regimen (60mg/m^2 daily for 4 weeks followed by 40mg/m^2 on alternate days for 4 weeks). Other reported definitions include failure to achieve remission following 4 weeks of daily oral prednisone at a dose of 60mg/m^2 and 4 weeks of daily oral prednisone at a dose of 60mg/m^2 followed by three doses of IV methylprednisolone.
- Renal biopsy is mandatory, as histology may alter the treatment options—rarer causes of nephrotic syndrome require a very different approach to therapy.
- Genetic analysis should also be mandatory, as the results may influence the intensity of subsequent treatment. Identification of an underlying genetic cause may obviate the need for renal biopsy, for instance in other affected family members. Furthermore, identification of mutations allows appropriate genetic counselling to take place.

Differential diagnosis

- FSGS.
- Minimal change disease (MCD).
- Diffuse mesangial proliferation.
- Membranoproliferative (mesangiocapillary) GN (see 📖 p.218).
- Membranous nephropathy (see 📖 p.222).
- Causes of congenital and infantile nephrotic syndrome (see 📖 'Congenital and infantile nephrotic syndrome', p.193): these are strictly steroid resistant, though therapeutic trials of steroids are very rarely given.

Histology

- The majority of cases of SRNS will have either FSGS, diffuse mesangial proliferation or MCD on biopsy:
  - these different histologies were previously thought to represent a disease continuum, with highly steroid sensitive MCD at one end and malignant non-steroid responsive FSGS at the other, with diffuse mesangial proliferation in the middle, able to resolve or progress to FSGS;
  - there is increasing evidence that significant differences exist and that children with a histological diagnosis of FSGS have a wide range of diseases which may or may not have a genetic aetiology (see 📖 'Genetics', p.211).
- Repeat biopsy may show apparent 'transformation' from MCD to FSGS. It is unclear whether such FSGS lesions were missed on the initial biopsy or have developed with time.
- US data suggest that the incidence of FSGS is rising, particularly in the African American population.

Genetics

(See 🕮 'Overview of genetics and renal abnormalities in inherited syndromes', p.336.)

- Mutations in the *NPHS2* (podocin) gene are the most commonly detected genetic mutations in SRNS.
- *NPHS2* mutations were first reported in cases of familial SRNS: almost 50 mutations in the *NPHS2* gene have now been identified.
- *NPHS2* mutations may be responsible for up to 30% of cases of sporadic SRNS and up to 55% of familial cases, but experience in the UK suggests a lower incidence (<10% of sporadic cases).
- The identification of NPHS2 mutations in sporadic cases of SRNS may be important for therapeutic decisions and genetic counselling:
  - one study reports no cases of complete remission amongst 29 patients treated with ciclosporin or cyclophosphamide—some patients may experience partial remission with ciclosporin; other drugs are probably best avoided due to lack of evidence of efficacy;
  - recurrence of nephrotic syndrome post-transplantation in patients with FSGS associated with NPHS2 mutations is rare.

Outcomes

- The outcome of SRNS that does not subsequently respond to immunosuppressive therapy is poor, with a high rate of development of CKD 5.
- With MCD histology, steroid resistance at 8 weeks results in CKD 5 in around 20%; the majority of cases will subsequently develop FSGS on biopsy.
- Of children with FSGS who failed to respond to steroids, 34% progressed to CKD 5 during a follow-up of 11 years.
- There appears to be a subset of patients with a malignant form of FSGS with very rapid progression to CKD 5. The ISKDC data show this group to progress to CKD 5 within 2–2.5 years in comparison with the non-malignant group who have a 50% actuarial renal survival at 7–18 years from onset.

Treatment

- The evidence to support most therapies for SRNS is poor and few large high quality trials have been performed.
- Of those trials that have been performed, none have stratified patients according to genetic mutation status (e.g. NPHS2); this is important given the significant influence of the presence of such mutations on response to therapy.
- Therapy is justified on the grounds that patients with persistent nephrotic syndrome have a poor prognosis with a high rate of decline into CKD 5.
- It should, however, be remembered that continued heavy immunosuppressive therapy in the persistently non-responsive patient may place the patient at significant risk of morbidity or mortality and in these instances abandoning 'active' treatment should be considered. Given the increasing evidence that children with *NPHS2* and other genetic mutations respond poorly to immunosuppressive therapy, the abandonment of further such therapy should be considered at an earlier point that in those with no known mutation.

Immunosuppression

Corticosteroids

- Many recommend the use of IV methylprednisolone (500–1000mg/m^2/dose, maximum dose 1g, daily for 3–5 days) prior to the renal biopsy as this may induce remission in a small proportion:
  - this depends upon the definition used of SRNS (see 📖 p.210);
  - a response to such therapy may indicate the presence of steroid sensitive disease which has been effectively 'undertreated' because of poor absorption of oral prednisolone over the preceding 28 days or non-compliance;
  - it is unclear as to whether responders should be classified as having steroid sensitive disease, though most will treat them as such;
  - an ISKDC study showed that the use of a prolonged course of alternate day steroid therapy (40mg/m^2 for 12 months) resulted in complete resolution of proteinuria in 28%.
- The Mendoza regimen consists of IV methylprednisolone (30mg/kg) given every other day for 2 weeks, weekly for 8 weeks, every other week for 8 weeks, monthly for 9 months and then every other month for 6 months in association with oral prednisone and if required cyclophosphamide or chlorambucil:
  - this was reported to induce remission in 21/32 at over 6 years follow-up with a 5 year rate of CKD 5 of approximately 5%, compared with 40% in historical controls;
  - other studies have been unable to confirm this success rate.
- Some other small uncontrolled series have reported success with the use of IV methylprednisolone alone.

Ciclosporin

- Meta-analysis of controlled studies comparing ciclosporin with placebo or no treatment showed that this agent increased the number of children with SRNS who achieved complete remission (three studies, 49 children—RR7.66, 95% CI 1.06–55.34). Ciclosporin also significantly increased the number with complete or partial remission compared with IV cyclophosphamide (one study, 32 children—RR 3.4, 95% CI 1.12–10.28).
- Similar findings were observed in an uncontrolled French study, which showed 27/65 patients to enter complete and 4 partial remission with 6 months of ciclosporin (target trough levels 100–200ng/mL) in conjunction with prednisone (30mg/m^2 daily for 1 month then alternate days for 5 months):
  - at longer-term follow-up 17/27 remained in complete remission and 8/27 had steroid sensitive relapses;
  - of the 34 non-responders, 12 had CKD 5 by 12–63 months.
- In both the meta-analysis and the French study, no difference was detected in the response to ciclosporin between patients with MCD and FSGS.
- This evidence probably warrants ciclosporin being favoured as the agent of first choice in SRNS.

Alkylating agents

- Meta-analysis of controlled studies of children with SRNS showed no significant difference in the number of children who achieved complete remission between oral cyclophosphamide with prednisone versus prednisone alone (two studies, 91 children—RR 1.06, 95% CI 0.61–1.87), IV versus oral cyclophosphamide or IV cyclophosphamide versus oral cyclophosphamide with IV dexamethasone (one study each).
- The Mendoza regimen is described in 📖 'Corticosteroids', p.212.

Mycophenolate mofetil

- A non-randomized Brazilian study has shown the use of 6 months of MMF to be of benefit in children with SRNS. Of 34 previously treated with ciclosporin, 21% achieved complete remission and 39% partial remission and of 18 treated with MMF *de novo* (no prior ciclosporin), 28% achieved complete remission and 33% partial remission.
- A US National Institutes of Health (NIH) sponsored study comparing ciclosporin and MMF for the treatment of FSGS is currently ongoing.

Rituximab

- There are many single case reports and small series of the use of this chimeric anti-CD20 monoclonal antibody in both steroid dependent NS and SRNS.
- Appears to be less efficacious in SRNS than in steroid dependent NS.
- A dose of 375mg/m^2 has been used, though the number of doses required (1–4) remains uncertain.
- Fatal pulmonary interstitial fibrosis has been reported, as has progressive multifocal leucoencephalopathy in patients with lupus.
- Appropriately powered randomized controlled trials of the use of agent are urgently required; a small number are currently ongoing.

Other agents

There are reports of SRNS being successfully treated with both tacrolimus, sirolimus, and vincristine.

Non-immunosuppressive treatment

Antiproteinuric agents

- ACE inhibitors and or ARBs may be used to reduce proteinuria either alone or in conjunction with immunosuppressive therapy. Whilst these will not eliminate proteinuria, they may make urinary protein losses more easily manageable.
- The use of these agents may be associated with deterioration in renal function, particularly where intravascular volume depletion is present.

Antihypertensive agents

- Therapy is needed where significant hypertension is present.
- ACE inhibitors and ARBs are a logical choice in light of their additional proteinuria reducing properties.

Diuretics

- May be of benefit in children with symptomatic oedema. Furosemide is most commonly used, often in combination with spironolactone.
- Need to be used with caution, as contraction of intravascular volume may already be present, and diuretic therapy may worsen this.
- Plasma electrolytes require regular monitoring.

Anti-infection strategies

- Persistently nephrotic children are at increased risk of infection, predominantly from *Streptococcus pneumoniae* peritionitis and septicaemia.
- Despite the importance of *Streptococcus pneumoniae*, many infections are caused by other Gram positive and negative organisms and broad-spectrum antibiotic therapy should be used until culture results become available.
- Classical signs of infection may be masked in the immunosuppressed child and there should be a low threshold for treating suspected infection.
- Whilst there is no evidence to support such an approach, prophylactic penicillin V (12.5mg/kg bd) should be given to children, whilst nephrotic in conjunction with immunization with Pneumovax II®.
- Varicella is a major threat to nephrotic children and their varicella immunity status should be known:
  - seronegative children should be immunized when off immunosuppressive therapy;
  - Varicella zoster immune globulin (VZIG) or possibly aciclovir should be given following proven exposure in the non-immune child;
  - where Varicella develops, this should be treated with high dose intravenous aciclovir (see 📖 'Urinary tract infection post-transplantation', p.547).

Hyperlipidaemia

- Children with persistent heavy proteinuria may develop significant dyslipidaemia including hypercholesterolaemia.
- There are no data regarding long-term cardiovascular outcomes in this group, although most authorities would recommend dietary modification and possibly the use of a statin where cholesterol levels are very high.

Thrombosis

- The nephrotic state confers an increased risk of both arterial and venous thrombosis.
- Proven episodes should be treated with formal anticoagulation with heparin or thrombolytic therapy where thrombosis is extensive or involves major organ systems (bilateral renal vein/IVC, massive pulmonary embolism, etc.). This should be followed by 3–6 months of warfarin therapy.
- To prevent the development of thrombosis, hypovolaemia should be avoided.
- There is no consensus about the use of prophylactic low molecular weight (LMW) heparin or anti-platelet agents such as aspirin or dipyridamole in persistently nephrotic children, although there may be a reasonable case for their use in those with a prior history of thrombotic complications.

Nutrition

- The urinary albumin losses and poor appetite seen in SRNS may result in the development of malnutrition.
- Expert paediatric renal dietetic advice is required to ensure adequate intake of protein, carbohydrate and essential vitamins. Enteral feeding may prove necessary in some. Sodium is a major driver of oedema formation and should be restricted in nephrotic children.

Hypovolaemia

- This is a common complication of the nephrotic state.
- Generalized abdominal pain is a common presenting feature of hypovolaemia.

Clinical assessment of the intravascular compartment of the oedematous child is difficult:

- *Hypovolaemia:*
  - increased capillary refill time (>3°C core peripheral temperature gap);
  - JVP not raised (may be difficult to see in the oedematous child);
  - normal BP usually, although the BP may be increased due to the vasoconstriction.
- *Hypervolaemia:*
  - normal capillary refill time;
  - BP normal or high;
  - JVP high.
- Urinary sodium must be interpreted with caution in nephrotic states as urinary sodium levels may be low (<10mmol/L) in both hypo and hypervolaemia:
  - in hypovolaemia, levels will be low due to avid salt and water retention by the kidney;
  - in hypervolaemia, however, levels may be low too;
  - there is good evidence for primary Na retention in nephrotic syndrome due to pathologically filtered proteases, such as plasmin, activating the sodium channel ENaC;
  - nephrotic syndrome is associated with a deficiency in certain proteases, such as corin, needed to activate natriuretic peptides;
  - urinary sodium levels are uninterpretable when loop diuretics, e.g. furosemide have been administered;
  - an elevated haemoglobin level is suggestive of haemoconcentration, i.e. hypovolaemia.
- Hypovolaemia should be aggressively treated to avoid the development of AKI and thrombosis.

Thyroid function

- Children may need thyroxine as levels may be low due to losses of thyroid-binding globulin in the urine.

Secondary steroid resistant nephrotic syndrome

- This refers to the development of steroid resistance in a child with previously steroid sensitive disease.
- May develop in up to 5% of patients with previous SSNS.

Biopsy has been recommended prior to the commencement of further immunosuppressive therapy (generally with alkylating agents), however there is some evidence that previously steroid sensitive patients are likely to respond to further treatment, regaining their steroid sensitivity and that biopsy should be reserved for those who remain unresponsive. Where there is unresponsiveness, this is very often associated with the development of FSGS on renal biopsy.

Further reading

Hodson EM, Willis NS, Craig JC. (2010). Interventions for idiopathic steroid-resistant nephrotic syndrome in children. *Cochrane Database System Rev*, Issue 11.

Ruf RG, Lichtenberger A, Karle SM, et al. (2004). Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome. *J Am Soc Nephrol* **15**: 722–32.

This page intentionally left blank

Membranoproliferative (mesangiocapillary) glomerulonephritis (MPGN)

Introduction

- Appears to be decreasing in incidence in developed nations.
- Rare; predominantly a disease of older children and young adults.
- Most presentations during childhood are in the second decade of life.
- ♂ and ♀ equally affected.
- Type 1 MPGN is the most common form and accounts for 1.5% of children with CKD 5 in the US.
- Cause of 5% of childhood nephrotic syndrome.

Presentation

- Haematuria (macroscopic or microscopic) and proteinuria (moderate to nephrotic proportion).
- Hypertension.
- Impairment of renal function.
- Anaemia.
- Diagnosis may be made in a child previously thought on clinical grounds to have acute nephritic syndrome secondary to post infectious glomerulonephritis where the clinical situation fails to improve and the C3 fails to rise after 6–8 weeks.
- Japanese children undergo screening for haematuria resulting in a larger number of mild cases (e.g. children with isolated haematuria) being detected.
- Type II MPGN may be associated with partial lipodystrophy (loss of fat tissue, particularly affecting the face and upper body). Partial lipodystrophy generally precedes the development of MPGN.

Diagnosis

- Histological.

Classification

Primary membranoproliferative glomerulonephritis (MPGN)

- Majority of cases.
- Aetiology uncertain.

Secondary membranoproliferative glomerulonephritis

- Streptococcal and Staphylococcal infection.
- SLE.
- Hepatitis B and C.
- HIV.
- Cryoglobulinaemia type II.

Complement abnormalities

- Low C3 levels in over 50–60%, more commonly in type II MCGN.
- C1q and C4 levels (classical pathway) may also be low in some.

- C3 nephritic factor (C3 neph) may be present if the C3 is low; more commonly in type II MPGN.
  - C3 neph is an autoantibody which combines with C3 converting enzyme, preventing its degradation by factor H;
  - other variants may exist acting on different parts of the complement cascade.
- A small number of children have inherited abnormalities of the complement system:
  - usually C3 or C2 deficiency.

Pathological classification

- Type 1 (subendothelial) MPGN:
  - commonest form;
  - mesangial proliferation;
  - capillary wall thickening;
  - EM changes of subendothelial deposits in the capillary wall;
  - double contouring of basement membrane.
- Type II MPGN (dense deposit disease):
  - mesangial proliferation;
  - capillary wall thickening;
  - basement membrane thickened due to dense deposits.
- Type III MPGN:
  - subepithelial deposits;
  - considered by some to be a variant of Type I due to the many histological similarities;
  - mesangial proliferation;
  - capillary wall thickening.
- Crescents may be present in 10-15% of cases.

Treatment

The evidence to support any specific therapeutic regimen is scarce, particularly so for type II, for which there is little evidence for any effective treatment. However, most would trial a course of steroid therapy even with type II, with the reservation that, if there is no benefit, the course is stopped (see 📖 'Great Ormond Street Hospital protocol', p.220). All would agree that if crescentic changes are present on biopsy and there is evidence of a rapidly progressive glomerulonephritis, this should be treated regardless of type of MPGN (see 📖 'The standard treatment of childhood vasculitis', p.282).

Immunosuppression for types I and III

Children with mild disease (no evidence of impairment of renal function, hypertension, or nephrotic range proteinuria) can be simply observed with no active immunosuppression.

- The decision not to treat should be regularly reviewed and changed should renal function or proteinuria worsen or should hypertension develop.

The use of cyclophosphamide, azathioprine and other agents has been described though there is no good evidence to support their use.

Long-term high dose alternate day prednisolone

- The evidence-base to support such therapy is not strong, though is better than for any other agent/regimen.
- Many different alternate day regimens have been proposed.

The Cincinnati group have used high dose alternate day prednisone (2mg/kg, max 80mg) for at least 2 years with subsequent dose reduction based upon results of urinalysis, plasma albumin, C3 levels and renal biopsy changes.

- Many children have received in excess of 5 years of prednisone therapy.
- 10 year renal survival is reported to be 80% for type I and 70% for type III.

Great Ormond Street Hospital protocol

For patients with plasma albumin <25g/L or an elevated plasma creatinine:

- 6 months prednisolone 40 mg/m^2 on alternate days.
- Monitoring during therapy:
  - Urine albumin/creatinine ratio, plasma creatinine, plasma albumin at each clinic visit.
- Particular attention must be paid to the BP when starting children on steroid therapy with this disease as hypertensive encephalopathy is well described.
- At 6 months, progress can be re-assessed. An increase in plasma creatinine of > 30% or a declining plasma albumin or increasing proteinuria should be classified as treatment failure and steroids should be withdrawn.
- If there is improvement or the child is stable, a suggested regimen for steroid management after the first 6 months is as follows:
  - 6 months to 1 year: 30 mg/m^2 on alternate days (i.e. during the first year of treatment);
  - 1 to 2 years: 20 mg/m^2 on alternate days;
  - 2 to 3 years: 15 mg/m^2 on alternate days;
  - 3 to 4 years: 10 mg/m^2 on alternate days.
- At the end of each 6 month period, the child should be assessed for treatment failure as defined at the initial 6-month reassessment and if this is felt to be the case, the use of steroids should be reassessed.

Other therapies

Adult studies have failed to show a long-term benefit of dipyridamole, either alone or in combination with cyclophosphamide and warfarin.

There are small series of patients reported to have responded to either ciclosporin, tacrolimus, or mycophenolate mofetil, though randomized controlled trial data are lacking.

ACE inhibitors

May be useful in reducing proteinuria (see 🕮 Chapter 18, p.409).

Treatment of the underlying infection or other disease in secondary MCGN

Spontaneous resolution rates are high with MCGN following treatment of bacterial infection.

Outcome of primary MPGN

- Without treatment over 50% will ultimately develop CKD 5.
- Follow-up studies have shown treated patients to have a 10 year renal survival of 61–84%.
- The prognosis of Type II MPGN is poorer given the general unresponsiveness to therapy.

Factors associated with a poor outcome

- Nephrotic syndrome at presentation.
- Low GFR at 12 months post-diagnosis.
- Significant amount of chronic damage (interstitial fibrosis, tubular atrophy, glomerular sclerosis) on initial biopsy.
- Type II MPGN.

Transplantation

There is a high rate of disease recurrence of all types of MPGN post-transplantation.

Reference

Alchi, B. and Jayne, D. (2010). Membranoproliferative glomerulonephritis. *Pediatr Nephrol.* **25**:1409–18.

Membranous nephropathy

Introduction

In contrast to nephrotic syndrome affecting adults, this is a rare disorder in children, accounting for around 1–5% of cases of idiopathic childhood nephrotic syndrome.

- Estimated incidence 1 per million childhood population.
- ♂ and ♀ equally affected.
- Membranous nephropathy (MN) may additionally be diagnosed in children being investigated for asymptomatic non-nephrotic proportion proteinuria.
- There are no clear aetiological factors in the majority of children (idiopathic MN).
- Up to 43% of cases (a higher proportion than in adult MN) are secondary to:
  - infection (including hepatitis B, malaria (Plasmodium malariae) congenital and secondary syphilis, leprosy, schistosomiasis);
  - multisystem disease (including SLE (WHO Class V lupus), diabetes mellitus, inflammatory bowel disease, sarcoidosis);
  - drugs (including penicillamine, captopril, gold, NSAIDs);
  - malignancy.
- The incidence of secondary MN will be higher in areas where hepatitis B is endemic.
- A small number of cases may be familial.
- *De novo* MN may develop in the transplanted kidney in a previously unaffected individual (incidence 1–2%) and may also recur post-transplantation where CKD 5 has occurred secondary to MN (see 📖 'Recurrent and *de novo* renal disease following renal transplantation', p.541).
- Neonatal MN is very rare and occurs secondary to feto-maternal alloimmunization: mothers are deficient for a gene encoding a protein expressed in placenta and glomerulus. If the child expresses the protein on the placenta, the mother produces antibodies which cross the placenta and bind to the antigen in the glomerulus. One such recognized antigen is neutral endopeptidase. The disease improves with degeneration of the maternal antibodies over time.

Presenting clinical features

- Nephrotic syndrome (70%).
- Asymptomatic proteinuria (30%).
- Macroscopic haematuria (2%).
- Microscopic haematuria (70%).
- Hypertension (20%).
- Renal impairment at presentation (<5%).

Diagnosis

- C3 and C4 levels are normal in idiopathic MN but depressed in MN secondary to SLE or hepatitis B.
- Diagnosis is histological:

  - biopsy shows uniform thickening of the capillary wall within the glomerulus secondary to deposition of subepithelial immune aggregates (between the basement membrane and the podocyte). There is no inflammatory cell infiltrate or proliferative change (see Fig. 1.11). Advanced cases show glomerular sclerosis with tubular atrophy and interstitial fibrosis;
  - immunofluorescence shows finely granular IgG deposits. Positive staining for IgA or IgM indicates the presence of secondary disease, e.g. SLE;
  - electron microscopy shows the presence of subepithelial immune deposits.
- Where the diagnosis is made a search should be made for aetiological factors (causes of secondary MN), particularly where the C3 and C4 levels are low.

Treatment and outcome

- Where possible, causes of secondary MN (e.g. infection, malignancy) should receive specific treatment:
  - this often results in resolution of the proteinuria without the need for immunosuppressive therapy;
  - hepatitis B associated MN has a high rate of spontaneous remission, but in those with persistent disease there is a good response to interferon α.
- There is no evidence base for the management of idiopathic childhood MN.
- Recommendations have to be made on the basis of uncontrolled reports in children and controlled trials performed in adults.
- Around 20% of children will develop CKD 5. This is more common in those with heavy proteinuria and hypertension at presentation. CKD 5 does not appear to develop in those with asymptomatic low-level proteinuria; proteinuria in this group may resolve within 12–18 months.
- Children with nephrotic syndrome due to idiopathic MN should generally receive immunosuppressive therapy, this being more intensive where there is evidence of renal impairment or hypertension at presentation.

Corticosteroids

- Have produced conflicting results in controlled adult studies.
- There are reports of successful outcomes in uncontrolled studies performed in children.
- Many will have received at least 4 weeks of daily steroids prior to diagnosis as empiric treatment for childhood nephrotic syndrome.
- One recommended schedule is prednisolone 2mg/kg/day (max 60mg) for 4–8 weeks followed by a similar dose on alternate days with a gradual taper of this dose to a dose of 10–30mg on alternate days over 6 months to 5 years depending on clinical response.
  - most children who respond do so within 2–3 months.

Alkylating agents

- Controlled studies in adults have shown alkylating agents in combination with steroids to significantly increase the rate of disease remission.
- Ponticelli regimen: 3 consecutive doses of IV methylprednisolone (1g in adults), then oral prednisolone at 0.5mg/kg for 27 days, then chlorambucil 0.2mg/kg/day for 1 month, alternating the prednisolone and chlorambucil monthly for a total of 6 months.

Ciclosporin

- Adult controlled studies have also shown the use of this agent (with target trough levels of 125–225ng/L) for six to twelve months to reduce proteinuria and the incidence of declining renal function.
- If treatment is going to be effective, children will generally have entered remission by 6 months.

Other treatments

- Hypertension should be well controlled, ACE inhibitors or angiotensin receptor blockers being the logical agents of first choice as they also reduce proteinuria.
- Dyslipidaemia should be managed with dietary modification ± the use of statins.
- Antithrombotic prophylaxis (e.g. aspirin) may be considered in children with persistent nephrotic syndrome.
- Children with nephrotic syndrome should receive pneumococcal vaccine or penicillin V prophylaxis.
- Some may need thyroxine replacement therapy due to loss of binding protein in the urine. TSH (not free T4) is the best guide to monitor thyroid function in nephrotic syndrome.

Children with asymptomatic proteinuria alone

(i.e. no hypertension, renal impairment or nephrotic syndrome.)

- Have a very low rate of progression to CKD and may enter spontaneous remission.
- Should be treated with ACE inhibitors ± angiotensin receptor blockers to reduce proteinuria.
- The adverse effects of immunosuppressive therapy probably outweigh the benefits.

Reference

Menon, S. and Valentini, R.P. (2010). Membranous nephropathy in children: clinical presentation and therapeutic approach. *Pediatr Nephrol.* **25**(8):1419–28.

Chapter 10

Systemic disease affecting the kidney

Systemic lupus erythematosus: background, clinical evaluation, and investigation

Background

- Systemic lupus erythematosus (SLE) is an episodic, multisystem, autoimmune disease with polyclonal B cell activation and widespread production of autoantibodies.
- There is a defect in clearance of apoptotic cells, which may contribute to autoantibody and immune complex formation ('garbage disposal' hypothesis).
- There is widespread inflammation of blood vessels and connective tissues due to immune complex deposition.
- Its incidence in the paediatric population is between 0.5 and 0.6 per 100,000, most cases presenting in the teenage years.
- More common in females (5–10:1) and in the Black population.
- Haematological and renal disease is more severe in patients with childhood-onset lupus than in those with adult-onset disease.
- Renal involvement occurs in 20–80% of paediatric patients. In prospective studies of childhood-onset lupus, the prognosis is most closely related to the severity of renal disease.
- The classification of lupus nephritis, initially developed by the World Health Organization, has been modified (see 📖 'Systemic lupus erythematosus: classification and treatment of lupus nephritis', p.237).
- SLE is associated with significant morbidity and mortality, although this appears to be improving:
  - 9-year follow-up of 201 children with lupus nephritis (LN) from a single centre reported 3% mortality and 8% CKD 5;
  - mortality is most commonly due to infections, followed by renal involvement.
- Increasingly, late cardiovascular morbidity and mortality from premature atherosclerosis is of major concern in patients with SLE:
  - this is now the commonest cause of death in adults with SLE;
  - in one study, the increased risk of death from cardiovascular disease (CVD) was 16 times that of the general population.

The American College of Rheumatology classification criteria of systemic lupus erythematosus

Four of the following 11 criteria are required for the classification of SLE. It should be noted that, in children, the features may present sequentially with different manifestations of lupus evolving over time.

1. *Malar rash:* fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.
2. *Discoid rash:* erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
3. *Photosensitivity:* skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.

4 *Oral or nasopharyngeal ulceration:* usually painless, observed by a physician.
5 *Arthritis:* non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion.
6 *Serositis:*
   - pleuritis (convincing history of pleuritic pain, or rub heard by a physician, or evidence of effusion); *or*
   - pericarditis (documented by ECG or rub or evidence of pericardial effusion).
7 *Renal disorder:*
   - persistent proteinuria >0.5g/day or >+++ on dipstick analysis; *or*
   - cellular casts (may be red cell, haemoglobin, granular, tubular, or mixed).
8 *Neurological disorder:* seizures or psychosis in the absence of offending drugs or known metabolic derangements, such as uraemia, ketoacidosis, or electrolyte imbalance.
9 *Haematological disorder:*
   - haemolytic anaemia with reticulocytosis; *or*
   - leucopenia (less than 4×10^9/L on two or more occasions); *or*
   - lymphopenia (less than 1.5×10^9/L on two or more occasions); *or*
   - thrombocytopenia ($<150 \times 10^9$/L in the absence of offending drugs).
10 *Immunological disorder:*
   - *anti-DNA*—antibody to native DNA in abnormal titre; *or*
   - *anti-Sm (Smith antibody)*—presence of antibody to Sm nuclear antigen; *or*
   - *positive finding of antiphospholipid antibodies* based on—abnormal serum level of IgG or IgM anticardiolipin antibodies; positive test result for lupus anticoagulant; or false-positive serological test for syphilis.
11 *Anti-nuclear antibodies (ANA):* abnormal titre of ANA by immunofluorescence or an equivalent assay at any point in time, and in the absence of any drugs known to be associated with 'drug-induced lupus' syndromes.

Systemic lupus erythematosus syndromes in the paediatric population

- There are different clinical presentations of lupus disease, including drug-induced lupus, neonatal lupus, discoid lupus, systemic lupus erythematosus, and atypical lupus.
- It is important to note that a diagnosis of SLE can be made in a patient who has negative anti-double-stranded DNA antibodies—'seronegative' lupus. This is observed in 3–5% of cases at presentation and that, in children, clinical features of SLE may evolve slowly over time.

Clinical evaluation of systemic lupus erythematosus

General points in the history

- Pyrexia and weight loss.
- Fatigue, malaise, and lethargy.

- Anorexia, nausea, and vomiting.
- Poor school attendance.
- Drug, past medical, and family history.

Mucocutaneous
- Maculopapular eruption and discoid lesions.
- Alopecia, malar erythema, swollen fingers.
- Mucosal ulceration.

Neurological
- Headache and/or migraines.
- Confusion, delirium, psychosis.
- Deteriorating level of consciousness.
- Seizures, stroke, ataxia, or chorea.

Musculoskeletal
- Myalgia and arthralgia.

Cardiorespiratory
- Dyspnoea and pleuropericardial pain.
- Intermittent chest pain.
- Vasculitis.
- Major cutaneous vasculitis (e.g. ulcers).
- Recurrent thromboembolism.

Renal
- Oedema.

Examination findings

The important clinical parameters in examination should include:

General
- Weight, height centiles, and changes over time.
- Systolic and diastolic blood pressure (BP) and centiles.
- Lymphadenopathy and hepatosplenomegaly.

Mucocutaneous
- Maculopapular eruption and discoid lesions.
- Alopecia, swollen fingers, and sclerodactyly.
- Angio-oedema, panniculitis, and calcinosis.
- Telangiectasia, malar, and peri-ungual erythema.
- Mucosal ulceration, subcutaneous nodules.
- Brown fingernails ('lupus nails').

Neurological
- Confusion, delirium, psychosis.
- Deteriorating level of consciousness.
- Seizures, stroke, ataxia, or chorea.
- Peripheral or cranial neuropathy.
- Transverse myelitis.

Musculoskeletal
- Myositis, tendonitis, and arthritis.
- Contractures, fixed deformities, and aseptic bone necrosis.

Cardiorespiratory
- Cardiac failure, friction rub.
- Pericardial or pleural rub.

Vasculitis
- Raynaud's phenomenon.
- Purpura, urticaria, nail fold, and digital vasculitis.
- Livedo reticularis.
- Superficial phlebitis.

Renal
- Oedema (nephrotic syndrome).

Blood tests in systemic lupus erythematosus (first presentation)

Haematology
- Full blood count (FBC) and blood film.
- Erythrocyte sedimentation rate.
- Coagulation screen and international normalized ratio (INR).
- Direct Coombs' test.
- Reticulocyte count.
- Ferritin.
- Lupus anticoagulant.

Biochemistry
- Plasma U&Es, CO_2, Cl, urate, creatinine.
- C-reactive protein (relatively normal compared to erythrocyte sedimentation rate (ESR) in active SLE, but may rise in infection).
- Glucose.
- Liver function, albumin, crewatine kinase (CK), lactate dehydrogenase (LDH), and bone profile (Ca, Mg, PO_4, and ALP).
- Ionized calcium and intact PTH.
- Thyroid function tests.
- Amylase and lipase (for pancreatitis).
- Haptoglobins (if suspect haemolytic anaemia).

Immunology
- ANA.
- Anti-double-stranded DNA.
- Rheumatoid factor.
- Anti-neutrophil cytoplasmic antibody (ANCA).
- Extractable nuclear antibody (ENA) (Ro, La, Smith[Sm], RNP, Jo1, and other).
- *Complement:* C3 and C4, mannose binding lectin (if available).
- Anticardiolipin IgG and IgM antibodies.
- Anti-liver kidney microsomal (LKM) antibodies if hepatic dysfunction.
- Immunoglobulins G, A, M (can get hypogammaglobulinaemia, mimicking common variable immunodeficiency).
- Organ specific autoantibodies.
- Varicella IgG to check immunity prior to immunosuppression.

Urine investigations in systemic lupus erythematosus

- Dip test.
- Microscopy, culture, and sensitivity (M, C, and S).
- Ua:Ucr.
- Tubular reabsorption of inorganic phosphate (TRP), Unag:Ucr, and Urbp:Ucr if tubulopathy suspected.

Other investigations in systemic lupus erythematosus

The following investigations need to be considered where appropriate:

- Renal ultrasound (US).
- Electrocardiogram (ECG).
- Chest X-ray (CXR).
- Echocardiography.
- Pulmonary function tests.
- Broncho-alveolar lavage if opportunistic lung infection suspected.
- Bone marrow aspirate and trephine (exclude malignancy; macrophage activation syndrome).
- Lumbar puncture: microscopy and culture; viral polymerase chain reaction (PCR) (Herpes simplex virus (HSV), cytomegalovirus (CMV), Enterovirus, Varicella zoster virus (VZV)); protein; glucose; oligoclonal bands (present in cerebral lupus).
- Magnetic resonance imaging (MRI) brain +/– spinal cord (for central nervous system (CNS) lupus).
- Electroencephaloogram (EEG).
- Glomerular filtration rate (GFR).
- Tissue biopsy: skin, lung, intestinal, lymph node (Kikuchi–Fujimoto's disease: necrotizing lymphadenitis, sometimes complicating SLE); lymphoma—increased risk with SLE, as intrinsic aspect of disease, and/or complicating therapy.
- Renal biopsy if there is:
  - significant proteinuria, haematuria or hypertension;
  - deteriorating renal function.

Generally, renal biopsy is reserved for children with clinical or laboratory evidence of renal involvement with glomerular dysfunction, aiming to identify diffuse proliferative lupus nephritis (DPLN), which is the most severe subtype. DPLN adversely affects the prognosis and may influence patient management by requiring an increase in immunotherapy. However, extensive glomerular abnormalities have been identified on biopsies of patients who have no clinical evidence of renal disease. Renal biopsy can differentiate whether proteinuria is caused by renal scarring or active disease.

Follow-up investigations

At every follow-up visit (at least every 3rd month) the child should have:

- A full clinical evaluation including height and weight.
- BP.
- Urine dipstick and urine albumin:creatinine ratio (Ua:Ucr) on first morning urine.
- Blood tests including:
  - FBC, ESR, and C-reactive protein (CRP);
  - urea & electrolytes (U&Es);

- liver function tests (LFTs);
- ANA, ds-DNA, C3 and C4, anticardiolipin antibody (ACL). Also other autoantibodies if they previously have been shown to be present;
- coagulation screen and direct Coombs if low Hb.

Once yearly the following evaluations should be done:

- Bone density measurement (dual-energy X-ray absorptiometry (DEXA) scan) for osteoporosis.
- Fasting blood lipids; cholesterol, triglycerides, high-density lipoprotein (HDL) and very low density lipoprotein (VLDL).
- Pubertal status (self-reported using validated self-reporting tool is acceptable).

Further reading

Hagelberg S, Lee Y, Bargman J, *et al.* (2002). Long-term follow-up of childhood lupus nephritis. *J Rheumatol* **29:** 2635–42.

Systemic lupus erythematosus: treatment of non-renal systemic lupus erythematosus

In an attempt to reduce the burden of short- and long-term therapy-related morbidity and mortality, recent paradigm shifts to the approach to therapy of SLE (renal and non-renal) include:

- Increasing use of mycophenolate mofetil (MMF) in place of IV cyclophosphamide (IVCYC) for induction of remission.
- Attempts to minimize corticosteroid exposure where possible.
- Increasing use of rituximab or other B cell depletion strategy (see 'Systemic lupus erythematosus: B cell-targeted therapies', p.241) for those who fail standard therapy or where cumulative IVCYC toxicity is a concern.
- Where cyclophosphamide is used, this is given IV, rather than orally because of a better therapeutic index, i.e. lower cumulative IV dose required to induce remission.

The phases of treatment of systemic lupus erythematous

One approach to therapy is to consider the treatment of SLE in three phases:

- Induction of remission.
- Maintenance of remission.
- Maintenance withdrawal.

This approach provides a useful framework for the clinical management of patients, and informs the design of most clinical studies relating to SLE treatment.

Induction of remission

To rapidly reduce inflammation and gain control of disease activity, and limit organ damage or death.

- Typically with high dose of corticosteroids, with subsequent taper; immunosuppressant agents (MMF, IVCYC, azathioprine, or methotrexate); sometimes plasma exchange (see Box 10.1).
- Depending on severity this phase typically lasts 3–6 months.

Maintenance therapy

To maintain remission of disease activity whilst minimizing therapy-related toxicity:

- Low dose daily or alternate day corticosteroids (e.g. prednisolone 0.1–0.3mg/kg daily, sometimes alternate days).
- *Plus* least toxic immunosuppressant, e.g. hydroxychloroquine (HCQ), azathioprine, MMF, methotrexate (MTX).
- *Duration:* months to years (or indefinitely).

Maintenance therapy withdrawal phase

Attempts can be made to withdraw corticosteroids and immunosuppressants, e.g. after 2–3 years of remission on maintenance therapy:

- There is little or no evidence to guide this decision and relapse and disease progression is a major concern even after many years of disease quiescence.
- Thus, most patients with SLE require lifelong treatment in one form or another. There are active trials in progress, which in the future will guide long-term management.

General therapeutic considerations

Sun protection

All children with SLE and especially those with active skin disease should always use appropriate sunscreen and protect themselves from the sun, since UV exposure can precipitate cutaneous and systemic disease relapse.

Immunizations

- Children with SLE and treated with immunosuppressive treatment should avoid immunizations with live vaccines.
- Routine vaccination with killed vaccines is advised.
- Seasonal influenza vaccine should be given annually.
- Pneumococcal vaccination is now being recommended by the Department of Health for all patients likely to be on steroids for more than a month and all patients with renal disease.

Management of infection

Children on immunosuppressive treatment are more susceptible to severe infections then other children.

- It should be emphasized to the parents and the children that they need to seek medical advice early in the case of symptoms suggestive of an infection.
- Intercurrent infection can often precipitate flares of SLE so infection and active SLE often co-exist: increased corticosteroids under broad spectrum antibiotic cover may be required. Consider infection (rather than assume disease flare) if CRP elevated.

Management of specific non-renal organ systems

Skin and joint disease

- *NSAIDs:* e.g. naproxen 20–30mg/kg/day divided into 2 doses, maximum 500mg bd.
- *HCQ:* 5–6.5mg/kg/day—beneficial for skin and joint disease, may reduce fatigue, and is good for long-term cardiovascular protection:
  - the risk of HCQ retinal toxicity is exceedingly rare. In the UK, the Royal College of Ophthalmologists recommend baseline assessment of renal and liver function, inquiry about visual symptoms, and recording of near visual acuity at each visit and measurement of visual acuity annually. A yearly sight test including colour vision (local optician) is recommended.
- *Topical tacrolimus:* in resistant cutaneous lesions 0.1% topical tacrolimus may be useful.

- Thalidomide (50 mg orally on alternate days to 100 mg orally daily) can be used to treat severe recalcitrant cutaneous lupus that does not respond to more conventional therapy: thalidomide is associated with risk of peripheral neuropathy and teratogenicity—**seek expert advice if considering this approach** (refer also to the relevant guideline in the 📖 *Oxford Handbook of Paediatric Rheumatology*).
- Methotrexate (10–15mg/m^2, orally or subcutaneous, once a week) can be used for those with more severe arthritis.

Moderate multi-systemic disease (including haematological involvement)

- HCQ at dose as per 📖 'Skin and joint disease', p.233:
  - there may be a role for high dose HCQ (10mg/kg once daily) for pulmonary involvement, although retinal toxicity becomes more of a concern at higher doses;
  - HCQ is usually given in addition other immunosuppressants if these latter agents are required (other immunosuppressants are dealt with in the sections that follow).
- Oral prednisolone at 2mg/kg once daily, *or*
- Pulsed IV methylprednisolone (IVMP) 30mg/kg/dose for 3 days followed by oral prednisolone.
- Azathioprine 2–3mg/kg/once a day: many advocate checking red cell thiopurine transmethyltransefersase (TPMT) levels or genotyping prior to starting—individuals with both intermediate and absent TPMT activity have an increased risk of developing thiopurine-induced myelosuppression, compared with individuals with normal activity.

The following serves only as a guide, and remember that those with normal TPMT levels can also develop myelosuppression thus everyone should have standard azathioprine monitoring (see 📖 'The standard treatment of childhood vasculitis', p.282). Units quoted here are pmol/h/mgHb, but this may vary between laboratories:

- Normal TPMT 26–50: azathioprine starting dose 2mg/kg od.
- Intermediate TPMT (carriers of mutant allele) 10–25mL—starting dose 1mg/kg od, then work up whilst monitoring full blood count.
- Deficiency (homozygotes, 1:300 of the population) of TPMT—<10: 0.5mg/kg/ od (or less) and monitor closely for myelosuppression; or consider another agent.
- Oral MMF 1200–1800mg/m^2/day in 2–3 divided doses:
  - evidence in adults now suggests that MMF also improves non-renal SLE;
  - the dose is slowly increased over 2–3 weeks from a starting dose of approximately 300mg/m^2 bd to a target dose of 600–900mg/m^2 bd (maximum 3g/day, but approximately 2g/day is tolerated by most);
  - this approach is to avoid the main side effects of gastric upset, diarrhoea, and leukopenia;
  - if gastrointestinal (GI) side effects are a continuing problem the daily dose may be divided up and given 3 or 4 times a day.

For severe life-threatening multisystemic SLE, Box 10.1 describes one suggested approach.

Box 10.1 One approach to induction therapy for life-threatening multi-systemic SLE +/– HLH

- IV methylprednisolone 30mg/kg (maximum 1g) for three daily doses (may need to be repeated 5–7 days later) followed by:
- Oral prednisolone 2mg/kg/day, weaning to 0.5mg/kg od by 2 months
- IVCYC 250–1000mg/m^2 (max 1.2g with 2-mercaptoethanesulfonic acid sodium salt (MESNA) cover):
  - reduce dose to lower end of range if renal, hepatic, or cardiac failure present;
  - if able to take oral medication MMF could be considered as an alternative to IVCYC, but experience in critically ill patients is limited
- Consider plasma exchange (5–10 daily sessions).
- ?Rituximab (see 📖 'Systemic lupus erythematosus: B cell-targeted therapies', p.241)
- Consider IV ciclosporin 1mg/kg bd if secondary *haemophagocytic lymphohistiocytosis (HLH)* is suspected clinically or confirmed on bone marrow aspirate, and has not responded to the measures given here. Suspect HLH in a clinically deteriorating patient if one or more of:
  - haemophagocytosis observed on bone marrow aspirate (not always present);
  - progressive cytopenia observed (low Hb, falling white cell count (WCC), falling platelets);
  - ferritin >5000μg/mL;
  - high aspartate aminotransferase (AST), alanine transaminase (ALT), γ-glutamyltransferase (γGT), LDH;
  - falling or low fibrinogen or other progressive unexplained coagulopathy;
  - falling ESR, but patient getting worse clinically (hepatosplenomegaly, unremitting fever, encephalopathy, purpuric rash or other haemorrhage;
  - high fasting triglycerides;
  - low serum sodium.

Central nervous system involvement

- IV methylprednisolone followed by oral prednisolone (see Box 10.1).
- Pulsed IV cyclophosphamide: 250–1000mg/m^2 (maximum 1.2 g) monthly for 6 months; then 3-monthly for 6–18 months OR consider switching to azathioprine or MMF.
- MMF may be a reasonable alternative to IVCYC for induction of remission of CNS disease, although there are limited data to support this.
- Consider rituximab or other B cell depletion therapy (currently limited data in children—see 📖 'Systemic lupus erythematosus: B cell-targeted therapies', p.241).
- Plasma exchange as Box 10.1 (and see 📖 'Plasmapheresis and immunoadsorption', p.508).
- Anticonvulsants if seizures (cerebral lupus).

Antiphospholipid syndrome (thrombosis* plus *presence of lupus anticoagulant and/or anticardiolipin antibodies)

Standard treatment of SLE as appropriate *plus*:

- Aspirin, *and*
- *Warfarin:* lifelong treatment if one major thrombotic episode has occurred (such as pulmonary or femoral arterial thrombus). **NB.** Initial warfarinization *must* be covered with full heparinization to prevent 'paradoxical' thrombosis, which can occur at INR levels <2.
- Consider IV immunoglobulin, plasma exchange, and/or rituximab in addition for 'catastrophic antiphospholipid syndrome' (CAPS):
  - CAPS is a rapidly progressive life-threatening disease causing multiple organ thromboses and dysfunction in the presence of antiphospholipid antibodies;
  - despite treatment mortality is still 48%.

Alternative Induction therapies (limited formal trial data available to support use)

IV immunoglobulin Can be useful particularly in haematological disease. Dose 2g/kg IV over 12h, maximum 70g.

Further references

Ginzler EM, Wofsy D, Isenberg D, *et al.* (2010). Non-renal disease activity following mycophenolate mofetil or intravenous cyclophosphamide as induction treatment for lupus nephritis. *Arthrit Rheumat* **62:** 211–21.

A G Lee. (2005). Hydroxychloroquine screening. *Br J Ophthalmol* **89:** 521–2.

Systemic lupus erythematosus: classification and treatment of lupus nephritis

This chapter should be read in conjunction with 🕮 'Systemic lupus erythematosus: treatment of non-renal systemic lupus erythematosus', p.232.

Clinical features of lupus nephritis in children

- Renal involvement occurs in 20–80% of paediatric patients. In adults, the widely quoted frequency of renal involvement is 60%.
- Children may have earlier and more severe presentation of renal involvement than adults.
- Renal SLE presents (in variable combination) with proteinuria, nephrotic syndrome, microscopic haematuria, hypertension, and renal dysfunction, and is confirmed by renal biopsy.
  - tubulointerstitial nephritis with or without glomerulonephritis is also observed;
  - renal impairment +/– haematuria and hypertension can occur from small vessel thrombosis in the kidneys due to antiphospholipid syndrome (APS);
  - renal impairment should be distinguished from glomerulonephritis and will (in most cases) be detected by renal biopsy;
  - treatment of renal impairment requires full anticoagulation (see 🕮 'Systemic lupus erythematosus: treatment of non-renal systemic lupus erythematosus', p.232).
- In prospective studies of childhood-onset lupus, the prognosis is most closely related to the severity of renal disease:
  - advances in treatment (see 🕮 'Systemic lupus erythematosus: B cell-targeted therapies', p.241) have led to an improved prognosis for renal SLE;
  - despite this, SLE is still associated with significant morbidity and mortality;
  - 9-year follow-up of 201 children with LN from a single centre reported 3% mortality and 8% CKD 5.

Histological classification of lupus nephritis

- The classification of lupus nephritis is critical to patient care and for the comparison of outcome results from therapeutic trials. This classification provides useful information to assist in how aggressively to treat patients.
- Consensus concerning the definition of the different classes of SLE nephritis is therefore imperative.
- A group of renal pathologists, nephrologists, and rheumatologists have recently updated the classification of lupus nephritis.[1] (see Table 10.1).

1 Weening JJ, D'Agati VD, Schwartz MM (2004). International Society of Nephrology Working Group on the Classification of Lupus Nephritis; Renal Pathology Society Working Group on the Classification of Lupus Nephritis. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Dis* **65**, 521–30.

Table 10.1 Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (2003)

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis[a]
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis[b]
Class V	Membranous lupus nephritis[c]
Class VI	Advanced sclerosing lupus nephritis

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

[a]Indicate the proportion of glomeruli with active and with sclerotic lesions.

[b]Indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents.

[c]Class V may occur in combination with class III or IV, in which case both will be diagnosed.

Treatment

See also 🕮 'Systemic lupus erythematosus: treatment of non-renal systemic lupus erythematosus', p.232.

Class I and II

- No specific therapy: same treatment as mild to moderate non-renal disease if present (see 🕮 'Systemic lupus erythematosus: treatment of non-renal systemic lupus erythematosus', p.232).

WHO Class III, IV, and V lupus nephritis: evidence for MMF

- Most nephrologists (paediatric and adult) now advocate MMF in place of IVCYC as first line 'standard of care' for severe lupus nephritis based on the results of randomized controlled trials (RCTs) in adults:
  - initial trials suggested superior efficacy and fewer adverse events for MMF versus IVCYC;
  - more recent trial data (the ALMS trial described here) suggest that MMF is equally efficacious to IVCYC, and that short-term adverse events are comparable;
  - MMF is associated with more diarrhoea, whereas IVCYC is associated more nausea and vomiting;
  - there is still a belief that MMF spares patients from late toxic side-effects of IVCYC such as infertility and bladder cancer, but this remains unproven;
  - the main practical concern regarding the use of MMF is adherence to therapy, a major issue particularly in adolescent patients.
- The biggest MMF trial was recently published by the ALMS (Aspreva Lupus Management Study) group.
  - 370 adult patients with classes III–V lupus nephritis were randomly assigned to MMF (target dose 3g per day) or IVCYC 0.5–1g/m^2/month in a 24-week induction study;
  - both groups received an identical weaning prednisolone regimen;

- the primary endpoint was a pre-specified decrease in urine protein–creatinine ratio and stabilization or improvement in serum creatinine;
- there was no difference in response rate between the two groups—56.2% responded to MMF compared with 53% in the IVCYC group;
- there were no significant differences with regard to rates of adverse events, including infections;
- there were nine deaths in MMF group and five in IVCYC group;
- class III may be treated as class IV and V, although these cases should be discussed on an individual basis, with other considerations such as presence or absence of TIN or vasculitis, and presence or absence of extra-renal disease.

Suggested induction treatment protocol using MMF and corticosteroids

- Oral prednisolone 2mg/kg/day to a maximum of 60–80mg/day, *or*
- IV methylprednisolone (IVMP) 30mg/kg (maximum 1g) for three consecutive days followed by oral prednisolone.
- In severe cases IVMP may be repeated 1 week later.
- To minimize corticosteroid side-effects, aim to wean the prednisolone over the following 6–8 weeks to a dose of 0.5mg/kg/day. Further weaning to 0.2mg/kg/day over the subsequent 2–3 months is dependent upon individual response.
- MMF is slowly increased over 2–3 weeks from a starting dose of approximately 300mg/m^2 bd to a target dose of 600–900mg/m^2 bd (maximum 3g/day, but approximately 2g/day is tolerated by most):
  - this approach is to avoid the main side effect of gastric upset and diarrhoea;
  - if GI side effects are a continuing problem the daily dose may be divided up and given 3 or 4 times a day.
- If patients are too critically ill to take MMF, or if there are concerns about adherence to oral medication or other clinical reason then IVCYC is still an option:
  - IV CYC 250–1000mg/m^2 monthly for 6 months (induction) then switch to steroid sparing agent (azathioprine or MMF);
  - MESNA prophylaxis is recommended to reduce risk of haemorrhagic cystitis and late bladder cancer (see 🕮 Appendix, 'Intravenous cyclophosphamide', p.609 for dose);
  - always document cumulative doses of CYC treatment (cumulative doses of 500mg/kg can cause azoospermia in males);
  - always start low-dose (such as 250–500mg/m^2) with renal impairment (beware cardiotoxicity and other side-effects).

Influence of ethnicity on choice of therapy

- The ALMS group report that black and Hispanic patients responded better to MMF than IVCYC.
- More data are required before making any firm recommendations.

WHO Class V lupus nephritis: alternative therapy

- Recent evidence from the ALMS group and others suggests that MMF or IVCYC are similar as induction therapy for class V lupus nephritis.
- Alternative agents used with corticosteroids as already described for induction of remission of class V lupus nephritis include:
  - IVCYC as 📖 'Treatment', p.238; *or*
  - oral ciclosporin at 5mg/kg/day (in two divided doses): aim for levels between 90 and 110micrograms/L.

Crescentic nephritis

- As per 📖 'WHO Class III, IV, and V lupus nephritis: evidence for MMF', p.238, but also consider plasma exchange. Most paediatric nephrologists would still consider plasma exchange for severe lupus nephritis or other life-threatening complications, such as pulmonary haemorrhage or severe cerebral lupus based on favourable retrospective clinical experience, although a meta-analysis in adult patients with severe lupus nephritis did not confirm any benefits from adding plasma exchange to the standard treatment of IVMP and CYC.
- Rituximab or other anti-B cell therapy for severe renal (+/– extrarenal) disease or for disease resistant to standard therapy—refer to 📖 'Systemic lupus erythematosus: B cell-targeted therapies', p.241.

Further references

Appel G, Contreras G, Dooley MA, *et al.* (2009). Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* **20:** 1103–12.

Isenberg D, Appel GB, Contreras G, *et al.* (2010). Influence of race/ethnicity on response to lupus nephritis treatment: the ALMS study. *Rheumatol* **49:** 128–40.

Radhakrishnan J, Moutzouris DA, Ginzler EM, *et al.* (2010). Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. *Kid Internat* **77:** 152–60.

Weening JJ, D'Agati VD, Schwartz MM (2004). International Society of Nephrology Working Group on the Classification of Lupus Nephritis; Renal Pathology Society Working Group on the Classification of Lupus Nephritis. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Dis* **65**, 521–30.

Systemic lupus erythematosus: B cell-targeted therapies

Why target B cells in systemic lupus erythematosus?

- A minority of patients with SLE will not have a sufficient clinical response to the present standard treatment with MMF, IVCYC, azathioprine and corticosteroids.
- In these cases there continues to be clinical and laboratory symptoms, and signs of active disease of such a degree that alternative approaches to treatment would be preferable.
- B cells have critical roles in the pathogenesis of SLE, including cytokine production, presentation of self-antigen, T-cell activation, and (indirectly via plasma cells) autoantibody production.
- Recently, several clinical trials have reported different approaches for the induction of remission in adults with SLE by targeting B cells.

Types of B cell-targeted therapy

- Currently tested B-cell targeted therapies include rituximab, ocrelizumab, belimumab, epratuzumab, and atacicept. The mechanisms of action of these agents are summarized in Table 10.2.
- At the time of writing, the vast majority of the paediatric SLE experience is only with rituximab, with little or no data on the role of these other agents in paediatric patients.

Clinical trials of B cell-targeted therapies in adults with systemic lupus erythematosus

- Very recently, several important prospective RCTs of B cell-targeted therapy have been reported in adults (summarized in Table 10.3), with mixed and perhaps (to many) surprising results:
  - both rituximab trials (EXPLORER and LUNAR) reported negative results;
  - both belimumab trials reported positive results.
- Methodological aspects of the clinical trials of rituximab could explain the 'unexpected' negative results of the EXPLORER and LUNAR trials despite early reported open label success in those with SLE resistant to conventional therapy (including children). Possible reasons include:
  - improvements in the standard care limb of these trials—MMF in place of IVCYC, which may result in a higher than anticipated response rate thus reducing the power of the study;
  - high corticosteroid doses in both the experimental and standard limbs of the trials;
  - over optimistic primary endpoints and sensitive cut-offs for non-response;
  - patient heterogeneity including the fact that some patients with minimal disease activity were included in these trials;
  - the EXPLORER and LUNAR trials do not answer the question relating to efficacy of rituximab for those with SLE resistant to standard induction therapy.

Table 10.2 Different types of B cell-targeted therapy

Drug name	B cell target	Proposed mechanism of efficacy
Rituximab	Chimeric (mouse-human) monoclonal antibody which binds specifically to the CD20 antigen located on pre-B and mature B lymphocytes, thus mediating B-cell lysis. CD20 is not expressed on plasma cells.	Depletion of peripheral blood B cells, with little or no decrease in serum immunoglobulin because plasma cells are spared. Efficacy thought to be the result of autoantibody independent effects of B cell depletion including reduced self-antigen presentation, reduced cytokine production and decreased T-cell activation.
Ocrelizumab	Fully human monoclonal antibody against CD20.	Same as rituximab.
Belimumab	Fully human monoclonal antibody against BAFF (B cell activating factor, also referred to as B-Lymphocyte Stimulator, BLyS). BAFF (and another related molecule called APRIL) are produced mainly by cells of the innate immune system, and promote B cell survival and differentiation.	BAFF levels are increased in SLE and correlate with disease activity- blocking BAFF therefore reduces pathological B cell survival and differentiation.
Epratuzumab	Fully human monoclonal antibody against CD22, a B-cell surface antigen involved in the regulation of signaling.	B cell depletion so similar in action to rituximab.
Atacicept	Chimeric molecule with a region which binds both BAFF and APRIL, fused to the constant region of human IgG1.	Has a dramatic inhibitory effect on plasma cells, hence reducing autoantibodies, but also reduces immunoglobin—very high rate of infections reported in early trials.

Table 10.3 Summary of recently (*or soon to be) reported RCTs of B cell targeted therapy in SLE

Trial name	Description	Design	Primary end point	Result	Adverse events
Explorer	The Exploratory Phase II/III SLE evaluation of rituximab; Non-renal lupus trial.	Double blind RCT; *n* = 257 all receiving PRED, and one of AZA, MMF, or MTX. Patients were randomized 2:1 to receive RTX or placebo. Moderate and severe LN or CNS lupus excluded.	Predefined improvement in BILAG score	No differences between placebo and RTX groups in the primary endpoint. Serological improvement observed in RTX group.	Safety and tolerability were similar in patients receiving RTX and those receiving placebo.
*Lunar	Lupus nephritis assessment with rituximab.	Double blind RCT; RTX or placebo was added onto standard therapy with MMF and high dose corticosteroids; *n* = 144, 1:1 randomization. Active class III or IV LN included; CNS lupus excluded.	Proportion of patients who obtained a predefined renal response at 52 weeks: either CRR, PRR, or NR.	No difference in primary endpoint between RTX and placebo groups. Serological improvement observed in RTX group.	More severe neutropaenia (3.6% RTX vs. 0% placebo); and non-serious herpes virus infections (15% RTX vs. 8% placebo); 4 episodes of serum sickness occurred in the RTX group.

(Continuied)

Table 10.3 *(Contd.)*

Trial name	Description	Design	Primary end point	Result	Adverse events
*Bliss-52	Belimumab International SLE study—52-week follow-up.	Double blind RCT; n = 865: standard care (corticosteroids and other immunosuppressant) plus either placebo or belimumab 1mg/kg, or 10mg/kg given at Days 0, 14, 28, and every 28 days until week 52. Severe LN and active CNS lupus excluded.	Improvement at week 52 in SRI, and no worsening of physician global assessment score or BILAG	Reduced disease activity and increased time to flare for both the low and high dose belimumab groups compared with placebo at week 52.	No difference in adverse events between placebo and belimumab groups with the exception of infusion reactions.
*Bliss-76	Belimumab International SLE study-76-week follow-up.	Second phase III RCT of belimumab: identical study design as BLISS-52; only difference is that blinding and follow-up remain for an additional 24 weeks		Reduced disease activity and increased time to flare in the high dose belimumab group only, compared with placebo at week 52. Week 76 results not yet reported.	Not yet reported.

RCT: randomized controlled trial; LN: lupus nephritis; CNS: central nervous system; BILAG: British Isles Lupus Assessment Group score; PRED: prednisone; AZA: azathioprine; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab; CRR: complete renal response; PRR: partial renal response; NR: non-response; SRI: SLE-response index.

The use of rituximab in paediatric systemic lupus erythematosus

- Given the negative recent trial data for rituximab 🕮 'Clinical trials of B cell-targeted therapies in adults with systemic lupus erythematosus', p.241, albeit with positive retrospective clinical experience with this therapy in children with SLE resistant to standard therapy, rituximab should only be given upon expert advice.
- In rare circumstances, rituximab can be considered for primary induction of remission—suggest under expert advice only.
- Adding to the complexity is the still ongoing controversy as to whether rituximab should be given with IVCYC for 'synergistic' B cell depletion or not, and what immunosuppression to follow rituximab therapy with:
  - data suggest that B cell activation in SLE makes these cells more resistant to antibody-mediated cell killing from agents such as rituximab, providing an (unproven) argument for combining rituximab with cyclophosphamide;
  - at the time of writing there are no data to provide firm recommendations on these issues;
  - treat each case on an individual basis.

Patient selection criteria

- Severe active lupus previously treated with standard lupus treatment either IVCYC or MMF for a minimum of 6 months, *or*
- As add on to standard induction therapy for those with severe life-threatening disease–little available evidence of its efficacy in this context.
- No known severe reaction to humanized chimeric antibodies.

Exclusion criteria

- Chronic active infection.
- Recent severe infection.
- Pregnancy or planned pregnancy.

Rituximab treatment protocol

Rituximab may be given in addition to CYC, except where cumulative CYC toxicity, side effects, or other clinical contraindication preclude this.

Suggested protocol

Day 1 and Day 15

- Rituximab infusion 750mg/m^2 (rounded up to the nearest 100mg); max dose—1g.
- Premedicate with chlorphenamine (5–10mg) and paracetamol (15mg/kg) 1h prior to the rituximab infusion.
- In addition a dose of methylprednisolone IV 100mg (absolute dose, not per kg) is given *immediately prior* to the rituximab infusion.
- This is followed with oral prednisolone for 3 days after the infusion: 30, 20, and 10mg (i.e. days 2, 3, and 4, and days 16, 17, and 18), and then with the patient's previous maintenance prednisolone dose.

Day 2 and Day 16

Cyclophosphamide infusion 375mg/m^2 as per infusion protocol (see 📖 Appendix, 'Intravenous cyclophosphamide', p.609).

Administration of Rituximab: practical aspects

- Dilute the required dose with sodium chloride 0.9% or glucose 5% to a final concentration of 1–4mg/mL.
- The initial infusion rate is 25mg/h, which can be increased by increments of 25mg/h every 30 min up to a maximum of 200mg/h as tolerated.

Rituximab: side effects

- *Serum sickness:* fevers and rigors, which usually present within the first 2 h. Other reported symptoms include pruritus and rashes, dyspnoea, bronchospasm, angioedema, and transient hypotension:
  - in the event of an infusion related adverse event, stop the infusion, and recommence at half the previous rate once the symptoms have resolved;
  - premedication with chlorphenamine, paracetamol, and methylprednisolone will reduce the incidence of adverse effects.
- *Infections:*
  - Herpes zoster infection described in children;
  - progressive multifocal leukoencephalopathy caused by JC virus (a polyoma virus).
- *Rituximab associated neutropaenia:* occurring usually several months following the administration of rituximab:
  - usually not clinically significant and is self-limited but should be differentiated with neutropaenia from other cause such as active SLE;
  - mechanism remains largely speculative.

Follow-up post-rituximab

Follow up carefully with:

- Clinical status.
- FBC including diff, ESR, CRP, U&Es and LFTs; Ua:Ucr (minimum of fortnightly FBC for 6 weeks then monthly).
- ANA, doubled-stranded DNA, C3, C4.
- Screen for B cell response and agammaglobulinaemia (see Table 10.4). The use of replacement immunoglobulins in deficient patients is not standard practice at this stage, but will be continually monitored. The decision to commence IVIG replacement will be decided on an individual basis and will depend on the findings of hypogammaglobulinaemia, and/or the occurrence and nature of infections.

Repeat rituximab dosing

- Repeated doses of rituximab are only recommended for those with evidence of return of disease activity after return of peripheral blood lymphocytes.
- Hypersensitivity reactions such as serum sickness and anaphylaxis may be of increasing concern for those re-treated with rituximab.

Table 10.4 Monitoring rituximab treatment in patients with SLE

Test	Timing (after 1st dose)	Notes
Lymphocyte subsets	Day 7–10 Monthly from 4 months after first dose until B cells normal	Measures T, B (CD19) and NK cells. Must do FBC same day
Immunoglobulins GAM	Day 7–10. 2 months after first dose. Monthly from 4 months after first dose until B cells normal.	

Note: B cells express CD19 and CD20, and it is routine to measure CD19 as a B cell marker. Rarely (normally in the context of malignancy) B cells may not express CD20 and will not therefore be eliminated by rituximab. If there is concern that B cells are not eradicated after 7–10 days, routine B cell measurement should be repeated and direct measurement of CD20 may be helpful. This will rarely be required.

Further references

Looney RJ. (2010). B-cell targeted therapies for systemic lupus erythematosus. *Drugs*, **70:** 529–40.
Podolskaya A, Stadermann M, Pilkington C, Marks SD, Tullus K. (2008). B cell depletion therapy for 19 patients with refractory systemic lupus erythematosus. *Arch Dis Child* **93:** 401–6.

Diabetes and metabolic syndrome

Type 1 diabetes

Background

- Diabetic nephropathy is the commonest cause of CKD 5 in adults in the USA and accounts for 16% of CKD 5 in adult patients in the UK.
- Microalbuminuria can occur within 5 years of the onset of insulin dependent diabetes mellitus and therefore is seen in the paediatric population, as well as in adults.
- The natural history includes progression in several stages over 10–15 years, starting with apparent normality in the first few years after diagnosis, followed by incipient nephropathy characterized by the presence of small amounts of albumin in the urine (undetectable on dipstick), known as microalbuminuria, terminating in overt proteinuria and nephropathy.
- 20–30% of patients develop subclinical microalbuminuria, which is potentially reversible with tight glucose control.
- Once proteinuria has developed, it is irreversible and heralds the onset of CKD.
- 25–45% of patients develop overt clinical nephropathy (the minimal criterion for which is a persistently positive urine dipstick for protein).
- Patients with nephropathy will almost invariably have other signs of diabetic microvascular disease, such as neuropathy or retinopathy.
- There is no specific therapy for diabetic nephropathy, and all patient management should be targeted at preventing the onset of CKD, and slowing its progress once detected.

Pathology

The three major histological changes in the glomeruli in diabetic nephropathy are:

- Mesangial expansion.
- Glomerular basement membrane thickening.
- Glomerular sclerosis which may have a nodular appearance: the Kimmelstiel–Wilson lesion.

There may be associated hyaline deposits in the glomerular arterioles. Renal biopsy in diabetics with microalbuminuria only may reveal normal histology or evidence of glomerulosclerosis or other changes of diabetic nephropathy. Normal histology is more likely where the level of albumin excretion is low and there is no hypertension or impairment of GFR.

Microalbuminuria

- Microalbuminuria refers to levels of albuminuria that are too low to be detected by conventional dipstick analysis and require the use of sensitive laboratory techniques.
- Microalbuminuria is defined as an excretion of 30–300mg/day (20–200micrograms/min) of albumin in an adult. In comparison, dipstick positive albuminuria reflects values greater than 300mg/day (200micrograms/min).
- It is common practice to use early morning spot Ua:Ucr for the detection of microalbuminuria in children: Ua:Ucr >2.5mg/mmol would define microalbuminuria.

- The renal excretion of albumin can be elevated by vigorous exercise, acute illness, fever, severe cardiac disease, urinary tract infection (UTI), menstrual bleeding, severe hypertension, poor glycaemic control and ketoacidosis. Sample collection should therefore be avoided when such intercurrent problems are present, and vigorous exercise avoided for 24 h prior to testing. Three serial early morning urine samples should be checked to rule out problems such as these.

Management of the child with microalbuminuria

The presence of overt diabetic nephropathy in childhood is rare, so:

- Management should concentrate on the prevention of the development of and screening for the presence of microalbuminuria.
- Microalbuminuria screening should be annual.
- When microalbuminuria is detected, treatment strategies should be introduced to reduce the degree of albumin excretion with the aim of postponing the progression to overt nephropathy.
- The optimal management of diabetic renal disease should address all possible risk factors: hyperglycaemia, hypertension, microalbuminuria and dyslipidaemia.

Glycaemic control

A number of studies in adult patients have shown that strict control of the plasma glucose through the use of intensive insulin therapy results in a reduction in the cumulative incidence of microalbuminuria, and can also halt the progression to overt diabetic nephropathy in those with existing microalbuminuria;

Angiotensin-converting enzyme inhibition (ACEI)

Systematic review of adult studies confirms that ACEI result in a significant reduction in albumin excretion and a lowering of systemic BP, though there is some controversy as to whether this reduction in albumin excretion rate is associated with a postponement of CKD 5; similar anti-albuminuric effects are seen with ARBs, diltiazem, and verapamil, although not other antihypertensive drugs.

Management of hypertension

The presence of hypertension is a known adverse risk factor for the progression of microalbuminuria to overt nephropathy:

- As ACE inhibitors reduce albumin excretion in addition to BP, they are the logical drug of first choice.
- It is fairly well established that the use of antihypertensive agents in diabetic patients is beneficial (when compared with no treatment), in terms of maintaining renal function and protein excretion.
- Several uncertainties still exist:
  - while it is accepted that ACE inhibitors and ARBs are effective, it is still unclear whether this is true for any of the other antihypertensive agents;
  - it is not clear whether any of these individual agents are more effective or if the combination of ACE inhibitors and ARBs is better than monotherapy;
  - other aspects to consider include the use of combination drug therapies and the achievement of specific goals for BP.
- *Lifestyle:* avoidance of obesity and smoking, increased physical activity.

Type 2 diabetes and obesity

Background

- One third of 2–19-year-olds in the USA have a BMI ≥85th percentile and 17% are frankly obese (BMI≥95th percentile). Similar figures are developing in Europe.
- Childhood obesity is associated with an increased risk for insulin resistance, glucose intolerance, and type 2 diabetes.
- In the USA, type 2 diabetes accounts for almost half of all cases of diabetes diagnosed among children and adolescents, and its incidence is rising.
- Microalbuminuria is more common in type 2 than type 1 diabetes in children.
- Children with type 2 diabetes have a five-fold increased risk of CKD 5 over patients with adult-onset.

Pathogenesis of obesity-related renal disease

Several studies have highlighted an association between obesity, and the risk of renal damage and CKD 5. Obesity is associated with:

- Hypertension, dyslipidemia, and type 2 diabetes.
- Increased renal sodium reabsorption, which can contribute to hyperfiltration and glomerular morphological changes.
- Activation of neurohormonal systems, which can induce renal hemodynamic changes.
- Elevated plasma leptin levels and increased inflammatory cytokines.
- Proteinuria in children and adolescents with severe forms of obesity, with FSGS on biopsy.

Non-diabetic renal disease

It is important to remember that albuminuria may occasionally be due to an alternative glomerular disease. Clues pointing to a non-diabetic nephropathy include:

- The early onset of proteinuria (within 5 years of diagnosis).
- Acute onset of proteinuria.
- The presence of an active urinary sediment (red cells and casts).
- The absence of diabetic retinopathy or neuropathy.

Management

- As for type 1 diabetes, but with particular attention to body mass.

Further reading

Loredana Marcovecchio M, and Chiarelli F. (2011). Microvascular disease in children and adolescents with type 1 diabetes and obesity. *Pediat Nephrol* **26:** 365–75.

Sickle cell disease

Haematuria may occur in sickle cell disease due to sickling of red blood cells in the renal medulla. This occurs because the:

- PaO_2 in the renal medulla is below the threshold for sickling.
- Osmolality of the medulla is high.
- Medulla is relatively acidic.

Characteristics of renal problems in sickle cell disease

- Haematuria may occur with HbSS or HbAS.
- Renal involvement causing haematuria may be unilateral and associated with discomfort in the loin of the affected side.
- Haematuria may be severe and prolonged.
- The medullary pyramids are echobright on US.
- Papillary necrosis may occur (see 📖 'Papillary necrosis', p.251).
- FSGS may develop.

Treatment of macroscopic haematuria

- 0.45% saline at 4L/1.73m^2/day.
- Furosemide to increase urine flow.
- Alkalinization with oral sodium bicarbonate.

Papillary necrosis

- May develop even without obvious haematuria and in young children.
- It can be identified by CT scan or IVP, when clubbed calyces and an irregular medullary cavity are seen.
- It causes a urine concentrating defect so patients with sickle cell disease should be encouraged to ingest a high fluid intake.

Other renal pathology

- Repeated vaso-occlusive episodes in the vasa recta lead to ischaemia–hyperperfusion injury, early glomerular enlargement, then FSGS, the most common cause of CKD in sickle cell disease.
- The ischemia–hyperperfusion generates a chronic inflammatory response which leads to tubulointerstitial changes, loss of nephrons, and eventual sclerosis.
- Proteinuria is the most common clinical manifestation of these changes and may progress to nephrotic syndrome.
- In the distal nephron, the loss of the vasa recta results in impaired concentrating ability.

Renal involvement in cystic fibrosis

- As the prognosis improves for patients with cystic fibrosis (CF) renal complications of the illness are more frequently seen.
- There are several possible mechanisms of renal injury in CF, including complications arising from chronic infection, immunological dysregulation (perhaps as a result of chronic infection or inflammation) and drug therapy.
- Even though the CF transmembrane regulator (CFTR) is widely expressed in the kidney, there is no evidence for a primary renal involvement.

Nephrocalcinosis and nephrolithiasis

CF is associated with an increased risk of nephrocalcinosis and nephrolithiasis for various reasons:

- Prolonged periods of immobilization.
- Use of steroids or furosemide therapy.
- *Secondary alimentary hyperoxaluria:* calcium usually complexes with oxalate in the gut, preventing oxalate absorption (i.e. calcium is an 'oxalate binder', as well as a phosphate binder, as used in CKD). In fat malabsorption as can occur in CF due to exocrine pancreatic dysfunction, fatty acids compete with oxalate for calcium binding, thereby increasing oxalate absorption.

Nephrotoxic drugs

- A number of potentially nephrotoxic drugs are routinely used in the management of children with CF including aminoglycoside antibiotics, cephalosporins, loop diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs). Nephrotoxic acute tubular necrosis (ATN) is a recognized complication of certain drug therapy (e.g. aminoglycosides) and differs clinically from ischaemic ATN in that the former is more likely to be associated with a non-oliguric presentation and gradual onset of renal failure.
- The drug most commonly associated with AKI in CF is gentamicin, which should therefore be avoided. Tobramycin appears to have less nephrotoxicity. As much as possible, antibiotics should be given nebulized, rather than systemically. The risk for AKI can be further minimized by once-daily dosing and close attention to drug levels.
- NSAIDs are used in CF for the management of CF-related arthropathy, and may be associated with renal vasoconstriction and acute renal dysfunction, especially in the context of the chronic salt depletion associated with CF.

Tubulointerstitial nephritis

- Tubulo-interstitial nephritis (TIN) may complicate CF as a result of an allergic reaction to antibiotics or infection. Polyuria/polydipsia is common and systemic signs of allergy, such as rash and non-specific symptoms, such as malaise, fever, and vomiting may be present.
- Laboratory investigations demonstrate elevation of plasma urea and creatinine, occasionally accompanied by hypokalaemia and hypophosphataemia (due to the proximal tubular dysfunction), and sometimes a peripheral blood and/or urinary eosinophilia (request Wright stain on urine sample).
- Urinary examination may reveal haematuria, proteinuria (positive dipstick for protein, but little urinary albumin implying tubular rather than glomerular protein leak) and glycosuria.
- US usually demonstrates large, echo bright kidneys.
- Renal biopsy demonstrates an interstitial infiltrate with frequent eosinophils, sometimes with tubular dilatation and areas of TIN fibrosis (see 🕮 'Tubulointerstitial nephritis', p.168).

IgA nephropathy

IgA nephropathy (IgAN) is a rare complication and co-existence may be coincidental, but there may be a real association due to recurrent respiratory tract infections, with increased circulating IgA with glomerular deposition.

Other renal manifestations of cystic fibrosis

- Amyloidosis may complicate CF due to the chronic inflammatory nature of the disease. The prognosis is generally poor with nearly all dying within a year of clinical onset, although there may be a role for colchicine.
- Systemic vasculitis occasionally complicates CF, the cause of which is unknown, but presumably reflects an aberrant immune response to chronic infection or drug therapy, or both. The vasculitis is predominantly cutaneous, but occasionally is more widespread with both cerebral and renal involvement (renal failure and focal glomerular sclerosis and capsular adhesions) reported.
- CF may be complicated by diabetes mellitus, and reports of diabetic nephropathy in this context have been documented.

Sarcoidosis

Background

- Idiopathic multisystemic inflammatory disease with non-caseating granulomata in affected tissues.
- The cause is unknown:
  - aberrant host responses (under genetic control) to infection (undefined organism) remain the main hypothesis;
  - candidate genes may reside in loci that influence regulation of antigen presentation and/or T-cell function resulting in increased granulomata formation and fibrosis.

Epidemiology

- Prevalence varies worldwide and by age: primarily a disease of 20–40-year-olds. It is twice as common in females.
- The disease is more common in Japanese and Black children, although this racial distribution varies with geographic location. Sarcoid is seen more commonly in developed than underdeveloped areas.
- True incidence and prevalence in children is unknown.
- In Denmark, where the disease has a high prevalence, the incidence in children younger than 15 years is 0.22–0.27 per 100,000/year; 0.06 per 100,000 children under the age of 4 years; and increases gradually with age to 1.02 per 100,000 in children aged 14–15 years.

Genetics of sarcoidosis

- There is an increased incidence of sarcoidosis in certain families.
- An HLA association has been described: DQB1*0603, DQB1*0604, and DPB1*0201:
  - in the US, familial clusters are observed in African-Americans in 19%, compared to 5% in white families;
  - monozygotic twins are 2–4 times more concordant for disease than dizygotic twins;
  - recent studies suggest a unique candidate gene BTNL2 in the MHC II region on chromosome 6.

Relationship between early onset sarcoidosis (EOS) and Blau's syndrome

- EOS refers to young children with disease onset in the first 5 years of life. These children differ from those with sarcoidosis of later presentation:
  - EOS typically presents with the classic triad of rash, arthritis, and uveitis (in that order), but without apparent pulmonary involvement or hilar lymphadenopathy;
  - EOS typically presents in the first year of life;
  - uveitis, which occurs in more than half the children with EOS, is relatively less common in patients with later onset disease.
- Blau's syndrome is an autosomal dominant granulomatous disease with the same classic triad of rash, arthritis, and uveitis, i.e. an identical clinical phenotype to EOS.

- Recent data suggest that EOS and Blau's syndrome represent the same disease since both share genetic mutations in the nucleotide binding oligomerization domain 2 gene (*NOD2*, also referred to as the *CARD15* gene).
- The *NOD2* gene probably has no major effect on sarcoidosis susceptibility in older patients, however.

Clinical features

This is a multisystem disease so presentation can vary greatly.

- *Multi systemic presentation:* older children usually present in a similar manner as adults with lymphadenopathy, pulmonary involvement, and systemic symptoms (fever, malaise, fatigue, and weight loss), in contrast to the presentation of EOS.
- *Renal and biochemical findings:*
  - renal involvement is rare in children and adults, and may be asymptomatic; renal involvement is usually secondary to hypercalcaemia and/or hypercalciuria (occurring in approximately 30% of paediatric sarcoid cases), rather than renal infiltration with granulomata;
  - polyuria, enuresis (secondary nephrogenic diabetes insipidus (NDI) from hypercalcaemia);
  - hypercalcaemia +/– hypercalciuria;
  - hypercalciuria in the absence of hypercalcaemia;
  - nephrocalcinosis and nephrolithiasis (only if hypercalciuria);
  - bilateral enlargement of the kidneys;
  - tubulointerstitial nephritis;
  - rarely glomerular lesions: classically membranous glomerulonephritis, but crescentic nephritis has also been reported.
- *Pulmonary disease:* is the most commonly involved organ:
  - chronic cough with or without dyspnea;
  - bilateral hilar lymphadenopathy with or without parenchymal involvement is the most common radiographic finding;
  - the hilar lymphadenopathy is usually symmetrical;
  - parenchymal disease, pleural effusions, and atelectasis occur less commonly in children than in adults (25% of affected adults are affected with these);
  - nearly half of all children with sarcoidosis demonstrate restrictive lung disease on pulmonary function tests;
  - an obstructive pattern secondary to intrabronchial granuloma or mediastinal lymph node airway compression may occasionally be observed.
- *Lymphadenopathy and hepatosplenomegaly:* lymphadenopathy, including retroperitoneal lymphadenopathy, is commonly observed, and can occur with or without hepatosplenomegaly.
- *Skin disease:* 77% of young children, and 24–40% of older:
  - sarcoid should be considered in the differential diagnosis of unusual skin lesions in children;
  - most common is a cutaneous eruption with soft, yellowish-brown flat topped papules found most frequently on the face;
  - larger violatious plaque-like lesions may be found on the trunk and extremities;

  - erythema nodosum is reported in 31%;
  - other lesions include nodules and subcutaneous tumours, hyper- or hypo-pigmented lesions, and ulcers.
- *Eye disease:* it should be remembered that young children may be asymptomatic, although blind in one eye at presentation. All of the following are described in sarcoid:
  - uveitis: general term used to describe inflammation of the uvea, comprising the iris, ciliary body and choroid;
  - iridocyclitis (inflammation of the iris and ciliary body);
  - posterior uveitis: predominantly choroid but not iridocyclitis;
  - lacrimal gland swelling;
  - conjunctival granulomata;
  - vitritis;
  - chorioretinitis;
  - optic neuritis;
  - proptosis;
  - interstitial keratitis.
- *Musculoskeletal disease:* affects 15–58% of affected children:
  - arthralgia;
  - arthritis, usually affecting multiple joints: boggy tenosynovitis with relatively painless effusion and little or no overlying erythema of skin; erosive changes on x-ray usually absent;
  - bone cysts (especially small bones of hand and foot);
  - muscle involvement can occur, but is unusual.
- *Neurological:* neurosarcoid is rare in children, but is described, and includes:
  - encephalopathy and seizures;
  - cranial nerve involvement;
  - cerebral mass lesion (rare in posterior fossa);
  - spinal cord involvement;
  - aseptic meningitis;
  - obstructive hydrocephalus.
- *Other:*
  - parotid enlargement (with uveitis sometimes called 'uveo-parotid fever');
  - rectal prolapse;
  - sicca syndrome;
  - testicular mass;
  - pericardial effusion;
  - myocardial involvement;
  - granulomatous large and medium size vessel vasculitis.

Differential diagnosis

- Infection causing granulomatous inflammation, including:
  - *Mycobacterium tuberculosis*;
  - leprosy;
  - histoplasmosis;
  - blastomycosis.
- Chronic granulomatous disease (exclude with nitroblue tetrazolium test; see 📖 'Laboratory findings and investigations', p.257).

- Blau's syndrome (see 📖 'Relationship between early onset sarcoidosis (EOS) and Blau's syndrome', p.254).
- Systemic onset juvenile idiopathic arthritis.
- Granulomatous small vessel vasculitis including Wegener's granulomatosis, and Churg–Strauss syndrome.
- Crohn's disease may rarely be confused with sarcoidosis.
- Lymphoma.
- Berylliosis: inhalation of beryllium has been associated with a granulomatous lung disease known as chronic beryllium disease (CBD).

Laboratory findings and investigations

No single test is diagnostic of sarcoid, and ultimately tissue diagnosis and the exclusion of other diseases that can mimic sarcoid is required. The historical Kveim–Siltzbach test, whereby intradermal injection of a splenic extract from a known sarcoid patient resulted in sarcoid granulomata in a suspected case, is antiquated, and the standard test reagent no longer available. Observed laboratory findings include:

- Leucopaenia, thrombocytosis, eosinophilia relatively common.
- High ESR and CRP.
- *Hypercalcaemia:* varies from 2 to 60% of cases. The mechanism of this appears to be that abnormal pulmonary macrophages synthesize $1,25(OH)_2$ vitamin D from 25-hydroxy vitamin D, and are relatively insensitive to feedback by hypercalcaemia.
- Abnormal liver function.
- Raised Ua:Ucr.
- Tubular function abnormalities (see 📖 'Tubulointerstitial nephritis', p.168).
- Raised serum angiotensin-converting enzyme (sACE). Epithelial cells in the granulomas produce sACE, which thus may be elevated. This can also be used to monitor response to therapy, but is neither absolutely sensitive, nor specific.
- Mantoux test (to exclude TB). *NB:* sarcoid patients commonly demonstrate anergy (no response) to purified protein derivatives of *Mycobacterium tuberculosis* even if previously exposed.
- Nitroblue tetrazolium (NBT) test (alternatively a flow cytometric test of neutrophil oxidative metabolism using dihydrorhodamine) to exclude chronic granulomatous disease.
- Eye screen for uveitis.
- X-rays of affected bones and joints.
- *CXR:* standard screen for pulmonary sarcoid.
- Increased sensitivity of detection of pulmonary involvement with high resolution CT of chest.
- Pulmonary function tests including transfer factor.
- Magnetic resonance imaging (MRI) of brain for suspected neurosarcoid.
- *Tissue biopsy:* skin, lung, salivary glands. Occasionally renal biopsy.
- ECG and echocardiogram for suspected cardiac involvement. Cardiac MRI may also have a role in this context.

Treatment

- Acute transient disease requires rest and NSAIDs.
- Chronic and/or severe multisystemic disease requires corticosteroid therapy, e.g. 0.5–2mg/kg daily prednisolone, tapering over 2–3 months.

- An additional immunosuppressant agent may be required for persistent progressive sarcoidosis: methotrexate, or azathioprine: a RCT of methotrexate in 24 adults with sarcoid demonstrated steroid sparing efficacy.
- Occasionally cyclophosphamide or ciclosporin have been used for more aggressive disease.
- Ocular involvement usually responds to corticosteroid administered locally or systemically.
- Biological therapy including anti-tumour necrosis factor (TNF) alpha has been used in some severe cases.

Prognosis

- Guarded prognosis for young children with EOS: nearly all develop long-term morbidity from uveitis, polyarthritis or other organ involvement.
- Older children have a variable prognosis, dependent on organ involvement, geography, sex, and race:
  - long-term follow-up of 46 Caucasian Danish children reported 78% complete recovery;
  - 11% still had chronic active disease with multi-organ involvement;
  - 7% died;
  - 4% were recovered, but with residual organ damage including unilateral loss of vision and abnormal chest radiography;
  - the presence of erythema nodosum was associated with a good prognosis, and CNS sarcoidosis was associated with a poor prognosis.
- In another series of 19 children followed up for a mean of 21 years:
  - 37% had persistent abnormalities on CXR;
  - 68% had impaired lung function;
  - 63% had abnormal findings on echocardiography.

Further reading

Shetty AK, and Gedalia A. (2008). Childhood sarcoidosis: a rare but fascinating disorder. *Pediat Rheumatol* **6**: 16.

Milman N, and Hoffman AL. (2008). Childhood sarcoidosis: long-term follow-up. *Eur Respir J* **31:** 592–8.

Marcille R, McCarthy M, Barton JW, Merten DF, Spock A. (1992). Long-term outcome of pediatric sarcoidosis with emphasis on pulmonary status. *Chest* **102:** 1444–9.

Mitochondrial cytopathies

Basic principles

- Mitochondria are intracellular organelles involved in ATP-generation (cellular 'power plants'). They are derived from symbiotic bacteria that were eventually incorporated into the cell. Consequently, they carry their own circular DNA—the mitochondrial DNA.
- Because mitochondrial DNA (which also encodes ribosomal RNA) is derived from bacteria, mitochondria are particular susceptible to antibiotics that target prokaryotic protein synthesis, such as aminoglycosides, chloramphenicol and tetracyclines. This is the basis for the human toxicity of these antibiotics—an acquired mitochondrial cytopathy.
- Mitochondrial DNA derives from the oocyte, not the sperm. Thus, it is inherited from the mother.
- The oocyte contains multiple mitochondria. A mutation may not be present in all of them. The passing on of mitochondria to daughter cells occurs randomly, thus some cells may contain more mutated mitochondrial DNA than others. This is referred to as heteroplasmy and explains why some tissues may be affected more than others in a given patient. Similarly, if a mother carries a mitochondrial mutation, some oocytes may receive a higher proportion of the mitochondria carrying the mutation than others, resulting in phenotypic variability.
- The mitochondrial genome is incomplete for the functioning of mitochondria as it encodes only 37 genes. A mitochondrium hosts about 3000 proteins and the genes encoding all the other proteins are localized in the nuclear DNA. Consequently, mitochondrial diseases can be inherited maternally (if the mutation is localized in the mitochondrial DNA) or autosomal recessive (if the mutation is in the nuclear DNA).
- Because mitochondria are responsible for ATP and thus cellular energy generation, the symptoms can be extremely variable. Several defined syndromes exist, but there is considerable overlap and variability.

Clinical manifestations of mitochondrial disease

- *Bone marrow:* Pearson's syndrome with pancytopaenia.
- *Brain:*
  - ataxia;
  - stroke;
  - seizures;
  - dementia;
  - migraine.
- *Eye:*
  - external ophthalmoplegia;
  - optic neuropathy;
  - pigmentary retinal degeneration;
  - cataract;
  - corneal dystrophy;
  - ptosis.

- *Heart:*
  - Cardiomyopathy;
  - conduction blocks;
  - Wolff–Parkinson–White syndrome.
- *Inner ear:* sensorineural deafness.
- *Intestine:* malabsorption.
- *Kidney:*
  - Fanconi syndrome;
  - nephrocalcinosis;
  - glomerulopathy/FSGS.
- *Liver:* hepatopathy.
- *Pancreas:*
  - diabetes mellitus;
  - exocrine dysfunction.
- *Skeletal muscle:*
  - myopathy;
  - fatigue;
  - weakness.
- *Other:*
  - short stature;
  - episodic nausea and vomiting;
  - hypoparathyroidism;
  - adrenal insufficiency;
  - lactic acidosis;
  - elevated cerebrospinal fluid protein;
  - peripheral neuropathy;
  - myoclonus.

Classical syndromes associated with mitochondrial cytopathy

- *MERRF:* myoclonic epilepsy with ragged red fibres.
- *NARP:* neuropathy, ataxia, and retinitis pigmentosa.
- *MELAS:* mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.
- *Leigh syndrome:* maternally inherited Leigh syndrome (somnolence, blindness, deafness, peripheral neuropathy, degeneration of brainstem).
- *Pearson syndrome:* pancytopaenia, exocrine pancreatic deficiency, hepatic dysfunction.
- *Kearns–Sayre syndrome:* ophthalmoplegia, pigmentary retinopathy, heart block, ataxia.
- *Alper's syndrome:* intractable epilepsy, liver disease, neuronal degeneration.

The kidney and mitochondrial cytopathy

- The most common renal manifestation associated with mitochondrial cytopathies is Fanconi syndrome, although a few patients have focal segmental glomerulosclerosis. Some may have nephrocalcinosis.
- Renal manifestations rarely occur alone and are usually associated with other symptoms, mainly neurological disease. Most patients present in the first months of life. The prognosis is guarded for infants with severe neurological and renal disease associated with mitchondrial cytopathy.

Investigations to be considered in suspected mitochondrial disease

- FBC, U&Es, creatinine, bicarbonate, albumin, bone and liver function, and fasting glucose.
- Formal GFR may be helpful as, due to poor muscle mass, creatinine may be deceptively low.
- Thyroid function.
- Parathyroid hormone (PTH).
- Plasma cortisol (24-h profile).
- Synacthen® test.
- Plasma lactate, pyruvate, ketone bodies (acetoacetate and β-hydroxybutyrate) and lactate: pyruvate molar ratio.
- CSF lactate: pyruvate ratio.
- Bone marrow aspirate/trephine if there is evidence of marrow failure as other causes of this, e.g. leukaemia must be excluded.
- ECG (24-h monitor), CXR, and echocardiogram.
- Ophthalmological review.
- EEG, electromyography (EMG), nerve conduction.
- MRI brain.
- Audiometry or other age-specific hearing test.
- Muscle biopsy (quadriceps): to include standard histological stains, electron microscopy, and respiratory chain assays.
- Skin biopsy for fibroblast culture.
- Blood for nuclear and mitochondrial DNA analysis.
- Urine for tubular function tests: amino acids, pH, tubular proteins, TRP.
- Ua:Ucr.
- Urine organic acids to exclude other inborn error of metabolism associated with acidosis.
- Renal and abdominal US.
- Renal biopsy.

Treatment

There is no cure although some forms can be dramatically improved, e.g. by coenzyme Q supplementation in patients with mutations in COQ2 or PDSS2, who cannot synthesize coenzyme Q themselves (see 📖 'Overview of inherited glomerular diseases', p.182). Expert advice is imperative in suspected mitochondrial disease in order not to miss such therapeutic opportunity. Therapy is divided into general supportive, and specific pharmacological attempts to improve the respiratory chain defect:

General

- Treat tubulopathy: adequate hydration, correction of acidosis, potassium, sodium, phosphate supplementation. Alfacalcidol for rickets and hypocalcaemia.
- Treat underlying endocrinopathy/exocrinopathy (diabetes, exocrine pancreas insufficiency, adrenocortical insufficiency, hypoparathyroidism, hypothyroidism).
- Treat seizures.
- Cochlear implants for deafness (*NB.* There can be no more MRI scans after insertion of cochlear implants since they contain metal).
- Eyelid (ptosis) and cataract surgery.

- Cardiac pacing.
- Gastrostomy.
- Speech and physiotherapy.
- Renal transplantation (and cardiac/hepatic transplantation) has been performed in children with mitochondrial disease. On the whole, however, the prognosis remains guarded because of the extra renal disease.

Specific: seek expert advice (systematic studies lacking)

- Ubiquinone (coenzyme Q10).
- Vitamin C, E, and K.
- Carnitine.
- Vitamins B1 and B2.
- Avoid drugs known to interfere with respiratory chain: valproate, barbiturates.
- Avoid drugs that inhibit mitochondrial protein synthesis: aminoglycosides, tetracyclines, chloramphenicol.
- Ketogenic diet.
- Genetic counselling.

Fabry disease

Background

- An X-linked recessive lysosomal storage disorder caused by mutations of the gene encoding the lysosomal hydrolase, ∝-galactosidase A, resulting in systemic accumulation of globotriosyceramide (GB3).
- Usually presents in young adults, but may present in childhood in hemizygous males and some heterozygous females, but the diagnosis is often unrecognized owing to its variable presentations and low incidence.
- Classical presenting symptoms are neuropathic pain, angiokeratomas, and hypohidrosis
- Later there is cardiac, cerebral, and renal involvement, leading to multi-organ dysfunction and death.
- A family history is present in up to one half of patients.

Renal involvement

- Presents with nephrogenic diabetes insipidus, proteinuria, haematuria, and/or CKD, although this is rare in childhood.
- GB3 is deposited in glomeruli, particularly the podocytes, leading to proteinuria. Nephrotic-range proteinuria is uncommon,
- GB3 is also deposited in the tubules, so proteinuria may also be tubular in origin. The distal tubules are affected first, leading to decreased urinary concentrating capacity, so polyuria and polydipsia may be the earliest symptoms. Eventually, the proximal tubules become affected, occasionally producing Fanconi syndrome.
- Urine sediment contains oval fat bodies (degenerating tubular epithelial cells).
- Urinary excretion of GB3 may be increased.

Diagnosis

- Diagnosis is confirmed by measurement of ∝-galactosidase A activity in leucocytes, plasma, or cultured skin fibroblasts.
- More than 300 mutations have been identified, so detection of a mutation in a new family requires complete sequencing of the gene.

Treatment

- Enzyme replacement therapy decreases neuropathic pain and Gb3 deposition (seek expert advice).
- Early institution of this therapy may be able to prevent irreversible tissue damage.

Further reading

Ramaswami U, Najafian B, Schieppati A, Mauer M, Bichet DG. (2010). Assessment of renal pathology and dysfunction in children with Fabry disease. *Clin J Am Soc Nephrol* **5:** 365–70.

Amyloidosis

Background

- Amyloidosis refers to a heterogeneous group of diseases characterized by normally soluble proteins deposited extracellularly in an abnormally folded, insoluble fibrillar form.
- Can lead to organ impairment including CKD and premature death.
- Is now rarely seen largely since inflammatory diseases leading to secondary (reactive) amyloidosis are now better controlled with newer drugs.
- Similarly, dialysis-related amyloidosis is rare in the young, principally due to their shorter waiting times for renal transplantation.
- Genetic autoinflammatory diseases (also referred to as periodic fever syndromes) are now emerging as the leading cause of reactive systemic amyloidosis affecting children and adults.

Amyloid

- Amyloid represents a heterogeneous group of proteins. Present in most forms of amyloid, however, is a carbohydrate moiety in the form of glycosaminoglycans and proteoglycans. Most forms of amyloid also contain the protein amyloid-P. This can be exploited diagnostically (see 🕮 'Investigation of suspected amyloidosis', p.265).
- At least 17 different amyloid proteins are described. The two most clinically important are amyloid-A (AA) and amyloid-L (AL).
- AL comprises monoclonal immunoglobin light chains and occurs in patients with myeloma-associated amyloidosis. Hence it is usually seen in adults, although some genetic forms of amyloidosis contain AL.
- Protein AA (derived from serum amyloid A—SAA) is an acute phase reactant, and is associated with the amyloidosis of chronic inflammation such as that seen in poorly controlled juvenile idiopathic arthritis, and familial Mediterranean fever (see 🕮 'Familial Mediterranean fever', p.266).
- The remainder of this section will deal with this type of reactive AA amyloidosis, since it is the commonest type seen in children.

Causes of reactive amyloid-A amyloidosis

Poorly-controlled inflammatory disease of any cause, including:

Juvenile idiopathic arthritis

- Particularly systemic juvenile idiopathic arthritis (SJIA; previously called Still's disease).
- Adolescent onset rheumatoid arthritis.
- Other forms of arthritis in children including enthesitis (inflammation at tendinous insertions into bones) and related arthritis (including juvenile ankylosing spondylitis and its variants).

Autoinflammatory diseases

- *FMF:* associated with mutation of the *MEFV* gene.
- Cryopyrin associated periodic fever syndromes (CrAPS) associated with mutation in the *NLRP3* gene, which include:

  - chronic infantile neurological cutaneous and articular (CINCA) syndrome, also referred to as neonatal onset multisystemic inflammatory disease (NOMID);
  - Muckle–Wells syndrome;
  - familial cold autoinflammatory syndrome.
- TNF-alpha receptor associated periodic fever syndrome (TRAPS- previously known as 'familial Hibernian fever') associated with mutation in the *TNFRSF1A* gene.
- Hyper IgD syndrome ('Dutch fever'), associated with mutations in the *MVK* gene. Apart from FMF, these are beyond the scope of this chapter.
- Worthy of note is that SLE and systemic sclerosis are rarely associated with amyloidosis.

Clinical features of reactive AA amyloidosis

The spleen, liver, and kidneys are often involved first in reactive AA amyloidosis. Symptoms and signs develop insidiously, usually on the background of a chronic inflammatory disorder, and the clinician must remain vigilant to the possibility of amyloidosis. Symptoms and signs include:

- Weakness.
- Fatigue.
- Weight loss.
- Proteinuria and nephrotic syndrome with CKD—the major cause of death in AA amyloidosis.
- Malabsorption, bowel obstruction, diarrhoea, hepatosplenomegaly.
- Other manifestations relate mainly to AL amyloidosis, although may occur in AA amyloidosis, and include:
  - cardiac conduction defects;
  - restrictive cardiomyopathy and cardiac failure;
  - lung involvement;
  - skin papules;
  - neuropathy—particularly carpal tunnel syndrome;
  - arthropathy;
  - macroglossia;
  - vasculopathy;
  - autonomic dysfunction.

Investigation of suspected amyloidosis

- SAA will be chronically elevated.
- Renal function.
- Ua:Ucr.
- Radiolabelled serum amyloid P scintigraphy ('SAP scan'), available in specialized centres only. Helps localize the amyloid, and helpful imonitoring response to therapy. SAP scans are relatively poor at detecting cardiac amyloidosis. Cardiac MRI is increasingly used in this context.
- *Tissue biopsy:* rectal, renal, skin, or subcutaneous fat. Stain with Congo red, which reveals apple green birefringence when examined under polarized microscopy.

- Genetic studies to determine underlying cause if chronic inflammatory disease not apparent or undiagnosed—seek expert advice:
  - suspected autoinflammatory diseases;
  - other genetic tests for the many primary genetic types of amyloidosis—all rare in children but occasionally seen.

Treatment and prognosis of reactive AA amyloidosis

- Depends on cause.
- If not detected and treated early will ultimately progress leading to CKD and death since no definitive cure available. Thus, prevention is of prime importance.
- In chronic inflammatory diseases, cytotoxic therapy with chlorambucil and melphalan in combination with corticosteroids may improve the prognosis in JIA and rheumatoid arthritis (RA) patients. Increasingly, novel biological agents, such as anakinra (IL1 receptor antagonist) are being used to treat amyloidosis with some anecdotal success describing regression of amyloid.
- Colchicine plays an important role in the prevention of amyloidosis in FMF, and may also improve the prognosis for established amyloidosis in this context. Specifically it slows the progression of CKD and reduces proteinuria. Colchicine acts by inhibiting leukocyte chemotaxis through a direct effect on their microtubules. May also down-regulate cell adhesion molecule expression on leukocytes and endothelial cells.

Familial Mediterranean fever

- FMF is common in eastern Mediterranean countries, and is the commonest periodic fever syndrome with propensity to develop reactive AA amyloidosis.
- Inheritance is autosomal recessive, but 'pseudo-dominant' because of high carriage rates in prevalent areas. The MEFV mutations: exons 2, 10 (chromosome 16) result in abnormalities of the protein pyrin, an important regulator of inflammation.
- *Duration of fever attacks:* 1–4 days. Other features include:
  - serositis: abdominal pain, chest pain, pericarditis, scrotal pain;
  - splenomegaly;
  - erysipelas like rash on lower limbs;
  - HSP/PAN-like presentation in some patients;
  - propensity to reactive (AA) amyloidosis.

Treatment

Colchicine 500–2000micrograms/day. This will ameliorate fever attacks, lower SAA, and protect against the onset of reactive AA amyloidosis. It will also slow the progression of established AA amyloidosis. Concerns regarding long-term toxicity have not been borne out, and thus colchicine therapy in this context is for life. Colchicine is usually started at a low dose (e.g. 250micrograms/day) and increased over a few weeks in order to limit GI side effects, which are usually transient.

Corticosteroids are usually ineffective for the treatment of FMF.

Prognosis

With continuous colchicine therapy, most FMF patients are free from inflammatory attacks, and will not develop amyloidosis.

Amyloidosis can also recur in transplanted kidneys, so colchicine needs to be continued after renal transplantation for amyloidosis in FMF patients.

Dialysis-related amyloidosis

- A specific form of β_2 microglobulin amyloidosis related to long-term dialysis. Affects virtually all patients dialysed for more than than 20 years.
- Symptomatic amyloid is rare in children, but β_2 microglobulin may be raised.
- A prospective post-mortem study found deposition of amyloid in joints in 21% of patients haemodialysed for 2 years, 50% after 7 years and 100% after 13 years.
- Dialysis amyloidosis occurs because of the inability of conventional haemodialysis (HD) membranes and time schedules or peritoneal dialysis (PD) to remove the relatively large molecule β_2-microglobulin, the primary component of amyloid deposits. New high flux membranes offer better removal of β_2-microglobulin for HD patients as do haemodiafiltration and longer times on dialysis.
- Since there is limited β_2-microglobulin clearance by PD, those patients undergoing long-term PD are at risk.
- Histological demonstration of amyloid deposits in synovial, fat or tissue biopsy is diagnostic. β_2-microglobulin has a high affinity for collagen, which may explain the predominance of joint and bone disease in patients with dialysis-related amyloidosis. Synovial biopsy, aspiration, and joint fluid and radiographic features are especially important diagnostically.
- Diagnosis is supported by the finding of grossly elevated plasma β_2-microglobulin levels of the order of 30–50mg/mL (normal 0.8–3).

Clinical features appear after 10 to 15 years on dialysis and include:

- Carpal tunnel syndrome.
- Arthropathy.
- Chronic tenosynovitis of finger flexor tendons.
- Subcutaneous and glossal lumps.
- Destructive spondyloarthropathy of cervical spine.
- Cord compression from amyloidosis in the dural space.
- Pathological bone fracture.
- Cardiac amyloid causing arrythmias and/or cardiac failure from myocardial and conductive system involvement, valvular dysfunction, restrictive pericarditis.
- Genito-urinary deposition with renal, ureteric and bladder deposits causing urinary obstruction.

Further references

Ben-Chetrit E. (2003). Familial Mediterranean fever (FMF) and renal amyloidosis. Phenotype–genotype correlation, treatment and prognosis. *J Nephrol* **16:** 431–4.

Kastner DL, Aksentijevich I, and Goldbach-Mansky R. (2010). Auto-inflammatory disease reloaded: a clinical perspective. *Cell* **140:** 784–90.

Little MA, Cafferky M, Menon S, and Farrington K. (2005). Dialysis amyloid: the bottom line. *Nephrol Dialysis Transpl* **20:** 462–3.

The emergency renal management of inborn errors of metabolism

Background

Inborn errors of metabolism (IEMs) may first present in the neonatal/early infancy periods with hyperammonaemic encephalopathy, acidosis, and hypoglycaemia. Neonatal hyperammonaemia is a medical emergency, as brain damage ensues. These patients should only be treated in a centre with experience in neonatal dialysis and metabolic diseases. In addition, metabolic decompensation may occur at any age in patients with IEM during intercurrent illness.

The following is a guideline for the acute renal management of neonates/infants who present with metabolic crises when the diagnosis is not established, and for those who present with metabolic decompensation in the context of an established diagnosis. This section does not provide a comprehensive review of the many and varied metabolic diseases.

Important general points of note

- The key to success for the management of hyperammonaemia is rapid removal of ammonia from the body. Unlike the rapid removal of urea, this is not associated with a disequilibrium syndrome.
- Children with IEMs may be significantly malnourished, therefore plasma creatinine provides a poor estimate of GFR.
- Renal replacement therapy (RRT) (HD, PD, continuous veno-venous hemofiltration (CVVH), plus dialysis (CVVHD), exchange transfusion) are rarely required for the management of metabolic crises, for which diet and emergency metabolic regimens form the main of treatment.

Acute severe encephalopathy (including hyperammonaemia and aminoacidopathies)

Hyperammonaemia (>170μmol/L) strongly suggests metabolic disease. Lower levels may be a non-specific consequence of illness. Children with IEMs may develop permanent brain damage as a result of the accumulation of ammonia and other toxic low-molecular weight molecules. Those with ammonia levels >1000μmol/L rarely escape without neurological handicap.

Possible causes include:

- Urea cycle disorders (e.g. ornithine transcarbamylase deficiency, arginosuccinic acid synthetase deficiency (ammonia levels typically >400μmol/L with respiratory alkalosis).
- Maple syrup urine disease (*NB:* ammonia normal in most cases).
- Organic acidaemias (methylmalonic acidaemia, propionic acidaemia (ammonia levels typically 200–500μmol/L and ketones in urine are characteristic findings).

Investigations

Diagnostic investigations

- Plasma amino acids.
- Urine organic and amino acids including orotic acid.
- Acyl carnitines (Guthrie card).

To monitor response to treatment:
- Ammonia, U&Es, creatinine, LFTs (6-hourly).
- Clotting.
- Glucose.
- Plasma amino acids.
- Blood gas.
- Plasma lactate.

Emergency treatment

The goals of treatment are to decrease ammonia production and increase ammonia removal rate. Blood purification should be performed in any child with a plasma ammonia > 400μmol/L. Whilst HD is the most efficient way of clearance, the most commonly used modality is CVVHD, as it is better tolerated and can be continued for prolonged periods of time:
- Provide adequate calories, fluid, and electrolytes IV (10% glucose).
- Avoid additional sodium supplements since metabolic drugs for hyperammonaemia have a high sodium content.
- Hyperammonaemia causes vasomotor instability, and boluses of colloid may be required.
- Additional therapies employed for hyperammonaemia are sodium benzoate and sodium phenylbutyrate (250–500mg/kg/24h. Seek expert advice regarding dosing for individual cases); arginine and carnitine.

Management of severe metabolic acidosis in organic acidaemias, and severe lactic acidosis

- Calculate the anion gap (AG): (Na) – (HCO_3 + Cl) (normal range 8–12mmol/L). In organic acidaemias and lactic acidosis (e.g. methylmalonic acidaemia (MMA), proprionic acidaemia (PA)) the AG is increased, whereas in renal tubular acidosis, the AG is normal or decreased. Ensure that hypovolaemia and sepsis are adequately treated.
- Consider correcting acidosis using a 'half correction' based on the formulae:

Pre-term: (0.6 × weight (kg) × base excess)/2

Term neonate/children: (0.3 × weight (kg) × base excess)/2
= mL of 8.4% IV $NaHCO_3$

This is hyperosmolar and should be administered diluted (in normal saline or 5% albumin) by at least 50%, i.e. give as 4.2%).
- Multiple corrections may be required. Beware hypernatraemia/carbia—consider tris(hydroxymethyl)aminomethane (THAM) if this occurs (1 mL of 7.2% THAM = 1 mmol of sodium bicarbonate); however, the use of THAM involves the administration of a significant volume of fluid and should only be administered in an intensive care unit: beware fluid overload and secondary hypokalaemia (due to shift into cells).
- If there is considerable encephalopathy, acidosis, or large amounts of bicarbonate have been required, consider CVVHD or HD. If vascular access is not feasible, consider PD using a bicarbonate-containing solution such as Physioneal.

Methylmalonic acidaemia

With early diagnosis and treatment, the more severe cases of MMA are surviving longer. There are 4 important renal considerations in MMA:

- Prerenal AKI during metabolic decompensation, with acute tubular dysfunction resulting in severe tubular sodium leak.
- CKD possibly secondary to urate nephropathy or chronic interstitial nephritis, particularly in non-B12 responders.
- Renal tubular dysfunction, impaired urinary concentrating ability.
- Hypertension.

It is important to appreciate that children with MMA may have pre-existing renal impairment since this will contribute to the acidosis and dehydration, which occur during episodes of acute decompensation. The severity of AKI may be masked by a relatively low plasma creatinine because of small muscle bulk and low protein diet. Consider HD in severe metabolic decompensation.

Successful management of CKD 5 in MMA with dialysis, and isolated kidney or combined liver-kidney transplant has been achieved.

Cystinosis

Background

Nephropathic cystinosis is an autosomal recessive lysosomal storage disorder leading to cystine accumulation within all cells. Deposition of cystine in the kidney leads first to failure of the proximal tubule and renal Fanconi syndrome. Cystinosis is the commonest cause of the renal Fanconi syndrome in children (see 📖 'Disorders of renal salt handling: proximal tubule', p.144). The estimated incidence is 1 in 100–200,000 live births. Three broad types of cystinosis are described:

- Nephropathic (classic renal and systemic disease).
- Intermediate (a late-onset variant of nephropathic cystinosis).
- Non-nephropathic (clinically affecting only the cornea).

A recent consensus statement regarding cystinosis has highlighted key areas relating to the clinical presentation, diagnosis, and treatment of this disease.

Genetics

- Mutations in the gene *CTNS* cause all 3 forms of cystinosis. At least 70 mutations of different types have been reported, and genetic testing is now routinely available in most centres. The gene product, cystinosin, is a lysosomal transport molecule. Loss of function results in intracellular cystine accumulation, which if left untreated, ultimately leading to a variety of organ failures.
- For pregnancies at risk for nephropathic cystinosis, prenatal diagnosis is available through molecular genetic testing.

Nephropathic cystinosis

- Infants appear normal at birth, but develop failure to thrive and manifest renal tubular Fanconi syndrome, with its concomitant metabolic (normal anion gap) acidosis and volume depletion, electrolyte imbalances, growth retardation and hypophosphataemic rickets by 6–12 months of age.
- All racial groups are affected, so the typically described appearance of blond hair and fair complexion can be misleading.
- Later, photophobia reflects progressive corneal crystal accumulation. Crystals appear early in the disease (>16 months) and ophthalmological review should be part of the assessment of any child presenting with renal Fanconi syndrome.
- In the natural history of untreated cystinosis, CKD 5 develops by 10 years of age.
- Later in the untreated patient, extra-renal complications occur with varying frequencies. These include:
  - distal vacuolar myopathy (with wasting of the small muscles of the hand in particular);
  - swallowing abnormalities;
  - retinal blindness;
  - hepatosplenomegaly, sometimes with hypersplenism;
  - hypothyroidism;
  - hypogonadism, with pubertal delay (particularly males);
  - diabetes mellitus;

- pancreatic exocrine insufficiency;
- decreased pulmonary function due to muscle involvement;
- neurological deterioration.

Diagnosis

- Early diagnosis is critical and relies upon the findings of failure to thrive and renal Fanconi syndrome. Cystinosis remains the most common, and the most treatable, identifiable cause of renal Fanconi syndrome in children.
- Definitive biochemical diagnosis is by an elevated leucocyte cystine level in specialized labs, generally 3–20nmol half-cystine/mg protein, at any age. However, normal values are <0.2nmol half-cystine/mg protein, and values higher than this should raise suspicion sufficient to warrant discussion of the case with an expert in cystinosis.
- In addition to elevated leucocyte cystine levels, the finding of corneal crystals on slit lamp examination by an experienced ophthalmologist can also make the diagnosis, but some patients do not have crystals until 1–2 years of age.
- A reasonable goal would be to diagnose infants with cystinosis prior to 1 year of age. This aim can be accomplished if clinicians first consider cystinosis when they check for and see signs and symptoms of renal tubular Fanconi syndrome in any infant with failure to thrive.
- In addition, consideration should be given to developing a newborn screening test for cystinosis. Currently in the UK only newborns with affected siblings are screened.

Treatment

- Treatment should involve a team approach, including a paediatric nephrologist, a metabolic disease expert, a genetic counsellor, ophthalmologist, endocrinologist, and a local paediatrician or family practitioner, and dietician.
- Principle therapeutic issues include:
  - oral mercaptamine (Cystagon®) therapy should be initiated within days of diagnosis (see 📖 'Oral mercaptamine (cysteamine, Cystagon®) therapy', p.273 for dosage);
  - ready access to water and sodium (2–6mmol/kg/day);
  - provision of supplemental phosphate salts (see 📖 'Rickets', p.164);
  - oral repletion with potassium (2–6mmol/kg/day) and alkalinizing agents (e.g. K-citrate or bicarbonate 2–15mmol/kg/day);
  - vitamin D preparations (1-alfacalcidol or calcitriol at 0.2–1micrograms/day) may be needed to increase intestinal absorption of calcium and decrease urinary losses of phosphate, and for the healing of rickets which may have developed in some;
  - blood chemistry should be monitored frequently at the initiation of therapy, perhaps every other week for the 1st month, and then monthly for 6 months;
  - stabilization of blood chemistry should be complete within several weeks and healing of rickets within 3–6 months;
  - ophthalmic examination should be performed approximately every year to monitor corneal deposits and to rule out idiopathic intracranial hypertension (flat optic discs);

- neurological progress should be monitored on a regular basis to assess the presence of co-ordination problems and learning difficulties in childhood, and for myopathic changes and cognitive deterioration in adults;
- linear growth should be evaluated every 6 months. If after optimal control of blood chemistry, nutrition and initiation of cysteamine the growth velocity has not improved, or the patient remains below the 3rd percentile for height after a year of therapy, recombinant human growth hormone (rhGH) should be considered;
- poor appetite/poor adherence with medication and nutrition may require nasogastric tube or gastrostomy;
- thyroxine and testosterone (males over 14 years) replacement may be required. Insulin may be required for diabetes mellitus, particularly following renal transplantation;
- renal transplantation is the treatment of choice for CKD 5 in cystinosis, and is curative for the Fanconi syndrome, although some children may continue to need supplementation of water and electrolytes because of ongoing losses from their native kidneys;
- a glucose tolerance test prior to transplantation may help to assess the risk for diabetes with consequent consideration for altered immunosuppression (steroid and tacrolimus minimization/avoidance);
- steroid minimization or avoidance after transplantation can also help maximize growth potential. The use of carnitine for improvement in muscle function remains controversial, but may be used in selected circumstances.

Oral mercaptamine (cysteamine, Cystagon®) therapy

- Oral mercaptamine therapy provides the mainstay of cystinosis treatment and should be started as soon as possible. The main limitation of this therapy from the patient's point of view is that it is unpalatable. Cystagon® is available in capsules of 50 and 150mg.
- Initial dosing is incremental (over approximately 2–4 weeks) to achieve a dose of 60mg/kg per day divided in 6-hourly doses. Further dose increases, to between 60 and 90mg/kg per day (or between 1.3 and 1.95g/m^2 per day), should be implemented to achieve a leucocyte cystine level <1.0nmol half-cystine/mg protein. Since a level of <0.2nmol half-cystine/mg protein is normal, consideration should be given to administering doses that achieve leucocyte cystine values approaching this level. (For example, doses >60mg/kg per day can be prescribed to lower the leucocyte cystine value from 0.9 to 0.3nmol half-cystine/mg protein). The dose should never exceed 90mg/kg per day of cysteamine. The dose recommended for adults is 500mg every 6h, but higher doses are often required to achieve satisfactory cystine depletion. Cystagon® can be given with food or drink, but must be taken in bolus form (i.e. within 5 min), rather than dissolved and sipped over time.
- Leucocyte cystine levels should be monitored every 3 months to help monitor therapy. Because the effect of the drug wears off within hours, the levels should be obtained immediately before the next dose (4–6h after the last dose) to assess at the time of presumably highest cystine level.

- For patients with gastric acid-related symptoms, proton pump inhibitors may prove helpful.
- Cystagon® also maintains thyroid and muscle function so must also be used in post-kidney transplant patients to help preserve other organs.

Mercaptamine eye drops

Oral therapy does not influence corneal cystine deposition. Thus, in addition to oral therapy, mercaptamine eye drops are required. This can dissolve corneal crystals within months and relieve photophobia within weeks. Mercaptamine eye drops are given ideally up to 10–12 times per day as a 0.55% solution in normal saline with a preservative, although in practical terms most only manage up to 6 times a day.

Transfer to adult care

Transitioning of care from paediatric to adult services remains an important area of concern. Paediatric nephrologists should assist their adult colleagues in this pursuit, specifically via interactions with societies of adult nephrologists. Renal transplantation has improved the prognosis for nephropathic cystinosis, but this does not correct the accumulation of cystine in extra-renal tissues, and multi-systemic involvement may still occur, even with optimal mercaptamine treatment.

Key areas relating to the future of cystinosis

Key areas identified in the consensus statement include the possibility of newborn screening for cystinosis, and the development of alternatives to cysteamine for achieving cystine depletion.

Further reading

Gahl WA, Balog JZ, and Kleta R (2007). Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. *Ann Intern Med* **147:**242–50.

Kleta R, Kaskel F, Dohil R, *et al.* (2005). First NIH/Office of Rare Diseases Conference on Cystinosis: past, present, and future. *Pediatr Nephrol* **20:** 452–4.

Chapter 11

Vasculitis

The classification of paediatric vasculitis

Background to classification criteria

- Classification criteria (see Table 11.1) are often described for diseases where the pathogenesis and/or molecular mechanisms are poorly understood.
- They are used to facilitate clinical trials and improve epidemiological descriptions by providing a set of agreed criteria that can be used by investigators anywhere in the world.
- Classification criteria for vasculitis are designed to differentiate one form of vasculitis from another once the diagnosis of vasculitis has been secured. They are not the same as diagnostic criteria (such as those described for Kawasaki disease), but are often misused as such.
- Thus, classification criteria aim to:
  - identify a set of clinical findings (criteria) that recognize a high proportion of patients with the particular disease (sensitivity);
  - exclude a high proportion of patients with other diseases (specificity).
- Classification criteria typically include manifestations that are characteristics of the disease in question that occur with less frequency or are absent in other conditions.
- Symptoms or findings that might be typical or common, but may also be present in other diseases tend to be excluded.
- An important limitation to these criteria is that they are not based on a robust understanding of the pathogenesis and as such are relatively crude tools that are likely to be modified as scientific understanding of these diseases progresses.

Paediatric vasculitis classification 2010

- New paediatric classification criteria are now described, and validated in over 1300 cases worldwide.
- These criteria do not include Kawasaki disease (see 📖 'Kawasaki disease', p.294); nor do they include definitions for microscopic polyangiitis (too few cases included in dataset).
- For Takayasu arteritis, care must be taken to exclude fibromuscular dysplasia (or other cause of non-inflammatory large and medium vessel arteriopathy) since undoubtedly there could be scope for overlap in the clinical presentation between these two entities, although the pathogenesis and treatment are clearly distinct.

General scheme for the classification of paediatric vasculitides

- This is based on the size of the vessel predominantly involved in the vasculitic syndrome and is summarized in Box 11.1.
- It should be noted, however, that most vasculitides exhibit a significant degree of 'polyangiitis overlap': for example, Wegener's granulomatosis can affect the aorta and its major branches, and small vessel vasculitis can occur in polyarteritis nodosa.

Table 11.1 Classification criteria for specific vasculitic syndromes[1]

Vasculitis	Classification criteria	Sensitivity*	Specificity*
HSP	Purpura, predominantly lower limb OR diffuse* (mandatory) PLUS 1 out of: • abdominal pain • IgA on biopsy • haematuria/proteinuria • arthritis/arthralgia * If diffuse (i.e. atypical distribution) then IgA deposition on biopsy required	100%	87%
WG	At least 3 out of 6 of the following: • histopathology • upper airway involvement • laryngo-tracheobronchial stenoses • pulmonary involvement • ANCA positivity • renal involvement	93%	99%
PAN	Histopathology or angiographic abnormalities (mandatory) plus 1 out of 5 of the following criteria: • skin involvement • myalgia/muscle tenderness • hypertension • peripheral neuropathy • renal involvement	89%	99%
TA	Angiographic abnormalities of the aorta or its main branches (also pulmonary arteries) showing aneurysm/dilatation (mandatory criterion), plus 1 out of 5 of the following criteria: • pulse deficit or claudication • 4 limb blood pressure discrepancy • bruits • hypertension • acute phase response	100%	99%

HSP: Henoch–Schönlein purpura; WG: Wegener's granulomatosis; PAN: polyarteritis nodosa; TA: Takayasu arteritis. *Based on 1347 children with miscellaneous vasculitides.[2]

[1]Ozen S, Pistorio A, Iusan SM, *et al.* for the Paediatric Rheumatology International Trials Organisation (PRINTO) (2010). EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* **69**: 798–806.

[2]Ruperto N, Ozen S, Pistorio A, *et al.* for the Paediatric Rheumatology International Trials Organisation (PRINTO) (2010). EULAR/PRINTO/PRES criteria for Henoch–Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: Overall methodology and clinical characterisation. *Ann Rheum Dis* **69**: 790–7.

Box 11.1 Predominantly large vessel vasculitis

- Takayasu arteritis (TA).

Predominantly medium-sized vessel vasculitis

- Childhood polyarteritis nodosa (PAN).
- Cutaneous polyarteritis.
- Kawasaki disease.

Predominantly small vessel vasculitis

- Granulomatous:
  - Wegener granulomatosis (WG).
  - Churg-Strauss syndrome.
- Non granulomatous:
  - Microscopic polyangiitis.
  - Henoch–Schönlein purpura (HSP).
  - Isolated cutaneous leukocytoclastic vasculitis.
  - Hypocomplementemic urticarial vasculitis.

Other vasculitides

- Behçet's disease.
- Vasculitis secondary to infection (including Hepatitis B-associated PAN), malignancies and drugs, including hypersensitivity vasculitis.
- Vasculitis associated with other connective tissue diseases.
- Isolated vasculitis of the central nervous system (CNS; childhood primary angiitis of the central nervous system: cPACNS).
- Cogan's syndrome.
- Unclassified.

Further reading

Ozen S, Pistorio A, Iusan SM, *et al.* for the Paediatric Rheumatology International Trials Organisation (PRINTO) (2010). EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis* **69:** 798–806.

Ruperto N, Ozen S, Pistorio A, *et al.* for the Paediatric Rheumatology International Trials Organisation (PRINTO) (2010). EULAR/PRINTO/PRES criteria for Henoch–Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: Overall methodology and clinical characterisation. *Ann Rheum Dis* **69:** 790–7.

Investigation of primary systemic vasculitis

Background

Clinical features that suggest a vasculitic syndrome are:

- Pyrexia of unknown origin.
- Palpable purpura, urticaria, dermal necrosis.
- Mononeuritis multiplex.
- Unexplained arthritis, myositis, serositis.
- Unexplained pulmonary, cardiovascular, or renal disease PLUS one or more of:
  - leukocytosis;
  - eosinophilia;
  - hypocomplementaemia;
  - cryoglobulinaemia;
  - circulating immune complexes;
  - raised ESR or C-reactive protein (CRP), thrombocytosis.

Characteristic features of individual vasculitides

(See also 🕮 'The classification of paediatric vasculitis', p.276.)

- *PAN:* Either
  - biopsy evidence of necrotizing vasculitis of small or medium sized arteries; *or*
  - suggestive visceral angiography in a child who is systemically unwell (anti-neutrophil cytoplasmic antibody (ANCA) usually negative).
- *Microscopic polyangiitis:* small vessel vasculitis with focal segmental glomerulonephritis, but without granulomatous disease of the respiratory tract. Clinically, it can be difficult to distinguish from Wegener's granulomatosis and often presents with rapidly progressive glomerulonephritis. Typically associated with pANCA.
- *Renal-limited form of microscopic polyangiitis:* manifestation solely in the kidneys with crescentic nephritis (+/– pANCA positivity).
- *Wegener's granulomatosis:* combination of sinus, lung, and kidney disease with biopsy evidence of granuloma or necrotizing vasculitis. Typically associated with cANCA, occasionally pANCA or ANCA negative in the young.
- *Takayasu's arteritis:* symptoms or signs of large vessel disease; systemically unwell; characteristic angiography. May present with severe hypertension and pulse deficits ('pulseless disease').
- *Other vasculitides:*
  - there are many other vasculitic syndromes (see 🕮 'Kawasaki disease', p.294 and 🕮 'Henoch–Schönlein purpura', p.288). Goodpasture's syndrome is characterized by crescentic nephritis (linear staining on immunofluorescence) and pulmonary haemorrhage, associated with anti-glomerular basement membrane antibodies (anti-GBM).

Level 1 investigations

To be performed in the following cases:

Haematology and acute phase reactants

Full blood count (FBC), ESR, CRP, clotting, prothrombotic screen (if patchy ischaemia of digits or skin), blood film.

Basic biochemistry

Renal and liver function, creatine phosphokinase (CPK), thyroid function, lactate dehydrogenase (LDH), amylase/lipase, urine dip and urine albumin to creatinine ratio (Ua:Uc).

Infectious disease screen

- Blood cultures and urine microscopy, culture, and sensitivity (MC&S).
- Anti-streptolysin O titre (ASOT) and anti-DNase B.
- *Mycoplasma pneumoniae* serology.

Immunological tests

- Antinuclear antibodies (ANA), ds-DNA antibodies, extractable nuclear antibodies (ENAs), ANCA, rheumatoid factor (RF).
- Anti-GBM antibodies.
- Tissue transglutaminase (TTG) antibodies (coeliac disease screen).
- Immunoglobins IgGAM and E.
- Anticardiolipin antibodies, Lupus anticoagulant.
- C3/C4, mannose binding lectin, CH100.
- Varicella zoster virus (VZV) antibody status (prior to starting immunosuppressive therapy).
- Serum angiotensin-converting enzyme (ACE).

Radiological

Chest X-ray (CXR), abdominal and renal US.

Other

Electrocardiogram (ECG), echocardiography, digital clinical photography of lesions.

Level 2 investigations

To be considered on an individual basis.

- Selective contrast visceral angiography.
- DMSA scan.
- Magnetic resonance imaging/angiography (MRI/MRA) of brain (for suspected cerebral vasculitis).
- Computed tomography (CT) abdomen, thorax, brain.
- Sinus X-ray (for Wegener's).
- Labelled white cell scan (for extent and location of inflammation).
- Cerebral contrast angiography (for suspected cerebral vasculitis).
- Dual X-ray absorptiometry (DEXA) scan.
- Ventilation perfusion (V/Q) scan.
- Doppler US of peripheral arteries.
- Tissue biopsy: skin, nasal or sinus, kidney, sural nerve, lung, liver, gut, temporal artery, brain, other.

- Bone marrow analysis and/or lymph node excision biopsy (for suspected malignancy).
- Nitroblue tertrazolium test if granulomatous inflammation found on biopsy.
- DNA analysis for periodic fever syndromes that can mimic vasculitis: MEFV (familial Mediterranean fever (FMF) gene, TNFRSF1A (tumour necrosis factor (TNF) alpha receptor associated periodic fever syndrome, TRAPS), mevalonate kinase (MVK) (hyper IgD syndrome (HIDS)), NLRP3 (cryopyrin-associated periodic syndrome (CAPS)), and NOD2 (Crohn's/Blau's/juvenile sarcoid mutations).
- Serum amyloid A (SAA).
- Mitochondrial DNA mutations.
- Urinary catecholamines (consider plasma catecholamines as well), and urine vanyllylmandelic acid (VMA), homovanillic acid (HVA) (for phaeochromocytoma, or neuroblastoma).
- Organ specific autoantibodies.
- Nerve conduction studies (PAN, WG, Behçet's—before starting thalidomide).
- Mantoux 1:1000, and/or quantiferon.
- Polymerase chain reaction (PCR) for CMV, Epstein–Barr virus (EBV), enterovirus, adenovirus, VZV, hepatitis B and C viruses (HBV, HCV).
- Serology for human immunodeficiency virus (HIV), Rickettsiae, *Borrelia burgdorferi*.
- Thermography and nail-fold capillaroscopy.
- β2 glycoprotein 1 antibodies.
- Viral serology for:
  - HBV, HCV;
  - parvovirus B19.
- Formal Glomerular filtration rate (GFR).
- 24-h ambulatory blood pressure (BP) monitoring.
- 4-limb BP.
- X-ray of bones and joints.
- Ophthalmology review.
- IgD.
- Cryoglobulins (if there is a history of cold sensitivity/vasculitis mainly present in exposed areas of the body).
- Basic lymphocyte panel and CD19 count if monitoring post-rituximab.
- Positron emission tomography-computed tomography PET-CT: for differential of malignancy or Castleman's disease.

The standard treatment of childhood vasculitis

Standard vasculitis therapy (*excluding* crescentic glomerulonephritis)

See Fig. 11.1.

Prior to using this approach, there should be:

- A well-established diagnosis.
- Severe, potentially life-threatening disease.
- Inadequate response to less toxic therapy—milder cases of vasculitis (e.g. isolated cutaneous forms) may respond to less toxic agents, such as colchicine. So therapy should always be tailored for each individual.
- No known infection or neoplasm.
- No pregnancy or possibility thereof.
- Informed consent obtained and documented in notes.
- (See Table 11.2 for guidelines for the use of cytotoxic drugs in non-malignant disease.)

Other points of note

- Although the use of oral cyclophosphamide is highlighted in Fig. 11.1, increasingly IV cyclophosphamide is favoured over the oral route in children and adults because of reduced side-effects and lower cumulative dose, but comparable efficacy as suggested by a number of studies in adults with ANCA vasculitis (e.g. the 'CYCLOPS' trial).
- IV cyclophosphamide has the added advantage of ensuring adherence to therapy, of particular relevance in adolescents with vasculitis.

Use of biological therapy in systemic vasculitis of the young

- Whilst the therapeutic approach and drugs used as suggested in Figs. 11.1 and 11.2 undoubtedly have improved survival and long-term outlook for children with severe vasculitis, concerns relating to toxicity, particularly with cyclophosphamide, and relapses despite this conventional therapeutic approach has led to the increasing use of biological therapy, such as rituximab, anti-TNF alpha, or other biological therapy.
- Evidence to support the use of rituximab as a primary induction agent in place of cyclophosphamide for the treatment of ANCA-associated vasculitis is now available for adults with this group of diseases (RITUXIVAS, and RAVE trials, currently results in press).[1,2]
- Evidence to support this approach in children remains anecdotal, but undoubtedly rituximab is being increasingly used for children with ANCA vasculitis that is not adequately controlled using the conventional cyclophosphamide followed by azathioprine therapeutic regimen outlined in Fig. 11.1.

1 Jones R, Tervaert JW, Hauser T, *et al.* (2010). Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* **363:** 211–20.
2 Stone J, Merkel PA, Spiera R, ***et al.*** (2010). Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* **363:** 221–32.

- Evidence for the use of anti-TNF alpha or other biological agents, such as anakinra remains anecdotal for children and adults with vasculitis.
- Whilst there is not enough evidence to recommend specific biological therapy for specific vasculitic syndromes, a general approach favoured by the author is given in Table 11.3.

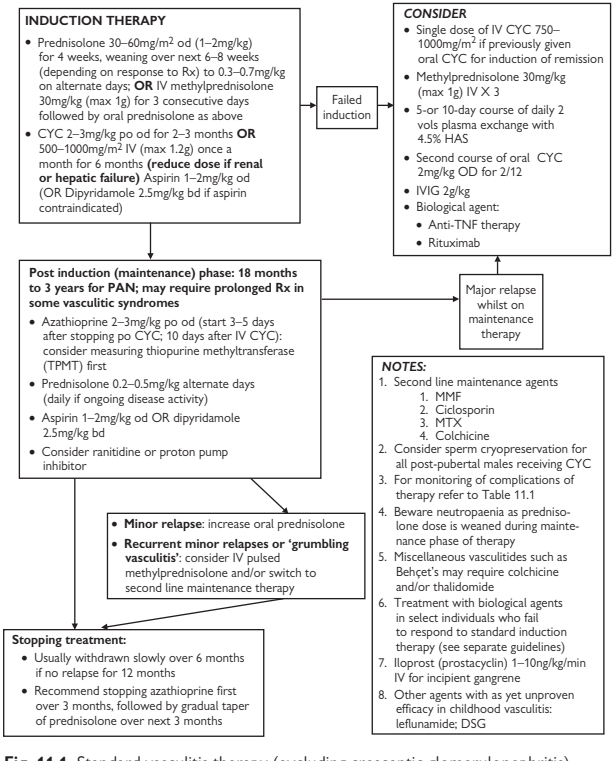

Fig. 11.1 Standard vasculitis therapy (excluding crescentic glomerulonephritis).

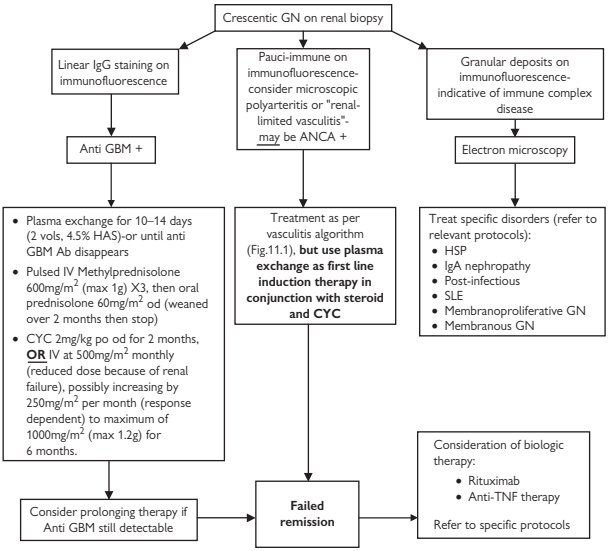

Fig. 11.2 Guideline for treatment of crescentic glomerulonephritis. Of major importance is early diagnosis and therapy.

Table 11.2 Doses, side effects, and clinical monitoring of commonly used immunosuppressant and cytotoxic immunosuppressant drugs used for the treatment of vasculitis

	Cyclophosphamide (CYC)	Azathioprine	Mycophenolate mofetil (MMF)	Ciclosporin	Methotrexate
Dose	2–3mg/kg od po 2–3 months; 0.5–1.0g/m^2 IV monthly with MESNA to prevent cystitis (see 📖 Appendix, p.599, for MESNA dose and IV CYC administration protocol).	0.5–2.5mg/kg od po for 1 year or more.	600mg/m^2 BD.	3–5mg/kg/day po in 2 divided doses.	10–15mg/m^2/week po or sc (single dose).
Side effects	Leucopenia; haemorrhagic cystitis; reversible alopecia; infertility; leukaemia, lymphoma, transitional cell carcinoma of bladder.	GI toxicity; hepatotoxicity; rash; leucopenia; teratogenicity; no increase in malignancy in adults with RA; no conclusive data for cancer risk in children.	Bone marrow suppression; severe diarrhoea; pulmonary fibrosis.	Renal impairment, hypertension, hepatotoxicity, tremor, gingival hyperplasia, hypertrichosis, lymphoma.	Bone marrow suppression and interstitial pneumonitis (decreased risk with folic acid), reversible elevation of transaminases, hepatic fibrosis.
Cumulative toxic dose	Not described for malignancy; 500mg/kg for azoospermia	Not described	Not described	Not described	Not described

(Continued)

Table 11.2 *(Contd.)*

	Cyclophosphamide (CYC)	Azathioprine	Mycophenolate mofetil (MMF)	Ciclosporin	Methotrexate
Clinical monitoring	Weekly FBC for duration of therapy (usually 2–3 months); Baseline and monthly renal and liver function. Temporarily discontinue and/or reduce dose if neutropaenia $<1.5 \times 10^9$/L, platelets $<150 \times 10^9$/L, or haematuria. Day 10 FBC if IV. Reduce dose if renal or hepatic failure e.g. to 250–300mg/m^2.	Weekly FBC for 1 month, then 3 monthly. Temporarily discontinue and/or reduce dose if neutropaenia $<1.5 \times 10^9$/L, platelets $<150 \times 10^9$ L, and check TPMT enzyme-patients deficient in TPMT require reduced doses (or may not tolerate) azathioprine because of increased marrow toxicity.	Fortnightly FBC for 2 months, then monthly for 2 months, 3-monthly when stable. Baseline monthly renal and liver function until stable. Discontinue temporarily and/or reduce dose if neutropaenia $<1.5 \times 10^9$ Ll, platelets $<150 \times 10^9$ L, or significant GI side effects.	Weekly measurement of BP; baseline then monthly renal and liver function; maintain 12-h trough level at 50–100ng/ml. 6–12 monthly GFR. Consider renal biopsy every 2 years.	Baseline CXR, FBC and LFTs, then FBC and LFTs fortnightly until dose stable, then monthly to every 6 weeks (after 6 months). Reduce or discontinue if hepatic enzymes >3X upper limit of normal, neutropaenia $<1.5\times 10^9$ L, new or worsening cough, severe nausea, vomiting, or diarrhoea, platelets $<150 \times 10^9$ L or falling rapidly.

Table 11.3 Recommendations for indication and choice of biological therapy for primary systemic vasculitis of the young based on published experience. Reproduced with permission from Eleftheriou D, Melo M, Marks SD, *et al.* (2009). Biologic therapy in primary systemic vasculitis of the young. *Rheumatology*. 2009; **48**:978–86.

Vasculitis type	Indication for biological agent	Proposed first choice of biological agent
ANCA-associated vasculitis	Critical organ or life-threatening disease, which has failed to respond to standard vasculitis therapy OR concerns regarding cumulative CYC dose.	Rituximab or other B cell depleting monoclonal antibody
Polyarteritis nodosa	Failed therapy with standard agents OR concern regarding cumulative CYC dose	Rituximab or anti-TNFα[*†]
Behçet's disease	Recalcitrant and severe disease; alternative to thalidomide	Anti-TNFα (infliximab, adalimumab or etanercept)

CYC, cyclophosphamide; IVIG, intravenous immunoglobulin.

[*]Authors have more experience with infliximab than etanercept for PAN, although etanercept has been used in individual cases of childhood PAN.

[†] No firm recommendation is made regarding first choice of biological for PAN.

[1] Eleftheriou D, Melo M, Marks SD, *et al.* (2009). Biologic therapy in primary systemic vasculitis of the young. *Rheumatology*. 2009; **48**: 978–86.

Further reading

Eleftheriou D, Melo M, Marks SD, *et al.* (2009). Biologic therapy in primary systemic vasculitis of the young. *Rheumatology* **48:** 978–86.

Henoch–Schönlein purpura

Epidemiology

- HSP (anaphylactoid purpura) is a multi-system small vessel systemic vasculitis.
- It is the commonest vasculitis in the paediatric population.
- The annual incidence is estimated at 20.4 per 100,000 children in the UK, with greater incidence in children from the Indian subcontinent (24 per 100,000) compared with White Caucasians (17.8 per 100,000) and Blacks, predominantly Afro-Caribbean (6.2 per 100,000).
- North American series also report a higher incidence of HSP in White compared with Black children.
- Other epidemiological studies from Holland and the Czech Republic place the incidence between 6.1 and 10.2 per 100,000 children respectively, possibly reflecting differences in ethnicities and/or methodological differences in data collection.
- Younger children are most frequently affected, the peak incidence occurring at around 4–5 years of age and the disease is more prevalent in boys. The disease appears to follow a seasonal pattern, with a higher incidence during winter and the early spring.

Pathogenesis

- Remains largely unknown.
- Probable polygenic contribution.
- The most commonly accepted theory of HSP nephritis pathogenesis is that polymeric galactose deficient IgA (formed under genetic control) is produced in response to infection or immunization in some individuals, resulting in pathological formation of immune complexes with naturally occurring anti-glycan IgG or IgA1, with subsequent glomerular deposition, and activation of mesangial cells and initiation of glomerulonephritis.

Clinical features of Henoch–Schönlein purpura

HSP is defined as a vasculitis with IgA-dominant immune deposits affecting small vessels and typically involving skin, gut and glomeruli and associated with arthralgias or arthritis. The classification criteria are:

- Purpura, commonly palpable and predominantly lower limb or diffuse (if diffuse (i.e. atypical distribution) then IgA deposition on biopsy is required (mandatory)) plus 1 out of 4 of:
  - abdominal pain;
  - IgA on biopsy;
  - haematuria/proteinuria;
  - arthritis/arthralgia.

Mainly affects skin, gastrointestinal (GI) tract, joints, and kidneys.

- *Skin:* purpura generally symmetrical, affecting the lower limbs and buttocks in the majority of cases, the upper extremities being involved less frequently; abdomen, chest, and face are generally unaffected. New crops of purpura may develop for several months after the disease onset, though generally fade with time. Lesions can be induced by mild trauma. Angioedema and urticaria can also occur.
- *Joints:* around two-thirds of children have joint manifestations at presentation. The knees and ankles are most frequently involved. Pain, swelling and decreased range of movement tend to be fleeting and resolve without the development of permanent damage.
- *Gastrointestinal tract:* three-quarters of children develop abdominal symptoms ranging from mild colic to severe pain with ileus and vomiting. Haematemesis and melaena are sometimes observed. Other complications include intestinal perforation and intussusception. The latter may be difficult to distinguish from abdominal colic, and the incidence of intussusception is significant enough to warrant exclusion by US when suspected.
- *Acute pancreatitis:* rare complication.
- One complication worth emphasizing for paediatric nephrologists is the rare, but well recognized complication of ureteric obstruction.
- Other organs less frequently involved include the central nervous system (cerebral vasculitis), gonads (orchitis may be confused with torsion of the testis), and the lungs (pulmonary haemorrhage).
- Many cases follow an upper respiratory tract infection and the onset of the disorder may be accompanied by systemic symptoms, including malaise and mild pyrexia.
- Multiple organ involvement may be present from the outset of the disease, or alternatively an evolving pattern may develop, with different organs becoming involved at different time points over the course of several days to several weeks.
- Around one-third of children have symptoms for less than 14 days, one-third 2–4 weeks and one-third greater than 4 weeks.
- Recurrence of symptoms occurs in around one-third of cases, generally within 4 months of resolution of the original symptoms. Recurrences are more frequent in those with renal involvement.

Henoch–Schönlein purpura nephritis

- Incidence reported between 20 and 61% of HSP patients, depending on criteria for definition of nephritis.
- Renal involvement is normally manifest between a few days and a few weeks after clinical presentation, but can occur up to 2 months or (rarely) more from presentation.
- There appears to be an increased risk of renal disease in those with bloody stools.
- May present with isolated microscopic haematuria, proteinuria with microscopic or macroscopic haematuria, acute nephritic syndrome (haematuria with at least two of hypertension, raised plasma creatinine and oliguria), nephrotic syndrome (usually with microscopic haematuria) or a mixed nephritic-nephrotic picture.

Pathological findings in Henoch–Schönlein purpura

- The skin lesion of HSP is that of a leucocytoclastic vasculitis with perivascular accumulation of neutrophils and mononuclear cells. Immunofluorescence studies reveal vascular deposition of IgA and C3 in affected skin, although similar changes may be observed in skin unaffected by the rash. An important caveat is that if biopsies are taken from the centre of a necrotic skin lesion then IgA may be falsely negative because it is cleaved by proteolytic enzymes involved in the inflammatory vasculitic process.
- The renal lesion of HSP nephritis is characteristically a focal and segmental proliferative glomerulonephritis.

Investigation of Henoch–Schönlein purpura

- No single laboratory test has been shown to be helpful.
- Immunological investigations including complement levels and anti-nuclear antibodies are normal.
- IgA is elevated in around one half of children and a small number exhibit ANCA positivity.
- Coagulation studies are normal and platelet numbers are normal or occasionally increased. Factor XIII may be low.
- Where significant nephritis is present at presentation, renal function and electrolytes may be correspondingly abnormal.

Differential diagnosis

- Sepsis.
- Other systemic vasculitides (SLE, PAN, Wegener's, microscopic polyangiitis, and hypersensitivity vasculitis), all of which can present with similar clinical features.
- FMF can also mimic HSP.

Who needs a renal biopsy?

- Nephritic/nephrotic presentation (urgent).
- Raised creatinine, hypertension, or oliguria (urgent).
- Heavy proteinuria (Ua:Ucr persistently >100mg/mmol) on an early morning urine sample at 4 weeks. Serum albumin not necessarily in the nephrotic range.
- Persistent proteinuria (not declining) after 4 weeks.
- Consider biopsy for persistent impaired renal function (GFR <80mL/min/1.73^2).

General treatment of Henoch–Schönlein purpura

- The large majority of cases of HSP are mild and immunosuppressive treatment is usually not justified; children should receive symptomatic treatment only.
- The skin lesion usually requires no treatment (except where there is severe haemorrhagic oedema affecting the face or scrotum, where systemic corticosteroid therapy may be indicated).
- Arthropathy should be treated with rest and simple analgesia (paracetamol or non-specific anti-inflammatory drugs (NSAIDs)).

- Whilst never subjected to a controlled clinical trial, there is some evidence to suggest that the more severe gastrointestinal symptoms, particularly abdominal pain and GI bleeding, respond well to corticosteroid therapy, which has also been used for the treatment of testicular involvement and pulmonary haemorrhage.

Treatment of Henoch–Schönlein purpura nephritis

Currently prescribed treatments for HSP nephritis are not adequately guided by evidence obtained in robust randomized control tests (RCTs).

Treatment with oral prednisolone to prevent development of Henoch–Schönlein purpura nephritis

- Meta-analysis of four RCTs, which evaluated prednisone therapy at presentation of HSP, showed that there was no significant difference in the risk of development or persistence of renal involvement at 1, 3, 6 and 12 months with prednisone, compared with placebo or no specific treatment.
- Thus, prophylactic corticosteroid does not prevent the onset of HSP nephritis.
- There could still be a role for early use of corticosteroids in patients with severe extrarenal symptoms and in those with renal involvement, however.

Rapidly progressive glomerulonephritis

- There are good data indicating that crescents in >50% of glomeruli and nephrotic range proteinuria carry an unfavourable prognosis.
- Unfortunately, to date, there is only one RCT evaluating the benefit of treatment, which shows no difference in outcome using cyclophosphamide vs. supportive therapy alone. This study did not examine combined therapy, i.e. cyclophosphamide and steroid, however, a regimen used in most other severe small vessel vasculitides.
- For patients with rapidly progressive glomerulonephritis (RPGN) with crescentic change on biopsy, uncontrolled data suggest that treatment may comprise aggressive therapy with corticosteroid, cyclophosphamide, and possibly plasma exchange, as for other causes of crescentic nephritis (see 📖 'The standard treatment of childhood vasculitis', p.282).
- Other therapies, such as ciclosporin, azathioprine, and cyclophosphamide have been reported by some authors to be effective.
- As HSP is probably the commonest cause of RPGN in childhood, more aggressive therapeutic approaches have been employed in some cases including:
  - 14 children with severe HSP nephritis treated successfully with plasma exchange alone;
  - these treatment options, whilst potentially important in select cases, are not yet supported by randomized controlled trials.

Treatment of Henoch–Schönlein purpura nephritis that is not rapidly progressive

Patients may include the following features: less than 50% crescents on renal biopsy, suboptimal GFR; heavy proteinuria that is not necessarily nephrotic range:

- 3 daily doses of IV methylprednisolone 30mg/kg (maximum 1g per dose).
- Followed by 4 weeks of 2mg/kg oral prednisolone for 4 weeks.
- At 4-week assessment, if there is no improvement the prednisolone will be rapidly weaned and stopped.
- If there is improvement, oral prednisolone could be continued for up to 6 months in total.
- Some advocate the use of steroids and cyclophosphamide in HSP nephritis with biopsy showing diffuse proliferative lesions or sclerosis, but with <50% crescentic change, who have ongoing heavy proteinuria. A typical regimen would comprise 8 weeks of oral cyclophosphamide (2mg/kg/day) with daily prednisolone, converting to alternate day prednisolone and azathioprine for a total of 12 months.
- The published evidence for the efficacy of this approach is lacking, but this may be a reasonable option bearing in mind the adverse prognosis of children with HSP who have a nephritic/nephrotic phenotype.
- Fish-oil treatment has been reported in analogy to IgA nephropathy, but no good evidence exists.

Use of ACE inhibitors in Henoch–Schönlein purpura nephritis

In patients with greater than 6 months duration of proteinuria an ACE inhibitor may be indicated to limit secondary glomerular injury.

Long-term outcome of Henoch–Schönlein purpura

The majority of children with HSP make a full and uneventful recovery with no evidence of ongoing significant renal disease.

- Renal involvement is the most serious long-term complication of HSP:
  - single study of long-term outcome of 78 subjects who had had HSP nephritis during childhood (mean of 23.4 years after onset) demonstrated overall that initial findings on renal biopsy correlated well with outcome, but had poor predictive value in individual patients;
  - 44% of patients who had nephritic, nephrotic, or nephritic/nephrotic syndromes at onset had hypertension or impaired renal function, whereas 82% of those who presented with haematuria (with or without proteinuria) were normal;
  - 7 patients deteriorated clinically years after apparent complete clinical recovery;
  - 16 of 44 full-term pregnancies were complicated by proteinuria and/or hypertension, even in the absence of active renal disease.
- A recent systematic review of all published literature with regards to long term renal impairment in children with HSP has been performed:
  - twelve studies with 1133 children were reviewed;
  - renal involvement occurred in 34% of children; 80% had isolated haematuria and/or proteinuria while 20% had acute nephritis or nephrotic syndrome;

- renal complications, if they did occur, developed early—by 4 weeks in 85% and by 6 months in nearly all children;
- persistent renal involvement (hypertension, reduced renal function, nephrotic or nephritic syndrome) occurred in 1.8% of children overall, but the incidence varied with the severity of the kidney disease at presentation, occurring in 5% of children with isolated haematuria and/or proteinuria, but in 20% who had acute nephritis and/or nephrotic syndrome in the acute phase;
- children with significant renal impairment at presentation, and/or persistent proteinuria should undergo regular assessment of their glomerular filtration rate (GFR), e.g. at 1, 3, and 5 years after the acute episode of HSP;
- some instances of hypertension have been reported many years after normalization of renal function and urinalysis;
- an increased incidence of pre-eclampsia has also been reported;
- interestingly, in children who underwent repeat renal biopsies the majority of children with HSP still had IgA deposition years later, which could explain in part late the renal morbidity sometimes described.

Recurrence of Henoch–Schönlein purpura in renal allografts

- It is recognized that HSP can occur in renal allografts.
- True recurrence should, however, be differentiated from IgA deposits, which are sometimes seen in renal transplants in patients who did not have HSP or IgA nephropathy.
- One worrying suggestion is that recurrence rates may be higher for living donor transplants, although data are limited.

Further reading

Narchi H. (2005). Risk of long term renal impairment and duration of follow up recommended for Henoch-Schonlein purpura with normal or minimal urinary findings: a systematic review. *Arch Dis Child* **90:** 916–20.

Zaffanello M, and Fanos V. (2009) Treatment-based literature of Henoch–Schönlein purpura nephritis in childhood. *Pediatr Nephrol* **24**: 1901–11.

Kawasaki disease

Kawasaki disease (KD) is a self-limiting vasculitic syndrome that predominantly affects medium and small-sized arteries. It is the second commonest vasculitic illness of childhood (after HSP) and is the leading cause of childhood acquired heart disease in developed countries.

Pathogenesis and epidemiology

- Pronounced seasonality and clustering of KD cases have led to the hunt for infectious agents as a cause. So far, no single agent has been identified.
- The aetiology of KD remains unknown, but it is currently felt that one or more widely distributed infectious agents evoke an abnormal immunological response in genetically susceptible individuals, leading to the characteristic clinical presentation of the disease.
- KD has a worldwide distribution with a male preponderance, an ethnic bias towards oriental children, seasonality, and occasional epidemics.
- Incidence of KD is rising world-wide, including the UK. Current reported incidence in the UK is 8.1/100,000 children aged <5 years old. May reflect a truly rising incidence or increased clinician awareness.

Clinical features

The principal clinical features of KD are:

- Fever persisting for 5 days or more.
- Peripheral extremity changes (reddening of the palms and soles, indurative oedema, and subsequent desquamation).
- A polymorphous exanthema.
- Bilateral conjunctival injection/congestion.
- Lips and oral cavity changes (reddening/cracking of lips, strawberry tongue, oral, and pharyngeal injection).
- Acute non-purulent cervical lymphadenopathy.

To diagnose KD, 5 of the 6 principal clinical features listed should be present.

- Patients with fewer than 5/6 principal features can be diagnosed with KD when coronary aneurysm or dilatation is recognized by 2-D echocardiography or coronary angiography.
- The cardiovascular features are the most important manifestations of the condition with widespread vasculitis affecting predominantly medium size muscular arteries, especially the coronary arteries. Coronary artery involvement occurs in 15–25% of untreated cases with additional cardiac features in a significant proportion of these including pericardial effusion, electrocardiographic abnormalities, pericarditis, myocarditis, valvular incompetence, cardiac failure, and myocardial infarction.
- Of note, irritability is an important sign, which is virtually universally present although not included in the diagnostic criteria.
- Another clinical sign that may be relatively specific to KD is the development of erythema and induration at sites of BCG inoculations. The mechanism of this sign is thought to be cross-reactivity of T cells in KD between specific epitopes of mycobacterial and human heat shock proteins.

- An important point is that the principal symptoms and signs may present sequentially, such that the full set of criteria may not be present at any one time. Awareness of other non-principal signs (such as Bacille Calmette-Guérin (BCG) scar reactivation) may improve the diagnostic pick-up rate of KD.
- Other clinical features include: arthritis, aseptic meningitis, pneumonitis, uveitis, gastroenteritis, meatitis and dysuria, and otitis.
- Relatively uncommon abnormalities include hydrops of the gallbladder, GI ischaemia, jaundice, petechial rash, febrile convulsions, and encephalopathy or ataxia, macrophage activation syndrome, and syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

Differential diagnosis

Conditions that can cause similar symptoms to KD and must be considered in the differential diagnosis include:

- Scarlet fever.
- Rheumatic fever.
- Streptococcal or staphylococcal toxic shock syndrome.
- Staphylococcal scalded skin syndrome.
- Systemic juvenile idiopathic arthritis.
- Infantile polyarteritis nodosa.
- SLE.
- Adenovirus, enterovirus, EBV, CMV, parvovirus, influenza virus infection.
- *Mycoplasma pneumoniae* infection.
- Measles.
- Leptospirosis.
- Rickettsiae infection.
- Adverse drug reaction.
- Mercury toxicity (acrodynia).
- Lymphoma- particularly for intravenous immunoglobulin (IVIG) resistant cases.

Investigations

In cases of suspected KD the following investigations should be considered:

- FBC and blood film.
- ESR.
- CRP.
- Blood cultures.
- ASOT and anti DNase B.
- Nose and throat swab, and stool sample for culture (superantigen toxin typing if *Staphylococcus aureus* and/or ß haemolytic streptococci detected).
- Renal and liver function tests.
- Coagulation screen.
- Autoantibody profile (ANA, ENA, RF, ANCA).
- Serology (IgG and IgM) for *Mycoplasma pneumoniae*, enterovirus, adenovirus, measles, parvovirus, EBV, cytomegalovirus.
- Urine M, C&S.
- Dip test of urine for blood and protein.

- Consider serology for rickettsiae and leptospirosis if history suggestive.
- Consider CXR.
- ECG.
- 2-D echocardiography to identify coronary artery involvement acutely and monitoring long-term changes.
- Coronary arteriography has an important role for delineating detailed anatomical injury, particularly for children with giant coronary artery aneurysms (greater than 8mm), where stenoses adjacent to the inlet/outlet of the aneurysms are a concern. Note that the procedure may need to be delayed until at least 6 months after disease onset since there could be a risk of myocardial infarction if performed in children with ongoing severe coronary artery inflammation.

Treatment

The treatment of KD (see Fig. 11.3) comprises of:

- IVIG at a dose of 2g/kg as a single infusion over 12h (consider splitting the dose over 2–4 days in infants with cardiac failure).
- IVIG should be started early preferably within the first 10 days of the illness. However, clinicians should not hesitate to give IVIG to patients who present after 10 days if there are signs of persisting inflammation.
- Aspirin 30–50mg/kg/day in four divided doses.
- The dose of aspirin can be reduced to 2–5mg/kg/day when the fever settles (disease defervescence). Aspirin at anti-platelet doses is continued for a minimum of 6 weeks.
- If the symptoms persist within 48h or there is disease recrudescence within 2 weeks a second dose of IVIG at 2g/kg over 12h should be considered.
- However IVIG resistance occurs up to 20% of cases.
- When a patient fails to respond to a second dose of IVIG, consider IV pulsed methylprednisolone at 15–-30mg/kg daily for 3 days to be followed by oral prednisolone 2mg/kg/day od weaning over 6 weeks.
- Some clinicians are increasingly using corticosteroids after disease recrudescence following one dose of IVIG based on the results of a recent study. This remains an area of controversy, but seems rational since this is associated in most cases with rapid resolution of inflammation.
- In refractory cases infliximab, a human chimeric anti-TNF-α monoclonal antibody, given IV at a single dose of 6mg/kg has been reported to be effective, and is increasingly used for IVIG resistant cases. Considering that rapid and effective interruption of inflammation is a primary target of KD therapy, TNF-α blockade may be a logical step following one failed dose of IVIG, particularly in very active disease with evidence of early coronary artery dilatation.
- Echocardiography should be repeated at 2 and 6 weeks from initiation of treatment (refer to paediatric cardiology).
- If the repeat echocardiogram shows no coronary artery abnormalities (CAA) at 6 weeks, aspirin can be discontinued and follow up at least every 2 years should be considered.

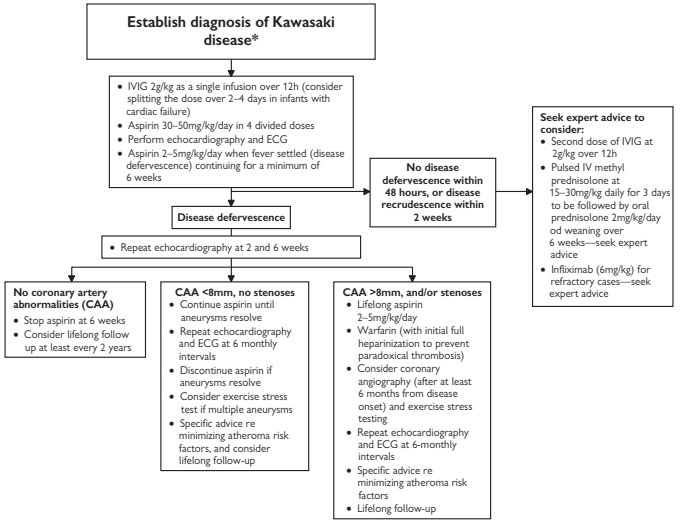

Fig. 11.3 Guideline for the management of Kawasaki disease.

*Treatment can be commenced before a full 5 days of fever if sepsis has been excluded. Treatment should also be given if the presentation is 10 days from fever onset.
†Refer to paediatric cardiologist.
‡Other specific interventions, such as PET scanning, addition of calcium channel blocker therapy, and coronary angioplasty at the discretion of paediatric cardiologist.

- In cases of CAA <8mm with no stenoses present, aspirin should be continued until aneurysms resolve.
- If CAA >8mm and/or stenoses is present, aspirin at a dose of 2–5mg/kg/day should be continued lifelong. The combination of aspirin and warfarin therapy in these patients with giant aneurysms has been shown to decrease the risk of myocardial infarction.
- In patients who develop CAA, echocardiography, and ECG should be repeated at 6-monthly intervals and an exercise stress test considered.
- Other specific interventions such as PET scanning, addition of calcium channel blocker therapy, and coronary angioplasty should be organized at the discretion of the paediatric cardiologist.

Outcome

- Treatment with IVIG and aspirin reduces CAA from 25 % for untreated cases to 4–9%.
- IVIG resistance occurs in approximately 20%, and is associated with a higher risk of CAA.
- The overall outlook of children with KD is good, with the acute mortality rate due to myocardial infarction having been reduced to <1% by increased alertness of the clinicians to the diagnosis and prompt treatment.
- Nonetheless, the disease may contribute to the burden of adult cardiovascular disease and cause premature atherosclerosis, an area of active ongoing research.

Polyarteritis nodosa

Background

- PAN is a necrotizing vasculitis associated with aneurysmal nodules along the walls of medium-sized muscular arteries.
- Despite some overlap with smaller-vessel disease, PAN appears to be a distinct entity and, in adults in Europe and the United States, appears to have an estimated annual incidence of 2.0–9.0/million.
- Although comparatively rare in childhood, it is the most common form of systemic vasculitis after HSP and KD.
- Peak age of onset in childhood is 7–11 years, often with a male preponderance.
- Classification criteria for PAN are not diagnostic criteria, and meeting classification criteria is not equivalent to making a diagnosis in an individual patient—see elsewhere in this section and 📖 'The classification of paediatric vasculitis', p.276.

Aetiology

- *Unknown:* possible interaction between infection and aberrant host response.
- There may be genetic factors that may make individuals vulnerable to PAN and other vasculitides, but these are not yet defined. There are reports of PAN occurring in siblings that add weight to this hypothesis, but there are no detailed genetic studies.
- There is a well-recognized association of PAN and FMF in parts of the world where this is common.
- There are data to support roles for hepatitis B and reports of a higher frequency of exposure to parvovirus B19 and cytomegalovirus in PAN patients compared with control populations.
- HIV has also been implicated, and PAN-like illnesses have been reported in association with cancers and haematological malignancies. However, in childhood, associations between PAN and these infections or other conditions are rare.
- Bacterial superantigens may play a role in some cases.
- Occasional reports suggest immunization as a cause, but this is not proven.

Clinical features of polyarteritis nodosa

A diagnosis is made by considering all clinical features in a patient, only some of which may be classification criteria. Clinical manifestations (and investigation findings) can be very confusing, especially in the early phase of the disease with absence of conclusive diagnostic evidence. There is an entity that involves the skin only (cutaneous PAN).

- The main systemic clinical features of PAN are malaise, fever, weight loss, skin rash, myalgia, abdominal pain, and arthropathy.

- Skin lesions are variable, and may masquerade as those of HSP or multiform erythema. The cutaneous features described in a recent international classification exercise for PAN in children occurred commonly and were defined as follows:
  - *livedo reticularis*—purplish reticular pattern usually irregularly distributed around subcutaneous fat lobules, often more prominent with cooling;
  - *skin nodules*—tender subcutaneous nodules;
  - *superficial skin infarctions*—superficial skin ulcers (involving skin and superficial subcutaneous tissue) or other minor ischaemic changes (nail-bed infarctions, splinter haemorrhages, digital pulp necrosis);
  - *deep skin infarctions*—deep skin ulcers (involving deep subcutaneous tissue and underlying structures), digital phalanx or other peripheral tissue (nose and ear tips) necrosis/gangrene.
- Renal manifestations such as haematuria, proteinuria and hypertension.
- GI features and abdominal pain are relatively common and include:
  - *indeterminate intestinal inflammation*—intestinal inflammation without characteristic histological features of either ulcerative colitis or Crohn's disease. **NB**: routine mucosal gut biopsies rarely detect overt vasculitis, since the small- and medium-sized arteries lie below the mucosa;
  - GI haemorrhage (upper and lower);
  - intestinal perforation;
  - pancreatitis.
- Neurologic features such as focal defects, hemiplegia, visual loss, mononeuritis multiplex, and organic psychosis may be present.
- Other important clinical features include: ischaemic heart and testicular pain. Rupture of arterial aneurysms can cause retroperitoneal and peritoneal bleeding, with perirenal haematomata being a recognized manifestation of this phenomenon, although this is rare.

Differential diagnosis

- *Other primary vasculitides:* HSP, WG, microscopic anglitis (MPA), KD. See 🕮 'Henoch–Schonlein purpura', p.288 and 🕮 'Kawasaki disease', p.294.
- Autoimmune or autoinflammatory diseases:
  - juvenile idiopathic arthritis (JIA)—particularly the systemic form;
  - juvenile dermatomyositis (JDM);
  - SLE;
  - undifferentiated connective tissue disease;
  - sarcoidosis;
  - Behçet's disease.
- *Infections:*
  - bacterial, particularly streptococcal infections, and sub-acute bacterial endocarditis;
  - *viral (many)*—specifically look for hepatitis B and C, CMV, EBV, parvovirus B19, and consider HIV.
- *Malignancy:* lymphoma, leukaemia, and other malignancies can mimic PAN.

Diagnostic laboratory and radiological investigation

Blood tests

- Anaemia, polymorphonuclear leukocytosis, thrombocytosis, increased ESR, and CRP.
- Platelets are hyper-aggregable.
- Circulating immune complexes, or cryoglobulins may be present.
- Positive hepatitis B serology in children is unusual in association with PAN, but can occur.
- ANCA are not thought to play a major part in the causality of PAN, but there are reports demonstrating their presence in some adults and children with PAN.
  - the presence of cytoplasmic ANCA (c-ANCA) with antibodies to proteinase 3 in a patient suspected of having PAN makes it mandatory to eliminate WG as a diagnosis;
  - likewise, a significant titre of perinuclear ANCA (p-ANCA) with antibodies to myeloperoxidase would necessitate steps to eliminate microscopic polyangiitis (MPA) as the diagnosis.

Tissue biopsy

Biopsy material is diagnostically important, especially skin or muscle, although tissue biopsy has overall low diagnostic sensitivity, since the disease is patchy and vasculitis can be easily missed.

- The characteristic histopathological changes of PAN are fibrinoid necrosis of the walls of medium or small arteries, with a marked inflammatory response within or surrounding the vessel.
- However, absence of such changes would not exclude the diagnosis, as the vasculitic features are variable and affected tissue may not have been sampled.
- Renal biopsy is usually not helpful and carries a greater risk than usual of bleeding and the formation of arteriovenous fistulae.

Radiological tests

- The most valuable investigative procedure is catheter selective visceral digital subtraction arteriography to include flush aortogram, and selective renal, hepatic, and mesenteric arteriography. This should be performed and interpreted only by those with expertise in this test in paediatric patients.
  - arteriography findings include aneurysms, segmental narrowing and variations in the calibre of arteries, together with pruning of the peripheral renal vascular tree (Fig. 11.4 and colour plate section);
  - treatment with prior corticosteroids will alter the arteriography and can result in false negatives;
  - non-invasive arteriography, such as CT or MRA are *not* as sensitive as catheter arteriography for the detection of medium-sized vessel vasculitis such as PAN;
  - consider formal cerebral arteriography if clinical and MRI features suggest cerebral vasculitis.
- Indirect evidence of the presence of medium-size artery vasculitis affecting renal arteries may be obtained by demonstrating patchy areas within the renal parenchyma of decreased isotope uptake on Tc-99m dimercaptosuccinic acid (DMSA) scanning of the kidneys.

- MRA usually fails to detect aneurysms of small- and medium-sized muscular arteries, although it may demonstrate large intra- and extrarenal aneurysms and stenoses/occlusions of the main renal arteries, and areas of ischaemia and infarction. A caveat is that MRA may overestimate vascular stenotic lesions.
- Computed tomography angiography (CTA) may also reveal larger aneurysms and arterial occlusive lesions, and demonstrate areas of renal cortical ischaemia and infarction, but:
  - at the expense of high ionizing radiation exposure;
  - with less sensitivity than catheter arteriography.
- Echocardiography can be useful for the identification of pericarditis, valve insufficiency, myocarditis, or coronary artery abnormalities.

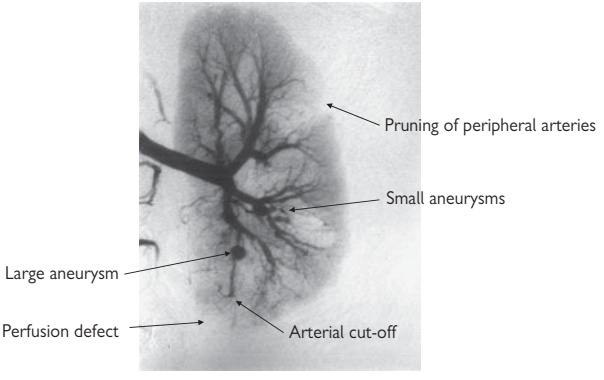

Fig. 11.4 PAN: renal arteriogram.

Treatment

(See Table 11.2.)

- In most patients, it is appropriate to treat aggressively to induce remission (typically 3–6 months), followed by less aggressive therapy to maintain remission (typically 18–24 months).
- In those presenting with mild predominantly cutaneous disease, corticosteroid alone may be appropriate, with careful monitoring of clinical and laboratory parameters as this is weaned.
- *Induction therapy:* high-dose corticosteroid with an additional cytotoxic agent such as cyclophosphamide:
  - cyclophosphamide is usually given as pulsed monthly IV injections for up to 6 months or for shorter periods in children if remission is achieved;
  - oral cyclophosphamide 2mg/kg per day for 2–3 months is an alternative, although for other vasculitides the IV regimen has been shown to have a more favorable therapeutic index.
- Aspirin 1–5mg/kg/day as an antiplatelet agent may be considered.

- *Maintenance therapy:* once remission is achieved, therapy with daily low-dose prednisolone and oral azathioprine is frequently used for up to 18–24 months:
  - other maintenance agents include methotrexate, mycophenolate mofetil, and ciclosporin;
  - some advocate alternate-day low-dose prednisolone in the maintenance phase with the intention of limiting steroid toxicity e.g. growth impairment), but data to support this approach are limited.
- Adjunctive plasma exchange can be used in life-threatening situations (see 📖 'The standard treatment of childhood vasculitis', p.282).
- Biological agents, such as infliximab or rituximab have been used for those unresponsive to conventional therapy.
- Treatment response can be assessed using a modified Birmingham Vasculitis Activity Score (BVAS); the paediatric version of BVAS, or 'PVAS', is currently still being validated and by monitoring of conventional acute phase reactants, urinary sediment, BP and growth.

Outcome

- PAN, unlike some other vasculitides, such as WG, appears to be a condition in which permanent remission can be achieved.
- Relapses can occur, but despite these, a real possibility of cure can be anticipated.
- However, if treatment is delayed or inadequate, life-threatening complications can occur due to the vasculitic process.
- Severe complications, especially infections, can occur from immunosuppressive treatment.
- In comparison with the almost 100% mortality rate in the pre-steroid era, mortality rates as low as 1.1% were reported in a recent retrospective multicenter analysis. However, this may not truly reflect mortality in circumstances of severe disease because 30% of patients in that series were considered to have predominantly cutaneous PAN.
- A mortality rate of 10% was recently recorded from a major tertiary referral centre seeing predominantly children with aggressive advanced disease.
- Late morbidity can occur years after childhood PAN from chronic vascular injury, possibly resulting in premature atherosclerosis. This remains a cause for concern and an area of ongoing research.

Further reading

Dillon MJ, Eleftheriou D, Brogan PA. (2010). Medium-size-vessel vasculitis. *Pediatr Nephrol* **25**: 1641–52. [Epub ahead of print Nov 28, 2009, PMID: 19946711]

Ozen S, Anton J, Arisoy N, *et al.* (2004). Juvenile polyarteritis: results of a multicenter survey of 110 children. *Pediatr* **145:** 517–22.

The anti-neutrophil cytoplasmic antibody-associated vasculitides

Background

- ANCA-associated vasculitides (AAV) are:
  - WG;
  - MPA;
  - Churg–Strauss syndrome (CSS);
  - renal limited vasculitis (previously referred to as idiopathic crescentic glomerulonephritis).
- Although rare, the AAV do occur in childhood.

Definitions of anti-neutrophil cytoplasmic antibody-associated vasculitides

Definitions for each of the AAV describing the salient major clinical and laboratory features are given here. These are not the same as classification criteria, which (for WG) are provided in 📖 'The classification of paediatric vasculitis', p.276.

- *WG:* granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels.
- *MPA:*
  - necrotizing vasculitis, with few or no immune deposits, affecting small vessels;
  - necrotizing arteritis involving small- and medium-sized arteries may be present;
  - pulmonary capillaritis often occurs—clinically, it often presents with rapidly progressive pauci-immune glomerulonephritis, in association with perinuclear anti neutrophil cytoplasmic antibody (pANCA, MPO-ANCA) positivity.
- *CSS:* an eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels; there is an association with asthma and eosinophilia.
- *Renal limited:* rapidly progressive glomerulonephritis, often with ANCA positivity (usually MPO-ANCA), but without other organ involvement.

Pathogenesis

- It is not known why patients develop ANCA in the first instance.
- When ANCA are present, the most accepted current model of pathogenesis proposes that ANCA activate cytokine-primed neutrophils, leading to bystander damage of endothelial cells and an escalation of inflammation with recruitment of mononuclear cells.
- However, other concomitant exogenous factors and genetic susceptibility appear to be necessary for disease expression.

Clinical features of Wegener's granulomatosis

From a clinical perspective, WG may be broadly considered as having two forms, which may co-exist or present sequentially in individual patients:

- A predominantly granulomatous form with mainly localized disease.
- A florid, acute small vessel vasculitic form characterized by severe pulmonary hemorrhage, and/or rapidly progressive vasculitis or other severe vasculitic manifestations.

Organ specific involvement

Includes:

- *Upper respiratory tract:*
  - epistaxis;
  - otalgia, and hearing loss (conductive and/or sensorineural); chronic otitis media; mastoiditis;
  - nasal septal involvement with cartilaginous collapse results in the characteristic saddle nose deformity;
  - chronic sinusitis;
  - glottic and subglottic polyps and/or large and medium-sized airway stenosis.
- *Lower respiratory tract manifestations* include (singly or in combination):
  - granulomatous pulmonary nodules with or without central cavitation;
  - pulmonary haemorrhage with respiratory distress, frank haemoptysis and/or evanescent pulmonary shadows on CXR;
  - interstitial pneumonitis.
- *Renal involvement:* typically a focal segmental necrotizing glomerulonephritis, with pauci-immune crescentic glomerular changes. The clinical manifestations associated with this lesion are:
  - hypertension;
  - proteinuria;
  - nephritic and nephrotic syndrome;
  - other protean manifestations of renal failure.
- *Ophthalmological disease:* retinal vasculitis, conjunctivitis, episcleritis, uveitis, optic neuritis. Unilateral or bilateral proptosis may be caused by granulomatous inflammation affecting the orbit (pseudotumour).
- Malaise, fever, weight loss or growth failure, arthralgia, and arthritis.
- *Other manifestations:* include peripheral gangrene with tissue loss, and vasculitis of the skin, gut (including appendicitis), heart, central nervous system and/or peripheral nerves (mononeuritis multiplex), salivary glands, gonads, and breast.

Investigations

(See 🕮 'Investigation of primary systemic vasculitis', p.279.)

- WG is commonly associated with a cytoplasmic staining pattern of ANCA by IIF, and ELISA reveals specificity against proteinase 3 (PR3; PR3-ANCA).
- MPA and renal limited AAV are typically associated with p-ANCA by IIF and with MPO-ANCA specificity on ELISA.
- ANCA-negative forms of WG, MPA, renal limited vasculitis, and CSS are well described in children.
- While the diagnostic value of ANCA is without question important, the value of ANCA for the longitudinal monitoring of disease activity is probably unreliable in many patients with WG.
- Tissue diagnosis, in particular renal biopsy, but also biopsy of skin, nasal septum, or other tissue, can be important diagnostically for diagnosing all of the AAV, and can help stage the disease for therapeutic decision-making.

- Other commonly observed non-specific findings include:
  - a mild normochromic normocytic anaemia together with a leucocytosis and thrombocytosis;
  - elevated ESR and CRP;
  - raised immunoglobulins (polyclonal IgG).
- Laboratory manifestations relating to renal involvement include:
  - dipstick haematuria and proteinuria positive;
  - raised Up:Ucr;
  - raised serum creatinine and other associated laboratory features of renal failure.
- CXR may be abnormal but high resolution CT chest has better sensitivity for demonstrating pulmonary infiltrates or discrete nodular and/or cavitating lesions.
- Plain X-ray or CT sinuses for sinusitis.

Treatment of anti-neutrophil cytoplasmic antibody-associated vasculitides

(See 🕮 'The standard treatment of childhood vasculitis', p.282.)

When considering therapy, it is useful to remember that most evidence for treatment is derived from adult trials. It is also useful to consider the different phases of the therapeutic journey for AAV:

- The pre-diagnostic phase: occasionally lasting years. Significant organ damage can accrue in this phase, or even death.
- Induction of remission phase: typically 3–6 months.
- Maintenance of remission phase: usually 18–24 months.
- Therapy withdrawal phase: not all patients achieve this.

The following general points are worthy of note:

- Key to successful treatment is early diagnosis to limit organ damage.
- Treatment for paediatric AAV is broadly similar to the approach used in adults, and involves corticosteroids, cyclophosphamide, and in some individuals plasma exchange (particularly for pulmonary capillaritis and/or RPGN 'pulmonary-renal syndrome') to induce remission; followed by low dose corticosteroids and azathioprine to maintain remission.
- Anti-platelet doses of aspirin can also be considered empirically on the basis of the increased risk of thrombosis associated with the disease process.
- Methotrexate in combination with corticosteroids may have a role for inducing remission in patients with limited WG.
- Co-trimoxazole is commonly added to therapeutic programmes for the treatment of WG, particularly in those with upper respiratory tract involvement, serving both as prophylaxis against opportunistic infection and as a possible disease-modifying agent.
- Newer immunosuppressive agents and immunomodulatory strategies such as MMF and rituximab (see the 'RAVE' and 'RITUXIVAS' trials in adults) have been reported to be effective at inducing or maintaining remission in adults with AAV and are increasingly used in children for recalcitrant disease.
- Anti-tumour necrotizing factor-α therapy is less effective for the treatment of AAV, although has been used anecdotally in this context with some success in select patients.

Outcome of anti-neutrophil cytoplasmic antibody-associated vasculitides

- The AAV still carry considerable disease-related morbidity and mortality, particularly due to progressive chronic kidney disease (CKD) or aggressive respiratory involvement, and therapy-related complications, such as sepsis.
- The mortality for WG from one recent paediatric series was 12% over a 17-year period of study inclusion. The largest paediatric series of patients with WG reported 40% of cases with CKD at 33 months of follow-up despite therapy.
- Mortality in paediatric patients with MPA during follow-up has been reported to be between 0 and 14%.
- For CSS in children, the most recent series quotes a related mortality of 18%.

Further reading

Brogan P, Eleftheriou D, Dillon M. (2010). Small vessel vasculitis. *Pediatr Nephrol* **25:** 1025–35.

Takayasu arteritis

Background

- Takayasu arteritis (TA) is an idiopathic, chronic inflammation of the large vessels, affecting the aorta and its major branches.
- Other names include 'pulseless disease', aortic arch syndrome, or idiopathic aortoarteritis.
- Classification criteria are provided in 📖 'The classification of paediatric vasculitis', p.276.

Epidemiology

- TA is more prevalent in Asian and African populations, and is rarer in Europe and North America.
- Most studies report an incidence of 1–3 per million/year in Caucasian populations: In Japan the estimated incidence is up to 100 times higher: 1 per 3000/year.
- In adult studies there is a 9:1 female predominance. In children, however, gender ratios vary amongst different studies. A recent study from Southeast Asia and Africa report a female to male ratio 2:1.
- TA is a rare vasculitis in children:
  - age of onset may range from infancy to middle age;
  - the peak period of onset is in the third decade of life.

Aetiopathogenesis

- The cause remains unknown.
- Genetic factors may play a role, and there are several reports of familial TA including in identical twins:
  - HLA associations include: HLA-A10, HLA-B5, HLA-Bw52, HLA-DR2 and HLADR4 in Japan and Korea; HLA B22 association has been described in the US population;
  - the presence of HLA Bw52 has been associated with coronary artery and myocardial involvement, and worse prognosis.
- TA is described in association with rheumatoid arthritis, ulcerative colitis, and other autoimmune diseases suggesting an autoimmune mechanism for the pathogenesis of the disease.
- Circulating anti-aortic endothelial cell antibodies in patients with TA have been reported; their exact role however is yet to be determined.

Histopathology

TA is characterized by granulomatous inflammation of all layers of the arterial vessels (panarteritis):

- Inflammation of the tunica intima is followed by intimal hyperplasia leading to stenoses or occlusions.
- Destruction of tunica elastica and muscularis cause dilatation and aneurysms.
- Endothelial cell damage leads to a prothrombotic tendency.
- The lesions have a patchy distribution.
- The initial finding is neutrophil infiltration of the adventitia and cuffing of the vasa vasorum with proliferation and penetration of the latter within the tunica intima.

- Various mixed chronic inflammatory cells including T cells contribute to granuloma formation in the tunica media and adventitia mediated by the release of interferon-γ and TNF-α.
- Later, the adventitia and media are replaced by fibrous sclerotic tissue and the intima undergoes acellular thickening, thus narrowing the vessel's lumen and contributing to ischaemia.

In paediatric series:

- Occlusions and stenoses were present in 98% of the patients, while aneurysms were only seen in 15.6% of the patients.
- Post-stenotic dilatations were present in 34% of cases.
- Lesions are most commonly seen in the subclavian arteries (90%), the common carotids (60%), the abdominal aorta (45%), the aortic arch (35%), and the renal arteries (35%). Pulmonary arteries are involved in 25% of the cases.

Clinical features

Acute phase

Non-specific features of systemic inflammation (systemic, pre-stenotic phase). In children, up to 65% of TA present abruptly with systemic features:

- Pyrexia, malaise, weight loss, headache, arthralgias and/or myalgias.
- Rash (erythema nodosum, pyoderma gangrenosum).
- Arthritis.
- Myocarditis causing congestive heart failure (+/– hypertension) or valvular involvement (aortic valve most commonly affected followed by mitral valve).
- Myocardial infarction.
- Hypertension.
- Hypercoagulable state: thrombotic tendency.

Chronic phase

Features and signs secondary to vessel occlusion and ischaemia (stenotic phase):

- *Asymmetric or absent pulses:* a measured difference of >10mmHg on 4-limb BP monitoring is likely to indicate arterial occlusion.
- *Systemic hypertension:* commonest finding.
- Arterial bruits.
- Congestive heart failure secondary to hypertension and/or aortic regurgitation when the valve is affected.
- *Angiodynia:* localized tenderness on palpation of the affected arteries.
- Claudication.
- Coronary angina.
- Mesenteric angina presenting with abdominal pain and diarrhoea from malabsorption.
- Recurrent chest pain from chronic dissection of the thoracic aorta or pulmonary arteritis.
- Pulmonary hypertension.
- *CNS involvement:* may be attributed to ischaemia +/– hypertension. Dizziness or headache; seizures; transient ischaemic attacks, stroke.

Eye involvement

Diplopia, blurry vision, amaurosis, visual field defect. Fundoscopy findings include:

- Retinal hemorrhage.
- Micro aneurysms of the peripheral retina.
- Optic atrophy.

Renal involvement

- Renal hypertension secondary to renal artery stenosis with secondary glomerular damage.
- CKD.
- Secondary amyloidosis.
- Glomerulonephritis (GN) has been described in association with TA: IgA nephropathy; membranoproliferative GN; crescentic GN; mesangioproliferative GN.

Differential diagnoses

- *Other vasculitides including medium and small vessel vasculitis:* KD; PAN; WG is a recognized cause of aortitis.
- *Infections:*
  - bacterial endocarditis;
  - septicaemia without true endocarditis;
  - tuberculosis;
  - syphilis;
  - HIV;
  - borelliosis (Lyme disease);
  - brucellosis (very rare).
- *Other autoimmune diseases:* SLE; rheumatic fever; sarcoidosis.
- Non-inflammatory large vessel vasculopathy of congenital cause. Treatment with immunosuppression will be ineffective or may worsen the disease:
  - fibromuscular dysplasia;
  - William's syndrome;
  - congenital coartctation of the aorta;
  - congenital mid-aortic syndrome;
  - Ehler-Danlos type IV;
  - Marfan syndrome;
  - neurofibromatosis type I.
- *Other:* post-radiation therapy.

Laboratory investigations

See also 🕮 'Investigation of primary systemic vasculitis', p.279.

- Normochromic normocytic anaemia, leukocytosis, thrombocytosis; raised ESR, raised CRP—may not be present in chronic (stenotic) phase of illness.
- Elevated transaminases and hypoalbuminaemia.
- Deranged renal function tests in cases of renal involvement.
- Polyclonal hyperglobulinaemia.

Further tests required to exclude other causes mimicking Takayasu arteritis or for disease monitoring

- Regular 4- limb BP measurement (preferably with a manual manometer).
- In cases of significant peripheral artery stenosis, central BP measurements may be required.
- Renal function tests, urinalysis.
- Autoimmune screen.
- Baseline immunology tests including lymphocyte subsets, nitroblue tetrazolium (NBT) test.
- Blood cultures (acute phase).
- Mantoux test or interferon gamma-releasing assays (IGRA).
- Syphilis serology.
- Tissue biopsy, rarely performed, but should include microbiological culture, 16S and 18S ribosomal PCR if available to exclude bacterial and fungal infection, respectively.

Imaging

- An echocardiogram (and ECG) and CXR are simple first line imaging tests and should be performed in all cases where TA is suspected.
- Conventional digital subtraction catheter arteriography is the method used routinely for obtaining a generalized arterial survey when TA is suspected, but essentially only provides 'lumenography' with no imaging of arterial wall pathology.
- MRI and MRA, and CTA, or a combination of these may help accurately diagnose TA and monitor disease activity, and (for MRA and CTA) provide cross-sectional aortic wall images allowing detection of arterial wall thickness and intramural inflammation:
  - MRI and MRA are gradually replacing conventional angiography in most centres and are useful for diagnosis and follow up;
  - however, they lack sensitivity in evaluation of the distal aortic branches, and may overestimate the degree of arterial stenosis, especially in small children;
  - cardiac MRI is increasing employed to look for valvular involvement and/or myocarditis.
- Angiographic findings form the basis of one classification for TA (Takayasu Conference, 1994; see Box 11.2).
- Doppler US scan:
  - high resolution duplex US technology is a valuable tool in evaluation and follow-up of TA;
  - this modality offers high resolution imaging of the vascular wall and can be useful for the detection of increased wall thickness;
  - 18F-FDG-PET co-registered with CTA can be a powerful technique combining information relating to the metabolic activity of the arterial wall (18F-FDG uptake detected using PET) with detailed lumenography (CTA) thus providing information on disease activity and anatomy. This technique is not available in all centres, and carries a high radiation exposure limiting its use for routine follow-up of disease activity.

Box 11.2 Classification of Takayasu arteritis

- *Type I:* classic pulseless type that affects blood vessels of aortic arch involving the brachiocephalic trunk, carotid and subclavian arteries
- *Type II:* affects middle aorta (thoracic and abdominal aorta)
- *Type III:* affects aortic arch and abdominal aorta
- *Type IV:* affects pulmonary artery in addition to any of types I to III
- *Type V:* includes patients with involvement of the coronary arteries.

Diagnosis

The diagnosis of TA is based on clinical and laboratory findings of systemic inflammation and/or of large vessel ischaemia, raised and angiographic demonstration of lesions in the aorta or its major branches, with exclusion of other causes listed in the differential diagnosis.

Treatment

See 🕮 'The standard treatment of childhood vasculitis', p.282.

Early diagnosis and aggressive treatment is fundamental for the outcome of the disease, although new lesions can continue to develop even in the presence of clinical remission in 60% of cases.

- Vascular damage already established in some patients will usually not respond to medical treatment.
- Medical management of TA includes high dose corticosteroids, usually in combination with methotrexate or cyclophosphamide for induction of remission. Maintenance agents include methotrexate, azathioprine, or more recently mycophenolate motofetil (MMF).
- Corticosteroids constitute the first line of treatment for active large vessel vasculitis. IV pulsed methylprednsiolone 30mg/kg/day (maximum 1g) for 3 days followed by a second course a week later and subsequent oral prednisolone 2mg/kg/day. Although 60% of patients respond there is a 50% risk of relapse while corticosteroids are tapered. Moreover, better and more rapid remission may be achieved with additional immunosuppressive treatment added early.
- Methotrexate (15mg/m^2/week po or SC) improves the remission rate in steroid dependent TA. Half of the cases will achieve complete and sustained remission on methotrexate for a follow up period of five years. It is the authors' personal preference to use the subcutaneous route for TA.
- *Cyclophosphamide:* a recent study showed promising results for oral cyclophosphamide for the induction of remission.
- *Azathioprine:* recently published data in adults advocate the use of azathioprine in combination with prednisolone as a safe and effective drug accomplishing both clinical remission and prevention of further vascular damage.
- *MMF:* in patients with TA who did not respond to steroid treatment the use of MMF has shown clinical improvement along with reduction of inflammatory markers. It may work as a safe alternative in cases where other immunosuppressants have failed.
- *Anti-TNFα:* case series of children and adults with TA treated with anti-TNFα such as infliximab suggest efficacy, although no data from RCTs exist yet to support this approach.

Hypertension

- At least 40% of TA patients are hypertensive.
- Optimal control of hypertension is essential in the longer term since it is a major contributor to long-term morbidity.
- Medical treatment of hypertension in TA may be challenging since renovascular hypertension may not respond to medical therapy alone.
- Revascularization procedures may be required (see 📖 'Revascularization and other surgical procedures', p.313).

Revascularization and other surgical procedures

Techniques include:

- Angioplasty (including percutaneous transluminal angioplasty; or patch angioplasty).
- Arterial bypass procedures.
- Endarterectomy.
- Arterial stenting.
- Cardiac valve repair/replacement.
- Surgery during the acute phase of the disease carries significant risk of re-occlusion and procedural complication, so should be deferred until the acute phase is treated.
- These techniques should only be undertaken in centers with expertise.

Indications for revascularization include:

- Hypertension from stenotic coarctation of the aorta or renovascular disease.
- End organ ischaemia or peripheral limb ischaemia.
- Cerebral ischaemia.
- Aortic or other arterial aneurysms, or aortic regurgitation.

Prognosis

- There is usually a significant time lag (approximately 18 months, occasionally much longer) between initial presentation and diagnosis of TA in children. Arterial damage accrues during this pre-diagnostic phase, and influences prognosis.
- The course of the disease is variable, but most patients experience new lesions over time. Typically, vascular inflammation persists even in patients thought to be clinically in remission.
- Aortic valve insufficiency and congestive heart failure are reported in 25%.
- Vascular claudication limiting activities occurs in up to 40%.
- Long-term mortality ranges from 10 to 30%: the main causes of death include congestive cardiac failure, myocardial infarction, aneurysm rupture, or renal failure.
- After commencement of treatment approximately 60% will respond to corticosteroids, while 40% will relapse when these are tapered off.
- Poor prognostic factors are severe aortic regurgitation, severe hypertension, cardiac failure, and aneurysms.

Further reading

Gulati A, Bagga A. (2010). Large vessel vasculitis. *Paediat Nephrol* **25:** 1037–48.

This page intentionally left blank

Chapter 12

Infections and the kidney

Infections and the kidney

Any infection causing septicaemia can cause acute kidney injury (AKI), the commonest being meningococcal septicaemia. Acute post-infectious glomerulonephritis and urinary tract infection (UTI) are described in 📖 Chapter 4, p.75 and 📖 Chapter 9, p.181. This chapter describes infections that specifically affect the kidneys.

The general principle in all infection-associated renal complications is that treatment should be aimed at the underlying infection. Eradicating or suppressing the underlying infection is usually the best treatment for the associated renal disease.

Hepatitis B

- Can cause secondary membranous nephropathy (see 📖 Chapter 9 'Nephrotic syndromes: definitions', p.192) but has been associated with other glomerulonephritides.
- Most have active hepatitis B infection (HBsAg and HBeAg positive) without antibodies, although core antibody may be present.
- Remission occurs with disappearance of the HBeAg and development of hepatitis B (HB) surface antibodies.
- No kidney-specific treatment is of proven benefit.
- HB surface antigen positive children being considered for renal transplantation require assessment by a paediatric hepatologist. Untreated active viral replication, chronic active hepatitis or cirrhosis has a poor prognosis post-transplant.

Hepatitis C

- Has been associated with glomerulonephritis of various types. The commonest is membranoproliferative glomerulonephritis (MPGN) associated with cryoglobulinaemia. Hepatitis C virus (HCV) leads to chronic overstimulation of B-lymphocytes and production of mixed cryoglobulins that are deposited in the mesangium and glomerular capillaries.
- Antiviral therapy includes interferon-alpha and ribavirin (seek expert advice). Long-term prognosis depends on sustained HCV RNA clearance from serum at least 6 months after cessation of therapy, but no treatment is of proven benefit to the kidney outcome.
- Hepatitis C positive children being considered for renal transplantation require assessment by a paediatric hepatologist. Survival post-transplantation is improved compared with remaining on dialysis.

Human immunodeficiency virus

- HIV-associated nephropathy (HIVAN) is defined by the presence of proteinuria associated with mesangial hyperplasia and/or global-focal segmental glomerulosclerosis, in combination with microcystic transformation of renal tubules. Glomerular capillary collapse associated with hyperplasia of podocytes (collapsing glomerulopathy) may also occur.
- Alternatively there may be mesangial proliferative lesions secondary to immune complex deposits and lupus-like changes.
- African Americans show a unique susceptibility to develop HIVAN.

- Children may present with nephrotic syndrome and chronic kidney disease (CKD).
- Treatment is with antiretroviral therapy.
- Renal transplantation in adults has been successful, provided there is stable maintenance of anti-retroviral therapy, the HIV viral load is undetectable for at least 6 months, and the CD4 cell count is greater than 200cells/mm^3.

Malaria

- *Plasmodium falciparum* can cause AKI as malarial parasites in red blood cells affect their circulation in the renal microvasculature.
- *Plasmodium malariae* infections can be associated with nephrotic syndrome, also called quartan malaria nephropathy; however, a direct causal link has not been demonstrated, and neither antimalarial therapy nor steroid therapy are effective.

Leptospirosis

- Infection is through skin contact with the urine of infected animals.
- Presentation is with fever, muscle pain, conjunctivitis, and in severe cases, renal and liver failure.
- Organisms invade the renal tubules and can be found in the urine.
- Treatment is with penicillin and tetracyclines. Occasionally, steroids are required to treat severe late immunological sequelae (caused by immune complex disease), such as pulmonary haemorrhage after the acute infection is treated.

Schistosomiasis

- Occurs in Asia, Africa, and South America.
- Renal disease is associated with *Schistosoma mansoni* infection.
- May present with dysuria and terminal haematuria as the worms lay their eggs in the venous plexuses surrounding the bladder and ureters.
- Fibrosis and obstruction may develop in the long term, as can bladder carcinoma.

This page intentionally left blank

Chapter 13

Renal cystic diseases and ciliopathies

Renal cystic diseases: basic principles

- Typically we separate multicystic from polycystic kidney disease.
  - 'multicystic' is a term usually used in the context of renal cystic dysplasia, including the MCDK (see 📖 'Renal dysplasia', p.333);
  - 'polycystic' refers to the defined genetic diseases autosomal dominant polycystic kidney disease (ADPKD), including the contiguous gene syndrome with tuberous sclerosis, as well as autosomal recessive polycystic kidney disease (ARPKD) (see Table 13.1).
- In nephronophthisis and related disorders, such as Bardet-Biedl syndrome, cysts are often microscopically small and thus escape the resolution of ultrasound (US), but lead to increased echogenicity.
- Glomerulocystic kidney disease is a histological diagnosis. It is typically seen in the renal cysts and diabetes syndrome (Table 13.1), but can occur with any cystic disease.
- Investigations into the causes of cystic kidney diseases identified dysfunction of primary cilia or the centrosome, an intracellular structure, closely associated with ciliary function as a unifying aetiology. Cilia are hair-like appendages, which can be motile or non-motile. They are important sensory organelles involved in cell-polarity and proliferation. Cilia are found on many epithelial cells explaining the wide spectrum of associated symptoms.
- In ADPKD, cysts develop due to a 'second hit', i.e. an acquired mutation in the second allele. This has been shown by genetic testing of individual cysts—each cyst has an individual mutation on one allele in addition to the inherited mutation on the other allele. This may explain some of the phenotypic variability within families, as 'second hits' occur essentially at random.
- 'Second hit' somatic mutations are also the disease mechanism in tuberous sclerosis.
- Nephronophthisis and cystic dysplasia probably form a spectrum of the manifestations of ciliopathies, as both forms can be associated with typical ciliopathies, such as Bardet-Biedl, Jeune, Joubert, and Ivemark syndrome.

Table 13.1 shows the inheritance, affected gene, age at onset, renal imaging, and symptoms of the inherited cystic renal diseases. Genetic testing for these genes is becoming increasingly available. However, US and associated clinical features can usually establish a clinical diagnosis.

Particular issues relevant to all cystic diseases

- A careful family history (including for diabetes) and US of the parents' kidneys may help in the diagnosis.
- Examination of the child for associated symptoms, such as hepatosplenomegaly, retinal changes, signs of tuberous sclerosis (TS; also in the parents) and Bardet-Biedl syndrome may help in the diagnosis.
- Screening of other family members or antenatal diagnosis can be offered (see 📖 'Genetic testing and antenatal diagnosis', p.38).
- Long-term follow-up is essential.
- At present, there is no proven treatment that retards or prevents disease progression in any of the cystic disorders. Thus, clinical management concentrates on symptomatic treatment and identification of potentially associated symptoms.
- Recurrence after transplantation has not been described for cystic diseases.

Table 13.1 The inherited cystic kidney diseases

Inherited cystic disease	Inheritance, genes and incidence	Age at onset	Imaging	Other manifestations
Autosomal dominant polycystic kidney disease (ADPKD)	Mutations of *PKD1* (80–90%) and *PKD2*, which results in less severe disease. Phenotype varies even within families. Affects 1 in 1000	May be detected antenatally, incidentally or on screening. Cannot be excluded until the fourth decade of life	Cysts may be isolated at presentation and progressively increase in number and size. May be asymmetrical. Kidneys are large	Cysts in liver and pancreas. Cerebral aneursyms Mitral valve prolapse
Tuberous sclerosis (TS)	AD, mutations of TSC1 and TSC2	Childhood	75% of patients with TS develop angiomyolipomata and 35% develop cysts Large, polycystic kidneys	Adenoma sebaceum, intracerebral tubers, ungual fibromas, cardiac rhabdomyomas, hypopigmented patches and shagreen patches
Contiguous gene syndrome (TSC2 and PKD1)	Disruption of TSC2 and the adjacent *PKD1* gene (2% of TS patients)	Early childhood		
Medullary cystic disease	AD, mutations in MCKD1 locus (gene unidentified yet) or UMOD	Early adulthood, rarely CKD in childhood	Kidneys may be normal or reduced in size. Mostly medullary cysts	May be associated with hyperuricaemia
Autosomal recessive polycystic kidney disease (ARPKD)	AR, mutations of PKHD1. Affects 1 in 20,000	May present antenatally with large bright kidneys, and oligohydramnios if severe with respiratory distress at birth; or with palpable kidneys in infancy or later childhood	Kidneys are large with poor cortico-medullary differentiation and scattered small cysts, usually 1 to 2mm	Dilated bile ducts with abnormal HIDA scan (after 1 year of age), hepatic fibrosis and varices

Nephronophthisis	AR, mutations in at least 10 NPHP loci. Most commonly in NPHP1 ~50% carrying a large deletion in exon 2. Affects 1 in 50,000	Infancy, childhood and adolescence	Normal sized kidneys with poor cortico-medullary differentiation, increased echogenicity; cysts at the corticomedullary junction	May be associated with retinitis pigmentosa (Senior-Loken Syndrome), oculomotor apraxia, cone shaped epiphyses, developmental delay and hypoplasia of the cerebellar vermis (Joubert Syndrome), situs inversus
Bardet-Biedl syndrome	AR, mutations in at least 12 BBS loci; 1 in 135,000	Childhood	Fetal lobulation; increased echogenicity; cystic dysplasia, calyceal abnormalities	Polydactyly, obesity, developmental delay, retinal dystrophy, hypogenitalism
Renal cysts and diabetes syndrome	AD, mutations of HNF1β	Any age, including antenatally (bright kidneys)	Variable renal size, glomerular cysts	Maturity onset diabetes, genital abnormalities in females, gout, deafness, hypomagnaesaemia

Autosomal dominant polycystic kidney disease

Background

- Most common inherited renal disease, incidence ~1:500.
- Due to mutations in either *PKD1* (16p13) or *PKD2* (4q21-23).
- About 10% of cases are due to spontaneous mutations (no family history).

Presentation and prognosis

- Wide spectrum of clinical severity: from intrauterine death with Potter sequence to mild CKD well into late adulthood.
- The phenotype may be variable even within families.
- Extrarenal manifestations include polycystic liver disease, pancreatic cysts and intracranial aneurysms (rarely seen in childhood).
- CKD 5 is extremely rare in childhood. The median onset of CKD 5 is in the 6th decade of life with *PKD1* and 8th decade with *PKD2* mutations.
- Complications of ADPKD do occur in childhood—hypertension incidence 15–30%, proteinuria 30–40%; CKD stage ≥2 is seen in up to 40% of teenagers.

Diagnosis

- Diagnostic screening of at-risk children is controversial—establishing the diagnosis may not provide a benefit, yet impose a burden of psychological stress, and may impair the child's ability to obtain health or life insurance or a mortgage later in life.
- Conversely, failing to rule out the diagnosis in at-risk children may unnecessarily relegate unaffected children to annual follow-up and continuing worries about being affected.
- These issues of diagnostic screening need to be discussed with the family. Many may want to delay diagnostic testing until the at-risk child is old enough to make a fully informed decision.
- Currently, the most common modality for diagnostic screening is a renal US. However, the first cysts may not appear until the fourth decade of life, so ADPKD cannot be excluded until then. The presence of any cyst in an at-risk child is highly suggestive of the disease; the presence of 2 or more cysts is considered diagnostic. Increasing availability of genetic testing enhances diagnostic accuracy.
- Diagnostic screening of all children at-risk will become standard of care, once a proven treatment slowing disease progression is available.

Management

- Annual review of BP and early morning urine for protein is recommended for affected children and those at risk (with family history of ADPKD). Treatment with angiotensin-converting enzyme inhibitors (ACEI) has demonstrated efficacy with respect to target-organ damage (cardiac hypertrophy). Long-term studies to assess effect of ACEI on progression of CKD are ongoing.
- US is used for diagnostic purposes (see 📖 'Diagnosis', p.324), but has no bearing on clinical management, once the diagnosis is established.
- Because of the high incidence of CKD stage ≥2, those with an established or suspected (presence of complications, such as hypertension or proteinuria) diagnosis should be monitored accordingly, including blood tests (see 📖 Chapter 18, p.409). Frequency of subsequent blood tests depends on kidney function.
- Routine screening for intracranial aneurysms is not recommended unless there is a strong family history of cerebrovascular accidents. Magnetic resonance angiography (MRA) can detect all but the smallest aneurysms.
- Studies of new treatments, such as mTOR inhibitors and somatostatin analogues have at best shown a slowing in the increases in kidney and/or liver volume, but no deceleration in the progression of CKD. Another trial, using a third class of medication, vasopressin receptor type 2 antagonists, is ongoing.

Renal structural abnormalities in tuberous sclerosis

Introduction

- TS is an autosomal dominant disorder caused by mutations in the *TSC1* (9q34) and *TSC2* (16p13.3) genes.
- *TSC2* lies adjacent to *PKD1*, the gene responsible for ADPKD, suggesting a role for *PKD1* in the aetiology of renal cystic disease in TS. A high proportion of patients with renal cystic disease have contiguous deletions of *TSC2* and *PKD1*.
- Neurological features predominate, although there are a number of significant renal manifestations.
- A severe form of angiodysplasia affecting any part of the arterial tree is also described in TS.

Renal disease in tuberous sclerosis

Angiomyolipomata

- Benign hamartomas.
- Present in 80% of TS patients and may be detected in early childhood.
- Major complications include bleeding and rarely mechanical obstruction—most lesions that bleed are >3.5cm in diameter. Bleeding lesions are treated by arterial embolization.
- Case reports have reported slowing of growth with the use of mTOR inhibitors. The role of everolimus is currently being investigated further in an ongoing clinical trial (EXIST-2).

Cystic disease (simple cysts and polycystic disease)

- 20% develop simple cysts.
- Polycystic kidney disease develops in <5%, and may result in CKD 5 in children and adults.

Renal cell carcinoma

- This develops in <1% and appears to follow a less aggressive course than in unaffected individuals.
- Suspicion should be raised where apparent angiomyolipomata appear to have a low fat content on US.

UK guidelines for the management of patients with tuberous sclerosis

See http://www.tuberous-sclerosis.org

- Annual measurement of BP.
- Regular testing of renal function in adults and children with polycystic kidney disease.
- Testing of renal function when angiomyolipomata are present.
- Renal US examination at presentation and repeated annually if an abnormality is detected, or if indicated. Solid lesions with a low fat content on ultrasound should undergo expert investigation.
- Refer for a specialist opinion if macroscopic haematuria develops.
- Refer to a specialist unit if treatment of a renal lesion is contemplated.

Autosomal recessive polycystic kidney disease

Background

- Due to recessive mutations in *PKHD1 (6p21–12).*
- Incidence of approximately 1:20,000 live births.

Presentation and prognosis

- *Clinical variability:* from severe renal disease with fetal or neonatal death with Potter sequence and pulmonary hypoplasia to exclusive liver disease (congenital hepatic fibrosis).
- *Some genotype-phenotype correlation:* 2 truncating mutations in *PKHD1* appear incompatible with life. Patients surviving the neonatal period have at least one missense mutation. However, no specific mutation profile is seen for patients with predominant liver disease.
- Those surviving the neonatal period have reported survival rates of 80–90% at 10 years of age.

Renal manifestations

- *Enlargement of the kidneys:* more than 90% have kidneys ≥2 SD for age. In severe cases, enlargement is massive with consequent pulmonary hypoplasia and abdominal protuberance. These kidneys are easily palpable as firm masses. Severe abdominal distension can cause problems with feeding and respiration to the extent that unilateral nephrectomy may be necessary.
- Hyponatraemia is often seen in early infancy, presumably due to impaired urinary dilution.
- Hypertension is a common complication (up to 80% of patients).
- Over 50% of patients will have developed CKD 5 by age 20 years.

Extrarenal manifestations

Mainly restricted to the liver:

- All patients have some degree of congenital hepatic fibrosis (Caroli disease).
- US may show dilated biliary ducts.
- A Hepatobiliary Imino-Diacetic Acid (HIDA) scan may show abnormal biliary drainage, but may be normal before the age of 1 year.
- Assessment for hepato-splenomegaly should be part of routine clinical examinations.
- Hypersplenism may present as a falling platelet and white cell count.
- Oesophageal varices may develop and screening with US is necessary, particularly pre-transplant.
- Cholangitis may present with recurrent septicaemia with enteric organisms (especially *Klebsiella*, *E. coli* and *Enterobacter*) without the classical features of 'Charcot's triad' (fever, hepatic pain, and jaundice).
- Occasionally pancreatic cysts are seen.

Diagnosis

- Usually a clinical diagnosis based on antenatal bright kidneys and nephromegaly.
- *Ultrasound appearance:*
  - antenatal screening typically shows bright and/or enlarged kidneys;
  - cysts are usually too small to resolve by US, but lead to increased echogenicity;
  - later in childhood cysts may become larger and can be difficult to distinguish from ADPKD.
- Genetic testing is becoming increasingly available, but is of limited clinical use. May be helpful for genetic counselling in cases without a family history, but where clinical phenotype resembles ADPKD.

Management

- Dependent on CKD stage (see 🕮 Chapter 18, p.409).
- Hypertension (HTN) typically responds well to ACEI (see 🕮 Chapter 16, p.353).
- Hyponatraemia is usually self-limited. Concentration of feeds to decrease fluid intake may help. Salt supplementation will worsen HTN, consistent with the hyponatraemia being due to water retention.
- Cholangitis needs treatment with appropriate IV antibiotics, followed by prophylactic antibiotics such as:
  - *cefalexin*—12.5mg/kg (maximum 500mg) once a day;
  - *amoxicillin*—25mg/kg (maximum 1 gram) once a day;
  - *trimethoprim*—2mg/kg (maximum 50mg) once a day.

  These can also be used in a rotating fashion, e.g. changing antibiotics every 12 weeks.
- Nephrectomies may need to be performed prior to transplantation because of nephromegaly. It may also be necessary prior to initiation of peritoneal dialysis (PD).
- Patients should be assessed for potential combined kidney-liver transplant when approaching CKD 5.

Nephronophthisis

Background

- The commonest inherited aetiology in a newly-presenting child with CKD 5.
- There are usually few preceding symptoms, other than long-standing polydipsia and polyuria.
- More than 10 genes have been identified so far (*NPHP1-11*), which account for approximately one-third of cases. Thus, more genes still await identification.
- The most common mutation (accounting for ~20% of cases) is a homozygous deletion of *NPHP1*.

Presentation and prognosis

Progression to CKD 5 is virtually universal. However, age at onset and extrarenal manifestations vary according to the underlying gene, but also individually.

Extrarenal manifestations include:

- *Eye:*
  - retinal dysplasia/retinitis pigmentosa (Senior–Løken syndrome);
  - oculomotor apraxia (Cogan syndrome).
- *Skeleton:*
  - thoracic deformity (Jeune asphyxiating thoracic dystrophy);
  - cone-shaped epiphysis (Mainzer–Saldino syndrome);
  - skeletal dysplasia (Ellis van Crefeld syndrome).
- *Heart:*
  - situs inversus (infantile nephronopthisis, Ivemark syndrome);
  - cardiac malformations.
- *Brain:*
  - cerebellar vermis aplasia (Joubert syndrome);
  - encephalocele (Mekkel-Gruber syndrome).
- *Liver:* ductal plate malformation.

Diagnosis

- On US, kidneys typically are of normal size, but echo-bright and may contain cysts.
- Anaemia is often severe because of the tubulointerstitial fibrosis affecting the peritubular erythropoietin-producing cells.
- The most important differential diagnostic consideration is tubulointerstitial nephritis (TIN), which can present with similar symptoms. Chronicity of symptoms, as assessed by history, degree of anaemia and parathyroid hormone (PTH) elevation will argue for nephronophthisis (NPHP). Renal biopsy can help distinguish between the two diagnoses: Histology in NPHP is characterized by the triad of renal tubular (and glomerular) cysts, tubular membrane disruption, and tubulointerstitial cell infiltrates with interstitial fibrosis. Conversely, TIN is characterized by an eosinophilic infiltrate.

Management

- No specific therapy is available but standard CKD management applies (📖 Chapter 18, p.409).
- All should have ophthalmological and cardiac reviews in view of the known extra renal manifestations.
- Recurrence of the disease post-transplant has not been reported.

Renal cysts and diabetes syndrome

Background

- Associated with mutations in the transcription factor hepatocyte nuclear factor 1-β (HNF1B); approximately 50% are due to microdeletions at chromosome 17q12, which typically include other genes.
- The most commonly found genetic abnormality in antenatal bright kidneys (~30%).

Presentation and prognosis

- Renal manifestations are highly variable and include multicystic dysplastic kidney (MCDK), hypo-, a- and dysplasia, cysts, including glomerular cysts, malformations such as horseshoe kidney, and occasionally lower urinary tract abnormalities.
- Progression to CKD 5 in childhood is seen in approximately 10–20% of patients.
- Associated features may include:
  - type 2 diabetes mellitus (onset usually in adulthood, but can occur earlier);
  - there may be an increased risk for new onset diabetes mellitus after transplantation (NODAT);
  - hyperuricaemic gout;
  - hypomagnesaemia with renal magnesium wasting;
  - abnormalities of the female genitalia, including bicornuate uterus, rudimentary uterus, uterus didelphys, hemiuterus, and vaginal aplasia;
  - abnormalities of the male genitalia, including epididymal cysts and atresia of vas deferens;
  - elevated liver enzymes;
  - pancreatic abnormalities, such as atrophy;
  - bi-allelic mutations in HNF1B are associated with renal chromophobe cancer;
  - in addition, autism, schizophrenia, developmental delay, epilepsy and eye abnormalities (coloboma and cataract) have been reported in patients with 17q12 microdeletions; these additional manifestations are likely represent a contiguous gene syndrome, and may not be directly related to the loss of HNF1B, but to those of other genes contained within the deletion.

Diagnosis

- HNF1B mutations should be considered in any child with a combination of these symptoms (📖 'Presentation and prognosis', p.331), especially if there is a family history of renal disease, early-onset diabetes, or gout.
- Genetic testing provides definitive diagnosis. Because of the high proportion of deletions, gene dosage assays (such as multiplexed ligation-dependent probe amplification (MPLA) or array comparative genomic hybridization (aCGH) (see 📖 'Genetic testing and antenatal diagnosis', p.38) need to be performed if sequencing is normal.

Management

- The large number of potential extra-renal manifestations suggests that patients with HNF1B mutations should be carefully screened for the presence of these.
- If hyperuricaemia is present, this should be treated with allopurinol.
- Hypomagnesaemia can be ameliorated with magnesium supplementation.
- Currently, there is insufficient experience to warrant modification of post-transplant immunosuppression because of potential increased risk of NODAT.

Renal dysplasia

Background

- The most common cause of CKD in childhood.
- May occur in association with vesicoureteric reflux (VUR), obstruction, or syndromes.
- The kidneys are usually small with increased echogenicity on US and may or may not contain cysts that, if present, are usually cortical.
- There is a familial incidence, with a recurrence risk of up to 10%.
- With the introduction of antenatal screening, which detects these lesions before potential infections, the diagnosis of reflux nephropathy has become rare. Presumably, many of the children previously diagnosed with reflux nephropathy actually had primary renal dysplasia.
- No imaging modality can distinguish between primary renal dysplasia and acquired renal scarring/reflux nephropathy.

Presentation and prognosis

- The majority of children are diagnosed antenatally.
- Renal dysplasia typically affects tubular salt handling, so polyuria and acidosis are common.
- Severity is variable, with some presenting at birth with severe CKD and others presenting later in childhood or even early adult life.
- CKD progression is slow. Infants and young children may even show an improvement in renal function in the first few years of life and then function can remain relatively stable or with a very slow decline throughout childhood with an increase in CKD progression at puberty.

Management

See 🕮 Chapter 18, sections on 'Management', pp.415–457.

- Because of the obligatory tubular salt and water losses, children need free access to water and some may need sodium supplementation. Hypertension is therefore unusual before CKD 5.
- Large doses of bicarbonate may be necessary due to renal wasting.
- Because urine output usually continues into CKD 5, children can be managed with very low GFRs without dialysis with good dietary care.

This page intentionally left blank

Chapter 14

Syndromes associated with renal diseases

Overview of genetics and renal abnormalities in inherited syndromes

Monogenic disorders

See Table 14.1.

Table 14.1 Monogenic disorders

Syndrome	OMIM	Gene(s)	Mode	Type of RM	Features other than RM
Alagille	118450 610205	JAG1 NOTCH2	AD	Dysplasia	Cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities, characteristic facies
Apert	101200	FGFR2	AD	Hydronephrosis	Craniosynostosis, midface hypoplasia, syndactyly
Beckwith–Wiedemann	130650	P57 CDKN1 CH19 LIT1	AD GI	Dysplasia	Exomphalos, macroglossia, gigantism, hypoglycaemia
Branchio-oto-renal	113650	EYA1 SIX1	AD	Agenesis, dysplasia	Pre-auricular pits, branchial fistulae, deafness
Campomelic dysplasia	114290	SOX9	AD	Dysplasia	Skeletal defects, abnormal genitalia
Duane-radial ray	607323	SALL4	AD	Agenesis, migration defect	Upper limb anomalies, ocular anomalies

Fraser	219000	FRAS1 FREM2	AR	Agenesis	Cryptophthalmos, syndactyly, abnormal genitalia, laryngeal malformations, anal stenosis
Kallman	308700	KAL1	XR	Agenesis, dysplasia	Hypogonadotropic hypogonadism, anosmia
	147950	FGFR1	AD		
	244200	PROK2	AD		
	610628	PROK2R	AD+R		
	612370	CHD7	AD		
	612702	FGF8	AD+R		
Pallister-Hall	146510	GLI3	AD	Dysplasia	Hypothalamic hamartoma, pituitary dysfunction, central polydactyly, and visceral malformations
Renal-Coloboma	120330	PAX2	AD	Hypo-/dysplasia, VUR	Optic disc coloboma,
Renal cysts and diabetes	137920	HNF1B	AD	Hypo-/dysplasia	Diabetes, gout, hypomagnesaemia, uterus malformation
Townes-Brocks	107480	SALL1	AD	Hypo-/dysplasia	Imperforate anus, hand, foot and ear abnormalities, deafness
Renal tubular dysgenesis	179820	Renin	AR	Tubular agenesis	Potter sequence with fetal death
	106150	AGT			
	106180	ACE			
	106165	AGTR1			

(Continued)

Table 14.1 (*Contd.*)

Syndrome	OMIM	Gene(s)	Mode	Type of RM	Features other than RM
Simpson-Golabi-Behmel	312870	GPC3	XR	Dysplasia	Polydactyly, macrosomia, cleft palate
	300209	CXORF5			
Zellweger	214100	PEX1,2, 3,5,6,12, 14, 26	AR	Dysplasia	Craniofacial abnormalities, hepatomegaly
Neurofibromatosis type I	162200	NF1	AD	Arterial stenosis and hypertension	Neurofibromas, pigmented patches
Nail-Patella	161200	LMX1B	AD	Congenital NS or glomerulonephritis	Ungual dysplasia, absent or hypoplastic patellae, elbow and other skeletal abnormalities
Meckel-Gruber	249000	MKS1	AR	Cystic dysplasia, NPHP	Encephalocele, hepatic ductal dysplasia and cysts and polydactyly
	603194	TMEM216			
	607361	TMEM67			
	611134	CEP290			
	611561	RPGRIP1L			

Jeune (asphyxiating thoracic dystrophy)	208500 611263 613091 603297 611177	ATD1 ATD2 ATD3 DYNC 2H1 IFT80	AR	Cystic dysplasia, NPHP	Severely constricted thoracic cage and respiratory insufficiency, cysts in the liver and pancreas, retinal degeneration, short limbs, abnormal pelvis
Joubert	613037 613277 608629 607100 610142 609884 610937 608922 612013 300804	INPP5E TMEM216 AHI9 NPHP1 CEP290 TMEM67 RPGRIP1L ARL13B CC2D2A OFD1	AR	Cystic dysplasia, NPHP	Cerebellar vermis hypoplasia, dysregulation of breathing pattern and eye movement, developmental delay, retinal dystrophy

(Continued)

Table 14.1 (*Contd.*)

Syndrome	OMIM	Gene(s)	Mode	Type of RM	Features other than RM
Senior-Loken	266900	NPHP1	AR	NPHP	Retinitis pigmentosa, retinal a-/dysplasia (Leber's amaurosis)
	606995	NPHP3			
	606996	NPHP4			
	609254	IQCB1			
	610189	NPHP6			
	613615	SDCCAG8			
Bardet-Biedl	209900	BBS1-15	AR	Abnormal calyces (on IVP)	Retinal dystrophy, polydactyly, mental retardation and obesity
				Cystic dysplasia, NPHP	
CHARGE	214800	CHD7 SEMA3E	AD	Dysplasia	Coloboma, heart defects, atresia (choanal), retarded growth and development, genital and ear anomalies

AD: autosomal dominant, AR: autosomal recessive, GI: genomic imprinting, XR: X-linked recessive. In AD diseases, parents may not show symptoms due to incomplete penetrance or spontaneous mutation in the child. Renal involvement is not obligate in many of the disorders. Dysplasia often includes cysts. NPHP: nephronophthisis.

Associations and chromosomal abnormalities

See Table 14.2.

Table 14.2 Associations and chromosomal abnormalities

Association	OMIM	RM	Clinical findings
VATER and VACTERL	192350	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)
COACH (variant of Joubert)	216360	Cystic dysplasia	Cerebellar vermis hypo/aplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis
Chromosomal abnormalities			
Trisomies and deletions (see 🕮 'Down syndrome', p.342)		Variable and common	Variable
Turner (45X-)		Variable structural anomalies	Short stature, webbed neck, heart defects
Williams (microdeletion chromosome 7)	194050	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)	188400	Unilateral renal agenesis, dysplasia, hydronephrosis	Hypocalcaemia arising from parathyroid hypoplasia, thymic hypoplasia, and outflow tract defects of the heart

Down syndrome

Introduction

Down syndrome (DS; trisomy 21) is the commonest chromosomal abnormality in live-born infants with an incidence of around 1 in 800. Current guidelines from the American Academy of Pediatrics (http://aappolicy.aappublications.org/cgi/content/full/pediatrics;107/2/442) and the UK Down Syndrome Medical Interest Group (http://www.dsmig.org.uk/publications/guidelines.html) do not recommend screening for renal or urological problems, although some small studies suggest an increased incidence of these.

Renal structural abnormalities in Down syndrome

- A variety of urological abnormalities have been reported in children with DS:
  - vesicoureteric reflux (VUJ) and vesicoureteric junction (VUJ) obstruction;
  - vesicoureteric reflux (VUR);
  - renal hypoplasia and dysplasia;
  - obstructive uropathy;
  - posterior urethral valves.
- There also appears to be an increased rate of glomerular microcyst formation, the significance of which is uncertain.
- As large population studies have not been performed, it is not possible to determine whether any of these abnormalities occur with any greater frequency in DS than in the general population.
- Autopsy studies have reported that the rate of renal abnormality such as hypoplasia, dysplasia, and obstruction may be as high as 21%.
- Some have recommended that all children with DS undergo US assessment of the urinary tract to screen for abnormalities, with further investigations being performed when US abnormalities are detected.

Renal functional abnormalities in Down syndrome

- A number of cases of CKD, including stage 5, have been reported in children with DS, including a number who underwent successful renal transplantation.
- DS *per se* is not a contraindication to dialysis and transplantation, although significant co-morbid features need to be considered as in all patients being assessed for suitability for CKD 5 active management.

Further reading

Mercer ES, Broecker B, Smith EA, *et al.* (2004). Urological manifestations of Down syndrome. *J Urol.* **171:** 1250–3.

Williams syndrome

Background

Autosomal dominant disorder which in the full-blown form includes:

- Supravalvular aortic stenosis classically, but any arterial stenosis can occur, including renal artery stenosis and multiple peripheral pulmonary arterial stenoses.
- Characteristic facial features with full lips and retrousse nose.
- Stellate iris pattern due to stromal hypoplasia.
- Short stature.
- Small wide spaced primary dentition.
- Idiopathic infantile hypercalcaemia.
- Learning difficulties with uneven profile of abilities.
- Characteristic behavioural phenotype.

Caused by a microdeletion on the long arm of chromosome 7, usually containing 26 genes including the elastin gene. The diagnosis is most commonly confirmed by fluorescent *in situ* hybridization (FISH) analysis, although DNA-based tests including multiplexed ligation-dependent probe amplification (MLPA) and microarray testing may also be used.

Urinary tract disease in Williams syndrome

- Structural renal abnormalities (agenesis, duplex, pelvic kidney).
- Nephrocalcinosis secondary to hypercalcaemia and hypercalciuria.
- Unilateral or bilateral renal artery stenoses.
- *Voiding issues:* frequency, urgency, enuresis, detrusor instability.
- Bladder diverticulae 50%.
- *Hypertension:*
  - more prevalent in adult life (50%);
  - may be associated with renal artery stenosis, generalized arterial stiffening or increased sympathetic drive;
  - the *NCF1* gene is located in the same region of chromosome 7, which is often deleted in Williams syndrome. Loss of this gene appears to lower the risk of hypertension.

Hypercalcaemia and hypercalciuria

- Aetiology unknown.
- Symptomatic hypercalcaemia usually resolves during childhood.
- Lifelong abnormalities of calcium and vitamin D metabolism which are poorly understood.
- Hypercalciuria is common and may predispose to nephrocalcinosis.
- Some infants with Williams syndrome require a low calcium containing feed, e.g. Locasol®.

Recommended renal investigations in Williams syndrome

(Full 2010 management guidelines available at http://www.dyscerne.org/dysc/Guidelines—provides much useful information including Williams syndrome growth charts.)

- US of the urinary tract including Doppler studies of the renal arteries.
- Echocardiogram (annual cardiac examination until 4 years of age).
- Urinalysis for presence of microscopic haematuria.

- Urine calcium:creatinine ratio.
- Plasma biochemistry including calcium.
- Measurement of BP annually.

Where nephrocalcinosis is detected, refer to nephrologist for 6-monthly screening. Where structural abnormality is detected, management or referral as necessary. Where renal artery stenosis is detected, refer to nephrologist.

Further reading

http://www.dyscerne.org/dysc/Guidelines.

Martin NDT, Smith WR, Cole TJ, and Preece MA. (2007). New height, weight and head circumference charts for British children with Williams syndrome. *Arch Dis Child* **92:** 598–601.

Branchio-oto-renal syndrome

Background

- Autosomal dominant disorder characterized by sensorineural, conductive and mixed hearing loss, structural defects of the outer, middle, and inner ear, branchial fistulas or cysts, and a range of renal abnormalities.
- Reduced penetrance and variable expressivity has been observed.

Renal abnormalities reported in branchio-oto-renal syndrome

(OMIM: http://www.ncbi.nlm.nih.gov/omim)

- Renal dysplasia (including cystic dysplasia) and hypoplasia.
- Renal agenesis.
- Distortion and duplication of the pelvicalyceal and collecting systems.
- Narrowing of pelviureteric junctions.

Two different genetic mutations have been identified

- BOR1 caused by mutation in the *EYA1* gene (8q13).
- BOR2 caused by mutation in the *SIX5* gene.

There is no obvious correlation between the mutation detected and the phenotypic expression. Studies performed at schools for hearing impaired children have suggested that the frequency may be higher than generally realized. The presence of a pre-auricular pit at birth suggests that the child has risk of hearing loss of at least 1 in 200.

This page intentionally left blank

Chapter 15

Renal tumours

Wilms' tumour

Introduction

- Incidence is 8.1 cases per million Caucasian children less than 15 years of age.
- Usually presents before 5 years of age.
- Nephrogenic rests (clusters of blastemal cells, tubules, and stromal cells found at the periphery of the renal lobe) are thought to be precursor lesions. The term nephroblastomatosis indicates the presence of multifocal or diffuse nephrogenic rests in one or both kidneys, and has a distinctive radiological appearance compared with Wilms' tumour.
- Associations with Wilms' tumour (see 📖 'Surveillance for Wilms' tumour in at-risk individuals', p.351):
  - Denys–Drash syndrome (cryptorchidism, diffuse mesangial sclerosis causing heavy proteinuria);
  - WAGR syndrome (Wilms' tumour, Aniridia, Genitourinary malformations, mental Retardation);
  - Frasier syndrome (male pseudohermaphroditism in males, progressive nephropathy and gonadoblastoma: associated with *WT-1* gene mutations and 4/48 published cases have developed Wilms' tumour);
  - Beckwith–Wiedemann syndrome;
  - Perlman syndrome;
  - Hemihypertrophy;
  - Simpson Golabi Behmel syndrome;
  - Fanconi anaemia;
  - Mosaic-variegated aneupolidy.

At least three genes are associated with Wilms' tumour, though the incidence of familial Wilms' tumour is <1%:

- *WT1 (11p13):* constitutional deletion in WAGR syndrome:
  - several constitutional mutations in Denys–Drash and Frasier syndromes;
  - specific mutations in less than 10% of sporadic Wilms' tumour.
- *WT2 (11p15.5):* same location as Beckwith–Weidemann gene abnormality.
- Familial WT genes (17q12 and 7p13).

Presenting features

- Abdominal mass or swelling (commonest).
- Abdominal discomfort.
- Gross or microscopic haematuria.
- Pyrexia.
- Hypertension: may be associated with hyperreninaemia, often due to distortion of the renal arteries, and responds to therapy with angiotensis-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockade (ARB).
- US abnormality detected during the screening of at risk individuals.

Diagnosis

Radiology

- Abdominal US and computed tomography (CT) to determine the extent of spread of tumour into adjacent structures, e.g. liver and inferior vena cava (IVC), with tumour, and radiological abnormalities of the opposite kidney.
- Chest CT to exclude pulmonary metastases.

Histology

- Needle biopsy performed by an experienced operator is recommended in the UK and does not change the tumour stage.
- Following pre-nephrectomy chemotherapy, nephrectomy is performed to confirm histology of excised renal tissue, and lymph nodes and local abdominal staging.
- Diffuse or focal anaplastic histological change, which is present in around 5% of cases, is associated with a poorer prognosis and is an indication for more aggressive therapy.

Staging

Depends on the involvement of sampled regional lymph nodes and direct examination of the contralateral kidney by the surgeon. The presence/absence of metastases is evaluated at presentation on the basis of imaging studies (see Box 15.1).

Treatment

- Combination of surgery, chemotherapy and radiotherapy, which is dependent on the stage and histology of the tumour.
- Most US centres advocate primary surgery followed by chemotherapy or radiotherapy: cited advantages include avoidance of possible modification of tumour histology and staging, and the administration of chemotherapy to children with non-Wilms' malignancies or benign lesions.
- In UK and Europe most patients receive pre-nephrectomy chemotherapy: vincristine/actinomycin D for localized disease and vincristine, actinomycin D, and doxorubicin for metastatic disease. Post-nephrectomy chemotherapy depends on abdominal stage and response to pre-op chemotherapy. Cited advantages include a lower tumour rupture rate at operation and the identification of good prognostic subgroups based on tumour response.
- The tumour is radiosensitive, although radiotherapy is reserved for high risk Wilms' tumours and abdominal stage III.
- In children with bilateral disease, consideration is given to renal sparing surgery.
- Treatment of nephroblastomatosis is somewhat different. As part of the recommendations in the current SIOP Wilms tumour protocol, chemotherapy should be tried first as long as the lesions respond and surgery is reserved for lesions, which progress or become radiologically suggestive of a Wilms tumour. This should be renal sparing as feasible.

Box 15.1 Staging of Wilms' tumours: International Society of Paediatric Oncology SIOP WT 2001 Study

Stage I

- The tumour is limited to kidney or surrounded with a fibrous pseudocapsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumour, but it does not reach the outer surface, and it is completely resected (resection margins 'clear')
- The tumour may be protruding ('bulging') into the pelvic system and 'dipping' into the ureter (but is not infiltrating their walls)
- The vessels of the renal sinus are not involved
- Intrarenal vessel involvement may be present.

Stage II

- The tumour extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into peri-renal fat, but is completely resected (resection margins 'clear')
- Tumour infiltrates the renal sinus and/or invades blood, and lymphatic vessels outside the renal parenchyma, but is completely resected
- Tumour infiltrates adjacent organs or vena cava, but is completely resected.

Stage III

- Incomplete excision of tumour which extends beyond resection margins (gross or microscopical tumour remains post-operatively)
- Any abdominal lymph nodes are involved
- Tumour rupture before or intra-operatively (irrespective of other criteria for staging)
- The tumour has penetrated through the peritoneal surface
- Tumour implants are found on the peritoneal surface
- The tumour thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon
- The tumour has been surgically biopsied (wedge biopsy) prior to pre-operative chemotherapy or surgery.

Stage IV

Haematogeneous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region.

Stage V

Bilateral renal tumours at diagnosis. Each side should be substaged according to above classifications.

Prognosis

- Overall survival rates of approximately 90% have been reported.
- For children with relapsed Wilms' tumour, high-dose chemotherapy with carboplatin, etoposide, and melphalan has been reported to confer a prolonged disease-free survival in approximately 50% of cases.
- Approximately 1% of children with unilateral Wilms' tumour develop disease in the contralateral kidney, and as for children with bilateral Wilms' tumour at presentation, consideration is given to renal sparing surgery.
- If bilateral disease results in CKD 5, it is arbitrarily suggested that transplantation be delayed until 2 years following completion of all therapy provided that post-therapy assessment has shown no evidence of recurrent disease.
- For the child with remnant renal tissue post-surgery who subsequently progresses to CKD 5, it is wise to remove the remnant tissue prior to transplantation as there is a risk of recurrent tumour developing in it following commencement of immunosuppression.

Surveillance for Wilms' tumour in at-risk individuals

UK Wilms' Tumour Surveillance Working Group recommendations

- Surveillance should be offered to children at >5% risk of Wilms' tumour (see 📖 'Introduction', p.348 for a list of associations with Wilms' tumour).
- Surveillance should only be offered after review by a clinical geneticist.
- Surveillance should be by renal US every 3–4 months.
- Surveillance should continue until 5 years in all conditions except Beckwith–Wiedemann syndrome, Simpson-Golabi-Behmel syndrome and some familial Wilms' pedigrees, when it should continue until 7 years.
- Surveillance can be undertaken in a local centre, but should be performed by someone with experience of paediatric ultrasonography.
- Screen detected lesions should be managed at a specialist centre.

Other renal tumours

Clear cell sarcoma

- Primary renal tumour.
- More common in boys.
- Presents at a median age of 1.5 years.
- Significantly higher relapse-and death-rate than favourable histology Wilms' tumour.
- Metastasizes most frequently to the lungs, and has a tendency to metastasize to bone and brain.
- Overall survival for clear cell sarcoma is 69%, with Stage I patients having 98% survival.

Malignant rhabdoid tumour

- Highly aggressive renal tumour, which is often lethal.
- Most diagnosed in the first year of life, typically with metastatic disease.
- All tumours have a deletion of the *SNF-INI1* gene.
- Associated with concomitant primary in the brain.
- Overall survival is less than 50 %, with stage IV patients less than 25%.

Chapter 16

Hypertension

Basic concepts of blood pressure and defining hypertension in children

The concept of blood pressure

- The force exerted by the blood against any unit area of the vessel wall (Fig. 16.1a).
- Physiologists (and intensivists) traditionally use end-on pressure obtained by catheters placed into vessels and measuring the pressure 'in line' with the vessel: this may not be the same as the lateral wall pressure of palpation, auscultation or oscillation (Fig. 16.1b).

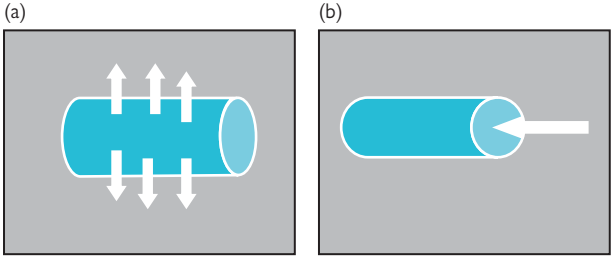

Fig. 16.1 (a) BP detected by auscultation or palpation. (b) BP detected by intra-arterial catheter.

- BP can be affected by changes in vessel size (vasoconstriction/dilatation) and the volume of blood pumped through the arterial system. The latter is affected by cardiac output, as well as fluid volume itself, which is regulated by the kidney.
- Short-term changes in blood pressure (BP) are mostly mediated by the heart and blood vessels (key hormones are catecholamines).
- Long-term BP is mediated by the kidney through regulation of salt reabsorption (key hormone: aldosterone).
- All forms of hypertension with defined aetiology are related (directly or indirectly) to altered renal salt handling, establishing the central role of the kidney in BP regulation.
  Example of phaeochromocytoma: the direct mediator of the hypertension is the increased catecholamine level which leads to vasoconstriction and increased cardiac output. However, this could be easily counteracted by the kidneys by adapting the arterial filling volume via excretion of salt and water. Yet aldosterone levels are typically increased! The reason for this is the fact that the renal arteries are exquisitely sensitive to catecholamines. The resultant constriction leads to decreased renal perfusion with up-regulation of aldosterone and distal salt reabsorption, thus sustaining the hypertension.

Defining hypertension in children

- *In adults:* epidemiological definition based on risk of adverse event (e.g. stroke): >140/90mmHg.

- *In children:* statistical definition: 95th centile for age, height, and gender. By definition, 5% of the general paediatric population are hypertensive.
- Thus, a fundamental difference in children as compared with adults is that, in children, hypertension is defined statistically, whereas in adults definitions are based on risk of an adverse event.

The importance of recognizing hypertension in the young

- Despite the relatively arbitrary definitions of hypertension, severe untreated hypertension carries a high risk of morbidity and mortality.
- Signs of target-organ damage are:
  - blood vessel changes (visible in the retina);
  - cardiac hypertrophy;
  - microalbuminuria.

Measurement of blood pressure in infants and children

Important points

- Measuring BP in young children can be difficult.
- BP measurements using different techniques give different results.
- Check unexpected values, especially when obtained by oscillometry (e.g. Dinamap). Check that the cuff size and circumstances of measurement are correct.

Techniques used to measure blood pressure in children

- Direct, which requires an intra-arterial catheter.
- Auscultatory, using either mercury or aneroid devices or Accoson Green Light.
- Doppler US (the technique of choice in young children because Korotkov sounds are not consistent under the age of 5 years).
- Oscillometry.
- Ambulatory BP measurement (see 🕮 'Ambulatory blood pressure measurement in children', p.373).

Selecting the right cuff size

- Too small a cuff will give an overestimation of BP.
- Underestimation of BP due to too large a cuff is more of a theoretical concern than a real clinical problem.
- The widest cuff that can be applied to the arm should be used. The length of the inflation bladder should be at least 2/3, and preferably 90–100% the circumference of the arm.
- To cover ages 0–14 years, a minimum of 3 cuff sizes are required:
  - 4 × 13cm;
  - 8 × 18cm;
  - 12 × 35cm (adult).
- An 'alternative adult' and thigh cuff (to use on the arm) are needed for obese patients.

Circumstances of measurement

- Child resting for at least 3min in a warm room.
- Measurements taken if the child is eating, sucking, or crying will be spuriously high.
- Brachial artery at level of heart, arm supported.

Korotkov phases (Nicolai Korotkov, 1905[1])

Inflate cuff until palpable pulse disappears.

- *K1:* corresponds to systolic BP.
- *K2:* tapping disappears.
- *K3:* tapping returns.

} 'auscultatory gap'

- *K4:* tapping muffled—paediatric diastolic BP until age 13 years.
- *K5:* tapping disappears—diastolic BP after age 13 years.

1. *Reports of the Russian Imperial Military Academy* (*Izvestie Imp. Voiennomedicinskoi Academii*) (1905): **11:** 365–7.

Comments

- K1 appears 10–12mmHg higher than the palpated pulse.
- K1 is, on average, 3mmHg below direct systolic (i.e. systolic measured using an intra-arterial catheter).
- K5 disappears on average 9mmHg above direct diastolic (K4 is even more unreliable).

Doppler ultrasound technique

Recommended for children less than 5 years.

- The technique of choice for children under 5 years of age.
- A Doppler probe held over the pulse is used to magnify the sound so that it is audible without a stethoscope.
- Preferable because phases of K may not be heard reliably by stethoscope in sick children, those under the age of 1 year and some healthy children less than 5 years.
- Using the mercury-Doppler technique ('Hg-D') the first sound heard is the systolic. However, Hg-D may be 5mmHg higher that K1 since the Doppler flow signal is likely to be detected before the K1 by auscultation.

Alternatives to mercury sphygmomanometers

There is a gradual disappearance of mercury sphygmomanometers from hospitals in the UK because of concerns regarding mercury toxicity. There are a number of alternatives.

Aneroid manometers

- Register pressure through a bellows and lever system.
- Accurate initially, but very sensitive to jolts and bumps; with time they usually underestimate BP, and require regular calibration and maintenance.
- 58% of aneroid manometers have errors greater than 4mmHg; 33% of these have errors >7mmHg.

Accoson green light

Validated as comparable with the mercury manometer. Reduces digital bias by a speed deflation rate light display. Self-calibrating each time the apparatus is switched on, less maintenance required.

Oscillometry

- Pulsatile blood flow through a vessel produces arterial wall oscillation that is transmitted to a cuff encircling the extremity.
- Systolic BP is recorded at the point where a rapid increase in the oscillation amplitude occurs (approximates to K1).
- Diastolic BP is recorded where there is a sudden decrease in the oscillation amplitude (approximates to K5). Newer oscillometric devices measure the mean arterial BP and then calculate the systolic and diastolic values.
- Some devices overestimate BP in young children and very few devices have been validated in children under 5 years old.
- Normative data for casual BP recordings is available, see 📖 Appendix, p.622.

Other important points in the clinical evaluation

Family history

- Essential hypertension, other familial hypertension.
- Sudden death, renal failure, heart attacks, or stroke.

Patient's history

- *Symptoms of renal disease:* e.g. polyuria, dysuria, enuresis; or of phaeochromocytoma, e.g. palpitations, flushing.
- *Symptoms of high BP:* failure to thrive, lethargy, visual disturbance, headache, nausea, and vomiting.
- *Drugs:* amphetamines, ecstasy, oral contraceptives.

Physical examination

- *Femoral delay and BP discrepancy between the arm and leg:* coarctation of the aorta or Takayasu disease.
- *Café au lait spots, axillary freckles:* neurofibromatosis type 1.
- *Abdominal bruit:* renovascular diseases (also check for orbital and cranial bruit).
- *Signs associated with CKD:* short stature, bone disease, anaemia, deafness.
- *Ambiguous genitalia:* adrenogenital syndromes.
- *Fundi and cardiovascular system:* assess end-organ damage.
- Check urine for protein and blood.

The investigation of hypertension in the young

The aims of investigation are to:
- Assess the presence and severity of target organ damage.
- Define aetiology.

See Table 16.1 for causes of severe hypertension.

First line investigations to be considered in all cases of paediatric hypertension

- Full blood count (FBC).
- Urea & electrolytes (U&E), creatinine, albumin, bicarbonate, Ca, PO_4, liver function tests (LFTs); +/– urine electrolytes.
- Fasting lipids.
- Plasma renin activity.
- Plasma aldosterone.
- Plasma catecholamines (adrenaline and noradrenaline).
- Dip test of urine.
- Spot urine albumin:creatinine ratio.
- Urine microscopy (to check for red cell casts).
- Spot urine for urine catecholamines (adrenaline, noradrenaline/metadrenaline, dopamine) to creatinine ratio.
- Electrocardiogram (ECG).
- Echocardiography.
- Chest X-ray (CXR).
- Fundoscopy.
- Renal ultrasound (US) with Doppler flow studies of the renal vessels.

Table 16.1 The causes of severe hypertension in the young, presentation by age

Age	Cause of hypertension
Neonatal period: 1 year	Renal artery stenosis (RAS) (fibromuscular dysplasia; thrombus of renal artery secondary to umbilical arterial catheterization)
	ARPKD
	ADPKD (may be associated with tuberous sclerosis)
	Renal venous thrombosis
	Drugs (corticosteroids)
	Neuroblastoma
	Raised intracranial pressure
	Coarctation of the aorta
	Wilms' tumour

(Continued)

Table 16.1 (*Contd.*)

Age	Cause of hypertension
1–5 years	Renal artery stenosis
	Middle aortic syndrome
	Glomerulonephritis
	Renal venous thrombosis
	Phaeochromocytoma
	Neuroblastoma
	Cystic kidney disease
	Corticosteroids
	Monogenic hypertension (e.g. Liddle's syndrome)
	Wilms' tumour
5–10 years	Reflux nephropathy
	Glomerulonephritis
	Cystic renal disease
	Renal artery stenosis
	Middle aortic syndrome
	Endocrine tumours: Cushing's syndrome and disease, Conn's syndrome, Phaeochromocytoma, Neuroblastoma
	Wilms' tumour
	Other parenchymal renal disease (e.g. glomerulocystic disease, nephronophthisis)
	Essential hypertension
	Obesity
10–20 years	Obesity
	Essential hypertension
	Reflux nephropathy
	Glomerulonephritis
	Renal artery stenosis
	Endocrine tumours
	Monogenic hypertension
	Pregnancy
	Drugs: oral contraceptive pill, corticosteroids, alcohol, amphetamines, ecstasy

This serves as a guide and is not an exhaustive list. There may be some overlap in causality at different ages. CKD or AKI (from any cause) should be considered at all ages. In addition pain and raised intracranial pressure should be excluded as a potential cause.

Second line investigations

See Table 16.2.

Table 16.2 Second line investigations to be performed in selected cases only, and usually only in specialist centres

Suspected aetiology	Investigations
Glomerulonephritis	ASOT/Anti DNase B
	Autoantibodies: ANA, DS-DNA, ENA, GBM, ANCA, C3NF (if low C3)
	C3, C4 CH100
	GFR
	Renal biopsy
Reflux nephropathy/	Cystogram (direct/indirect)
obstructive uropathy,	MAG3
pyelonephritic scars	GFR
	DMSA scan
Renovascular disease	See 🕮 'Renovascular hypertension', p. 362
Pheochromocytoma	meta-iodobenzylguanidine scintigraphy
	Adrenal/abdominal USS
	CT or MRI abdomen
	DNA for genetic testing: up to 70% of children with pheochromocytoma have an identifiable genetic basis. Recognized disease genes: include VHL (von Hippel–Lindau syndrome), RET (multiple endocrine neoplasia type 2), SDHD (paraganglioma syndrome type 1), SDHC (paraganglioma syndrome type 3), SDHB (paraganglioma syndrome type 4) and NF1 (neurofibromatosis type 1) SDHA, SDHAF2 and TMEM127
	Genetic identification is important to assess risk for associated morbidities, including cancer
Monogenic hypertension	Monogenic forms of hypertension all affect renal sodium reabsorption and are thus discussed in 🕮 'Disorders of renal salt handling: basic principles', p.140
Miscellaneous	Genetics when appropriate; urine toxicology screen (amphetamines, ecstasy)

Renovascular hypertension

- Renovascular disease (renal arterial stenosis being the commonest cause) is the cause of 5–10% of all cases of hypertension in children.
- Presents at all ages.
- After coarctation of the aorta it is the commonest surgically remediable form of hypertension.

Causes of renovascular disease

- Fibromuscular dysplasia.
- Neurofibromatosis type 1 (NF1).
- Williams' syndrome.
- Following vasculitis, in particular Takayasu's disease.
- Following trauma or renal artery thrombosis associated with umbilical artery catheterization.
- Following abdominal radiotherapy.
- External compression of renal arteries by hilar lymph nodes or tumour (including Wilms' tumour).
- Post-renal transplantation (5% of renal transplants).

Presenting symptoms

- Incidental.
- Congestive heart failure.
- Cerebral symptoms including:
  - cerbrovascular incident;
  - acute hypertensive encephalopathy;
  - headache;
  - facial palsy.
- Failure to thrive.
- Screening of children with syndromes, see 📖 'Causes of renovascular disease', p.362.

When to suspect renovascular disease

- Very high BP. Not uncommonly systolic of 200mmHg or more.
- Secondary symptoms of high BP including cerebral symptoms, cardiac failure, and facial palsy.
- Difficult to treat hypertension that is not well controlled on full doses of at least two antihypertensive drugs.
- Hypokalaemic, hypochloraemic metabolic alkalosis (the biochemical 'fingerprint' of aldosterone).
- Diagnosis of a syndrome with a higher risk of vascular disease.
- Signs of vasculitis.
- Known or suspected previous vascular insult.
- Transplanted kidneys.
- Bruit heard over the artery/ies.
- Elevated peripheral plasma renin/aldosterone.

Investigations

- Renal US and Doppler studies.
- Dimercaptosuccininc acid (DMSA).

- Computed tomography (CT) and/or magnetic resonance angiography (MRA).
- Selective renal arteriography. Note that all other imaging modalities have at least 10–20% false negative and false positive results.
- Renal vein renin studies can in some cases be used to define the kidney or the area of the kidney driving the hypertension.
- MR of the brain including both parenchyma and blood vessels.
- Peripheral plasma renin (see also 📖 'The investigation of hypertension in the young', p.359).

Involvement of vascular beds

- Bilateral renal artery disease is more common than unilateral.
- Intrarenal artery disease is seen in many patients and not amenable to interventional treatment.
- A quarter of the children have mid aortic syndrome, i.e. narrowing of their aorta.
- A third of the patients have stenosis of one or several of their intestinal arteries. This is often asymptomatic and does mostly not need treatment.
- At least a fifth of the patients do have cerebrovascular disease. The extent of this can affect how low you want to bring the BP.

Treatment

- The goals of the treatment are two-fold:
  - improvement of BP;
  - improvement or preservation of kidney function.
- Medical treatment in most cases is not sufficient.
- Interventional treatment includes:
  - angioplasty with or without stenting; in many centres this is now the most commonly used treatment modality;
  - surgery, now often used only in cases not amenable to angioplasty.
- Treatment should be individualized after discussions in teams including a nephrologist, interventional radiologist and vascular surgeon.
- Note that kidneys with seemingly no function, i.e. no DMSA uptake, can recover some or all of their function after revascularization. Thus a conservative approach to nephrectomy is advised unless the kidney looks severely shrunken or dysmorphic on US.

Further reading

Tullus K, Brennan E, Hamilton G, *et al.* (2008). Renovascular hypertension in children. *Lancet* **371:** 1453–63.

Treatment

Treatment of hypertensive emergency

- Children and adolescents with severe elevation of BP are at increased risk of hypertensive encephalopathy, seizures, and congestive heart failure. Severe, symptomatic hypertension with decompensation is a medical emergency and should be treated with IV antihypertensive drugs.
- If the crisis is of known short duration (<72h), e.g. a dialysis patient who enjoyed a high-salt diet, the BP can be brought down more quickly than in children who have long-standing hypertension (see 📖 'Long-term treatment in children and adolescents', p.368).
- If the patient is on dialysis, the treatment is immediate fluid removal by emergency dialysis.
- Conditions that may mimic hypertensive emergency, e.g. intracranial pathology, seizures, dysautonomia, must be excluded.
- In a new presentation of hypertension the duration is unlikely to be known so the BP must be brought down slowly. First 1/3 of total BP reduction to be aimed for over the first 12h, next 1/3 over 12h and final 1/3 over 24h.
- The preferred drug for hypertensive encephalopathy is labetalol by infusion. If there are contraindications, such as asthma and heart failure a sodium nitroprusside infusion can be used.
- Hydralazine as a slow IV injection or as an IV infusion may be given to stabilize the patient. The patient must have two large bore IV cannulae inserted so that intravenous sodium chloride 0.9% can be given if the BP is reduced too quickly.

It is preferable to use drugs with a short duration of action in the first instance so that if there is a sudden potentially harmful drop in BP this can be reversed more readily. Conversion to once daily agents can be made subsequently. Sublingual nifedipine may cause a precipitous drop in BP so should be avoided, particularly in those with long-standing (or uncertain duration) hypertension. It can be an option if IV access cannot be secured. See Fig. 16.2 for a general scheme for the management of paediatric hypertension.

Hypertensive crisis

See Boxes 16.1 and 16.2.

Initiation of treatment of acute severe (>99th %ile) hypertension (non-hypertensive crisis)

Acute treatment of hypertension as in-patient. Preferred first line drugs are oral nifedipine and IV hydralazine, or if fluid overloaded oral or IV furosemide (see Table 16.3).

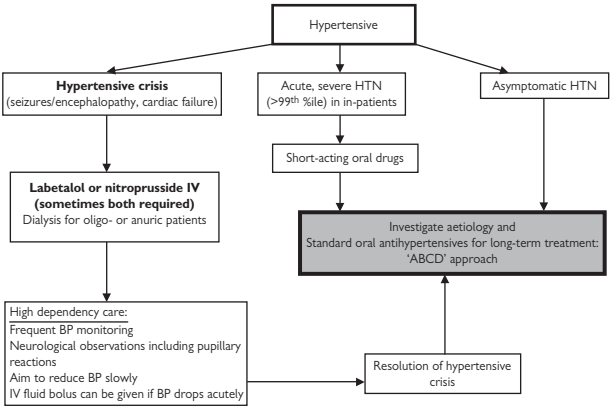

Fig. 16.2 General scheme for the management of paediatric hypertension.

Box 16.1 Labetalol infusion (combined α- and β-blocker)

- *Dose:* start at 500micrograms (0.5mg)/kg /h to maximum 3mg/kg/h
- *Administration:* dilute to 1mg in 1ml (max 2mg in 1ml) in glucose 5% or glucose 4%/NaCl 0.18% OR can be given neat (5mg in 1ml)—protect neat solution from light. Do not use NaCl 0.9% or mix with other drugs
- *Contraindications:* 2nd or 3rd degree heart block. Low cardiac output. Caution in asthmatics (control with salbutamol)
- *Side effects:* nasal congestion, rash, pruritus, nausea, vomiting. Severe hepatocellular damage has been reported after both short- and long-term treatment. Check for hepatic dysfunction.

Box 16.2 Sodium nitroprusside infusion

- *Dose:* start at 500ng (0.5micrograms)/kg/min to a maximum 8micrograms/kg/min. Increase dose slowly (risk of tachycardia) and discontinue over 15–30min to prevent rebound effect.
- *Administration:* mix contents of ampoule (50mg) in 2mL glucose 5%. Further dilute in 250mL–1L glucose 5% ONLY. Immediately wrap in foil to protect from light. Fresh infusion solution should have faint orange-brown tint. Do not use if highly coloured. Do not mix with other drugs and change infusion after 24h.
- *Contraindications:* sodium nitroprusside is rapidly converted to cyanide and to thiocyanate, which may interfere with the metabolism of vitamin B12. Do not use in patients with vitamin B12 deficiency, impaired liver function, Lebers optic atrophy. Thiocyanate inhibits uptake and binding of iodine, so caution should be used in hypothyroid patients.
- Side effects: nausea, retching, vomiting, headache, restlessness, muscle twitching, palpitations, dizziness are often associated with too rapid reduction in BP: slow rate of infusion or temporarily stop. Cyanide inhibits cellular oxidative metabolism. Excessive concentrations of cyanide can cause tachycardia, sweating, hyperventilation, cardiac arrhythmias and metabolic acidosis. The infusion may be continued for several days but the blood cyanide concentration must not exceed 100micrograms/100mL and the serum cyanide concentration must not exceed 8micrograms/100mL. If administering over more than 3 days blood thiocyanate concentration should be checked and should not exceed 100micrograms/mL.

Table 16.3 Drugs used in the treatment of acute severe (>99th %ile) hypertension

Drug	Route	Normal starting dose	Normal dose range (to Maximum)	Divided doses /day	Preparations
Furosemide	IV	500microgram/kg/dose	0.5–4mg/kg/day	2–4	Injection 10mg in 1mL
(if fluid overloaded)	oral	500microgram/kg/dose	1–4mg/kg/day	1–4	Tablets 20mg, 40mg
			(Maximum 12mg/kg/day)		Syrup 50mg in 5mL
Nifedipine SR	oral	250microgram/kg/dose	1–2 mg/kg/day	2–4	Drops 20mg in 1mL (not licensed—short-acting)
			(Maximum 3mg/kg/day up to 120mg/day)	2 (older children)	SR tablets 10mg, 20mg, preferably cut SR tablets with tablet cutter; when crushed and dispersed in water, long-acting effect reduced
Hydralazine	IV	100–500microgram/kg/dose or 10–50microgram/kg/h	Maximum 4-hourly (Maximum **3mg/kg in 24h)**	Slow iv or Infusion if required	Injection 20mg

Long-term treatment in children and adolescents

The focus here is to use drugs that preferably can be used once daily, maximizing treatment dosage before adding a further drug. The agent(s) used will come from the following 'ABCD' groups:

- Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin IIK inhibitors (ARBs).
- Beta–blocker.
- Calcium channel blocker.
- Diuretic.

The British Hypertension Society (BHS) launched this ABCD algorithm to provide more didactic advice on the sequencing of drugs for the treatment of hypertension in adults, but the principles also apply to the paediatric population (see Table 16.4):

- Children generally respond better to drugs that block the renin system. These include 'A' drugs (ACEIs and ARBs) and 'B' drugs (beta-blockers).
- If combination treatment is necessary it is recommended to combine A or B with C or D.
- The third step would involve triple therapy with either A+C+D or B+C+D.
- The clinical situation, including the presence of any proteinuria (for which ACE inhibition or angiotensin II blockade would be recommended), will determine which group you should start with. When the glomerular filtration rate (GFR) is <10mL/min/1.73m^2, always start with the lowest dose, although careful assessment of fluid status is required as the cause in the majority will be fluid overloaded and dialysis is likely the best treatment.
- *For infants (less than 1 year old):* use shorter-acting agents for flexibility of dosage—propranolol instead of atenolol; captopril instead of enalapril. Once stable, the patient may be changed to the longer-acting antihypertensives.
- Whilst approaches such as the ABCD algorithm are useful, in some cases it is possible to predict which drugs might be most efficacious depending on the cause of the hypertension (Table 16.5).

Table 16.4 Drugs commonly used in the ABCD algorithm

Drug	Route	Normal starting dose	Normal dose range (To Maximum)	Divided doses/day	Preparations and comments
Amlodipine	oral	100–200microgram/kg/dose	6–15kg 1.25mg 15–25kg 2.5mg >25kg 5mg (Maximum 10mg/day)	1	Tablets 5mg, 10mg Tablets may be dispersed in water and still maintain long acting effect
Atenolol*	oral	1mg/kg/dose	1–2mg/kg/day (maximum 100mg/day or 50mg/day when GFR<10)	1	Tablets 25, 50, 100mg Syrup 25mg in 5mL Caution in asthma although cardioselective
Enalapril	oral	100microgram/kg/dose	200–500microgram/kg/day (maximum 600microgram/kg/day up to 40mg/day)	1	Tablets 2.5, 5. 10mg C/I commencing treatment in pregnancy and hyperkalaemia Caution in renal artery stenosis and when GFR <30

(Continued)

Table 16.4 *(Contd.)*

Drug	Route	Normal starting dose	Normal dose range (To Maximum)	Divided doses/day	Preparations and comments
Irbesartan	oral	2mg/kg/dose	6–12 years: 75–150mg/day >13 years 150–300mg/day	1	Tablets 75, 150mg May be useful to add in presence of persistent proteinuria C/I in pregnancy and caution in renal artery stenosis
Bendroflumethiazide	oral	Maximum 400microgram/kg once a day initially then reduce to maintenance	Up to 12 months 1.25mg 1–4 years 1.25–2.5mg 5–12 years 2.5mg >12 years 2.5–5mg	1	Tablets 2.5, 5mg May exacerbate SLE
Furosemide	oral	500microgram/kg/dose	1–4mg/kg/day	1–4	Tablets 20, 40mg Syrup 50mg in 5mL

* Recent studies in adults (Lancet, systematic review & ASCOT data) have suggested that Atenolol should not be used alone as first line therapy.

Table 16.5 Treatment of choice for select causes of hypertension

Suspected aetiology	Treatment of choice
Acute glomerulonephritis	Diuretics Standard oral antihypertensives
Reflux nephropathy/obstructive uropathy	Relieve obstruction if present Standard oral antihypertensives ACEI
Renovascular disease	Standard oral antihypertensives (ACEI) Angioplasty Surgery
Phaeochromocytoma	Phenoxybenzamine β blocker Nifedipine Surgery (after adequate α and β blockade)
Endocrine (this category is low renin hypertension)	Much depends on the specific disorder and complicated and generally has may include: Spironolactone Triamterene/amiloride Dexamethasone Thiazide
Essential	Salt/weight/exercise Standard oral antihypertensives
Coarctation	Surgery Standard oral antihypertensives

Table 16.6 Suggested treatment for hypertension in phaeochromocytoma

Drug	Route	Normal starting dose	Normal dose range (to maximum)	Divided doses/ day	Preparations and comments
Phenoxy-benzamine	Oral	200micrograms/ kg/dose	1–4mg/kg/day	2	Capsules 10mg
Propranolol	Oral	1mg/kg/ dose	1–8mg/kg/day	3	Tablets 10mg, 40mg, 80mg

Phaeochromocytoma

- Both alpha and beta blockade is required (Table 16.6).
- Clinician should consult with the anaesthetist regarding discontinuation of drugs around the time of surgery. Drug would usually be given pre-operatively and discontinued subsequent to the procedure.

Additional medications

Drugs to be used when a combination due to any reason does not give full control of BP with acceptable side-effects (Table 16.7).

Table 16.7 Additional medications

Drug	Route	Normal starting dose	Normal dose range (to maximum)	Divided doses/ day	Preparations and comments
Clonidine	Oral	2.5micrograms/ kg/dose to a Maximum 25micrograms	Maximum 200 micrograms/ day	2	Tabs 25 micrograms, 100 micrograms Solution 5 micrograms/mL (made as extemp) May cause dry mouth and/or sedation Care in withdrawal due to rebound effect
Minoxidil	Oral	100micrograms/ kg/dose	200microgram/ kg/day– 1mg/kg/day (<12 years Maximum 50mg/day >12 years Maximum 100mg/day	1–3	Tablets 2.5, 5, 10mg Prolonged use can cause hypertrichosis
Prazosin	Oral	5micrograms/kg/ dose	50–400 micrograms/kg/ day Maximum 500 micrograms/ kg/day	2–4	Tablets 1, 2mg When GFR <50 start with a lower dose

Ambulatory blood pressure measurement in children

In recent years ambulatory BP monitoring (ABPM) has become an important additional tool in identifying hypertension and monitoring the effectiveness of antihypertensive medication. ABPM is well established in adult areas, but in children the results are variable, and validity and reliability are less consistent. Many of the established recommendations for ABPM apply to children, but substantial differences exist especially in children <5 years of age.

Advantages

- Allows multiple measurements typically during a 24-h period.
- Provides a truer picture of BP trends.
- Provides better BP correlation with cardiac outcome.
- Identifies 'white coat hypertension'.
- Identifies nocturnal hypertension (non-dippers—absence of the normal physiological drop in BP when asleep).

Disadvantages

- Some of the most commonly used devices have failed the rigorous validation procedures to which they have been subjected, particularly in relation to children <5 years. ABPM is usually limited to children >5 years old. This is because it is necessary to keep the arm completely still during the measurement and young children do not usually manage this over a 24-h period, resulting in a 24-h record with very few successful readings during the awake periods. Monitors can be used in the under-5's for night monitoring if required.
- Lack of large series providing normative data, especially for infants and toddlers. Many of the trials relating to hypertension and outcome refer to casual BP readings, so interpretation of ambulatory readings may be problematic.
- Requires training and expertise in analysis and interpretation of data.
- Can cause discomfort with high inflation pressures if the child moves excessively during the measurement or has significant hypertension.

Measuring ambulatory blood pressure in children

- More difficult in children over 6 months and under 5 years. Great care must be taken when interpreting results due to the wide variations of activity and emotional states (situations that cause a sympathetic response, crying, falling over, tantrums).
- The equipment selected must be validated for use in children and be lightweight with a selection of cuff sizes. The internal bladder size must cover 80–100% of the circumference of the arm.
- The software provided must allow for variations of frequency to be programmed into the monitor, and for the report to be customized to include actual sleep periods and paediatric reference data to calculated BP load automatically.
- The non-dominant arm is preferable, but the arm with the highest clinic reading should be used.

- Diaries should be given to the children to record activities, medication, and sleep periods; where possible use the real sleep time to calculate nocturnal mean BP values. Recording activity and the emotional state is particularly relevant for children.
- Must avoid immersion in water while the monitor is attached.
- Normal daily activity would be encouraged during the monitoring period, but the arm must be still during the measurement.
- Avoid placing cuff too low on elbow as this is uncomfortable.
- Warn the child that they should call if the arm becomes painful (provide contact number, including out of hours contact details).
- Ensure that monitor is calibrated yearly, and should be within 5mmHg of mercury sphygmomanometry.

Interpretation of results

- The ABPM percentiles of mean day and night time systolic and diastolic BP, and sleeping and waking time should be programmed into the report settings. The overall summary, wake period, sleeping period and night dip is provided.
- A diagnosis of hypertension can be based on a high day or night time BP load and poor night dip. However if only a few readings are obtained during the day the 24-h report is of limited use. It is important to look at the number of readings while asleep and awake, and interpret only the successful ones. In children intermittent extreme BP readings are unlikely to be valid and are most likely artifact; an accurate diary can help to confirm this.

Definitions

- *BP load:* is the percentage of valid ambulatory BP readings above the 95th percentile for age gender and height in a 24-h period. A load >25% is considered outside the normal range. If the mean BP in these children is only slightly elevated above the 95th percentile these children should have their BP monitored periodically.
- *Mean BP:* the average of daytime, night time, and 24-h BP measurement for systolic, diastolic and mean arterial pressure (MAP; see Table 16.8).
- *Nocturnal dip:* this is the decline of BP during the sleeping period. A 'non-dipper' is a person who's night time decline in mean systolic and diastolic ABP is <10%. A poor dip is typical for secondary hypertension.
- *Number of readings:* half-hourly readings during the day and hourly readings during the night are usually acceptable. The final report should give a percentage of successful readings. More than 90% is considered to be a good result. The lower the success rate the less valid the results.

All of these points need to be taken into consideration when reading an ABPM report. In children, the success of the test can be variable. In general, the accuracy of the test improves with age. Results for children <5 years should be interpreted with caution.

Table 16.8 90th and 95th percentiles of mean daytime and night time ambulatory systolic and diastolic BP, stratified according to gender and height. Reproduced with permission from Wuhl E, Witte K, Soergel M, Mehls O, Schaefer F. with the German Working Group on Paediatric Hypertension. (2002). Distribution of 24-h ambulatory blood pressure in children: normalized reference values and the role of body dimension. *J Hypertension*, **20**:1995–2007.

Height, cm	Systolic BP, mm Hg				Diastolic BP, mm Hg			
	Day		Night		Day		Night	
	90th pct	95th pct	90th pct	95th pct	90th pct	95th pct	90th pct	95th pct
Boys								
120	120.6	123.5	103.7	106.4	79.1	81.2	61.9	64.1
125	121.0	124.0	104.9	107.8	79.8	81.3	62.2	64.3
130	121.6	124.6	106.3	109.5	79.3	81.4	62.4	64.5
135	122.2	125.2	107.7	111.3	79.3	81.3	62.7	64.8
140	123.0	126.0	109.3	113.1	79.2	81.2	62.9	65.0
145	124.0	127.0	110.7	114.7	79.1	81.1	63.1	65.2
150	125.4	128.5	111.9	115.9	79.1	81.0	63.3	65.4
155	127.2	130.2	113.1	117.0	79.2	81.1	63.4	65.6
160	122.2	132.3	114.3	118.0	79.3	81.3	63.6	65.7
165	131.3	134.5	115.5	119.1	79.7	81.7	63.7	65.8
170	133.5	136.7	116.8	120.2	80.1	82.2	63.8	65.9
175	135.6	138.8	119.1	121.2	80.6	82.8	63.8	65.9
180	137.7	140.9	119.2	122.1	81.1	83.4	63.8	65.8
185	139.8	143.0	120.3	123.0	81.7	84.1	63.8	65.8

(Continued)

Table 16.8 (*Contd.*)

Height, cm	Systolic BP, mm Hg				Diastolic BP, mm Hg			
	Day		Night		Day		Night	
	90th pct	95th pct	90th pct	95th pct	90th pct	95th pct	90th pct	95th pct
Girls								
120	118.5	121.1	105.7	109.0	79.7	81.8	64.0	66.4
125	119.5	122.1	106.4	109.8	79.7	81.8	63.8	66.2
130	120.4	123.1	107.2	110.6	79.7	81.8	63.3	66.0
135	121.4	124.1	107.9	111.3	79.7	81.8	63.4	65.8
140	122.3	125.1	108.4	111.9	79.8	81.8	63.2	65.7
145	123.4	126.3	109.1	112.5	79.8	81.9	63.0	65.6
150	124.6	127.5	109.9	113.1	79.9	81.9	63.0	65.5
155	125.7	128.5	110.6	113.8	79.9	81.9	62.9	65.5
160	126.6	129.3	111.1	114.0	79.9	81.9	92.8	65.4
165	127.2	129.8	111.2	114.0	79.9	81.9	62.7	65.2
170	127.5	130.0	111.2	114.0	79.9	81.8	62.5	65.0
175	127.6	129.9	111.2	114.0	79.8	81.7	62.3	64.7

Chapter 17

Acute kidney injury

Background, pathophysiology, and causes

Background

Acute renal failure (ARF) is a sudden, potentially reversible inability of the kidney to maintain normal body chemistry and fluid balance. It is usually accompanied by oliguria (urine output <0.5mL/kg/h or <1mL/kg/h in a neonate), but polyuric ARF can also occur.

The term ARF is now being replaced by acute kidney injury (AKI). However, pre-renal ARF without renal injury (e.g. hypovolaemia), does not fulfill the definition of AKI.

Pathophysiology

- Renal insult causes vasoconstriction, desquamation of tubular cells (forming casts), intraluminal tubular obstruction, and back leakage of glomerular filtrate.
- Neutrophils adhere to ischaemic endothelium and release substances that promote inflammation.

The primary event is usually tubular damage, which leads to an adaptive fall in glomerular filtration rate (GFR) due to renal vasoconstriction, to compensate for failure to reabsorb filtered solute. This vasoconstriction may then perpetuate renal damage. For this reason research has focused on vasoactive compounds, such as angiotensin, prostaglandins, adenosine, endothelin, and nitric oxide. The role of inflammatory mediators has also been explored. As yet, there have been no real advances in the prevention/treatment of AKI.

Paediatric RIFLE (pRIFLE) criteria

Used for the detection and classification of AKI and for correlation with clinical outcomes:

- R = risk for renal dysfunction (serum creatinine x1.5).
- I = injury to the kidney (serum creatinine x 2).
- F = failure of kidney function (serum creatinine x 3).
- L = loss of kidney function.
- E = end-stage renal disease.

Causes

Causes are pre-renal, renal (including acute on chronic kidney disease (CKD)) and post-renal. Pre-renal causes may lead to established renal AKI.

Pre-renal acute renal failure

- *Hypovolaemia:* gastrointestinal (GI) losses, burns, third space losses (sepsis and nephrotic syndrome) and excess renal losses (renal tubular disorders).
- *Peripheral vasodilatation:* sepsis.
- *Circulatory failure:* congestive cardiac failure (CCF), pericarditis, cardiac tamponade.
- Bilateral renal arterial or venous thrombosis.
- Drugs (diuretics, angiotensin-converting enzyme inhibitors (ACEI), non-steroidal anti-inflammatory drugs (NSAIDS)).
- Hepato-renal syndrome.

Renal acute kidney injury

- *Arterial:* embolic, arteritis, haemolytic uraemic syndrome (HUS).
- *Venous:* renal venous thrombosis.
- *Glomerular:* acute glomerulonephritis.
- *Tubular:* established acute tubular necrosis (ATN) due to prolonged pre-renal ARF, ischaemia, toxins or drugs; obstructive (crystals).
- *Interstitial:* tubulointerstitial nephritis, pyelonephritis.
- *Acute on chronic:* decompensation of CKD due to intercurrent illness.

Post-renal acute kidney injury

- Obstruction in a solitary kidney.
- Bilateral ureteric obstruction.
- Urethral obstruction.
- Neuropathic bladder.

Obstruction may be congenital (e.g. at the pelviureteric junction (PUJ), vesicoureteric junction (VUJ), ureterocoele or posterior urethral valve (PUV)), or acquired (e.g. calculi, external compression).

Acute kidney injury in neonates

- More common in neonates than in older children.
- Occurs in 4/1000 live births, 34.5/1000 in neonatal units.
- Occurs particularly following:
  - birth asphyxia;
  - low birth weight/prematurity;
  - patent ductus arteriosus (PDA);
  - mother received antibiotics, NSAIDs or ACEI;
  - cardiac surgery.

Assessment and investigations

Important points in the history

The major differential diagnosis of AKI is the patient presenting for the first time with CKD, which may be either acute on CKD or just advanced CKD. The two may be difficult to distinguish from the biochemistry alone, so the history and US findings are particularly helpful (Table 17.1). This is important because, as well as different investigations and fluid management, patients with CKD may need plans for long term, more permanent dialysis access, while those with post-renal AKI need urgent urological review.

Table 17.1 Points in the history and examination that assist in the differential diagnosis of ARF/AKI

Pre-renal	Renal	Acute or chronic	Post-renal
Diarrhoea and vomiting	Bloody diarrhoea (HUS)	Antenatally diagnosed anomaly	Antenatally diagnosed anomaly
Cardiac impairment	Drugs	Previous UTIs	Previous UTIs
Birth asphyxia	Birth asphyxia	Polydipsia and polyuria	Poor urinary stream
Umbilical catheters	Recent throat or skin infection	Poor urinary stream	Calculi
Acute weight loss	Prolonged convulsions	Family history	Palpable bladder or kidneys
Poor capillary refill	Systemically unwell	Long-standing malaise	Spinal abnormality
Low BP*	Associated symptoms/signs	Small/syndromic	
		Renal osteodystrophy	

*It is possible for the BP to be paradoxically high if there is extreme vasoconstriction.

Initial assessment, examination, and resuscitation

- Attend to life-threatening features first i.e. volume status (see Table 17.2), oxygenation (colour, respiratory rate, oxygen saturation), and electrolyte derangements.
- Oedema may not be helpful in deciding fluid replacement as it can be present with both intravascular overload and hypovolaemia due to third spacing.
- BP should not be viewed in isolation—hypertension with cool peripheries suggests intravascular depletion, while hypertension with warm peripheries suggests fluid overload.

Table 17.2 Assessment and management of intravascular volume status

Hydration status	Clinical features	Initial management*
Dehydrated	Tachycardia, cool hands, feet and nose (>2°C core-peripheral temperature gap), prolonged capillary refill time, low BP (late sign), dry mucous membranes, sunken eyes	Fluid resuscitation 10mL/kg normal saline over 30min, assess urine output and repeat if necessary
Euvolaemic		Fluid challenge 10–20mL/kg normal saline over 1h, with furosemide 2–4mg/kg IV, max 12mg/kg/day
Intravascular fluid overload	Tachycardia, gallop rhythm, raised JVP and BP, palpable liver	Furosemide 2–4mg/kg IV; max 12mg/kg/day. Dialysis if no response

Investigations

Initial investigations

An US of the urinary tract is essential at the earliest opportunity (Fig. 17.1):

- *To exclude obstruction:* the absence of hydronephrosis does not rule out significant high pressure obstruction, so any degree of dilatation should be considered significant, as dilatation will not occur if there is anuria and may be minimal with oliguria. Nephrostomy drainage may be necessary if there is no other clear diagnosis.
- To see if there are signs of CKD (small or cystic kidneys), although in some conditions, such as nephronophthisis, renal size may be preserved.
- In most cases of AKI the kidneys are enlarged and echobright.
- To look at vascular flow using Doppler studies if an abnormality of renal blood flow is suspected.
- Urine biochemistry is useful in distinguishing between pre-renal ARF and established ATN: urinary sodium (U_{Na}) <10mmol/L (<20 in neonates), fractional excretion of sodium (see 📖 Appendix, p.599) (FeNa) <1% (<2.5% in neonates) and urine osmolality >500mOsm/kg (>400 in neonates) suggests pre-renal ARF.
- Urine for blood, protein, and casts.
- Urine microscopy, culture, and sensitivity (M,C&S).
- Urea and electrolytes (U&Es), creatinine, plasma bicarbonate, Ca, PO_4, and Mg, alkaline phosphatase, albumin, liver function tests (LFTs), glucose.
- Full blood count (FBC) including blood film if low platelets.
- Coagulation screen.
- Blood culture and C-reactive protein (CRP).
- Chest X-ray (CXR) if respiratory or cardiac signs.

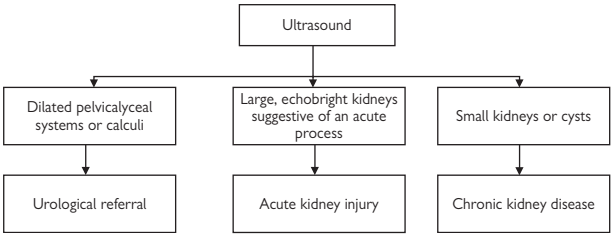

Fig. 17.1 US in the diagnosis of the cause of AKI.

Further additional investigations depend on clinical presentation

For suspected HUS

See 🕮 'Typical (D+) haemolytic uraemic syndrome: epidemiology and notes', p.397:

- Blood film to look for fragmented cells, lactate dehydrogenase (LDH).
- Group and save or cross-match.
- Stool culture.
- Verotoxin producing *Escherichia coli* (VTEC) serology.
- Non-diarrhoea associated (D negative) HUS may be due to T antigen exposure by: *Streptococcus pneumoniae*; systemic lupus erythematosus (SLE); abnormalities of complement regulation—factor H, autoantibodies to factor H, factors I and B, membrane cofactor protein and thrombomodulin; and Von Willebrand factor (vWF) protease deficiency.
- Haptoglobins.

For acute nephritis

See 🕮 Chapter 9, p.181:

- ESR.
- Throat or infected skin swab.
- Anti-Streptolysin O titre (ASOT), anti-DNAse B.
- Complement (C3, C4, C3 nephritic factor if C3 low).
- Immunoglobulins including IgA.
- Antinuclear antibodies (ANA), ds-DNA, anti-glomerular basement membrane (GBM), anti-neutrophil cytoplasmic antibody (ANCA), extractable nuclear antibodies (ENA), anti-cardiolipin antibodies.

Infections and acute kidney injury

See 🕮 Chapter 12, p.315:

- Meningococcal septicaemia.
- Hepatitis B, C, human immunodeficiency virus (HIV).
- Leptospirosis.
- Malaria.

For suspected rhabdomyolysis

e.g. prolonged convulsions; see 🕮 'Rhabdomyolysis', p.404:

- Creatine kinase.
- Urine myoglobin.

For tumour lysis

See 🕮 'Tumour lysis syndrome', p.406: Urate.

For renal hypouricaemia (a rare cause of AKI)

- History of loin pain and AKI post-exercise.
- Low plasma urate and high urine urate.

For acute on CKD

- PTH.
- Bone X-rays for renal osteodystrophy.

For obstruction

Will depend on US findings and surgical intervention plan.

Renal biopsy

Is indicated as soon as possible when:

- Renal function is deteriorating and the aetiology is not certain.
- Nephritic/nephrotic presentation.

As these features are suggestive of rapidly progressive crescentic glomerulonephritis, which needs urgent treatment to prevent long-term renal damage (see 🕮 Chapter 11, p.275).

Management

Ongoing management, the first 24h

Monitoring

- Weigh twice daily.
- Hourly input-output recording.
- Hourly observations including BP and monitoring of toe-core temperature gradient.
- 6-hourly BMs if disease may affect blood sugar control (e.g. HUS).
- Neurological observations-hourly.
- U&Es, creatinine and plasma bicarbonate, Ca, PO_4, FBC, frequency determined by clinical picture (may be appropriate to perform up to every 6h).

Fluids

- Further boluses of crystalloid or colloid and/or furosemide as indicated by hydration and urine output.
- A furosemide infusion may be of benefit (max 12mg/kg/24h).
- If nephrotic, consider bolus of albumin (see 📖 'Nephrotic syndromes: definitions', p.192).
- Give insensible losses (400mL/m^2/day or 30mL/kg/day) plus urine output, and other ongoing fluid losses. This can be given as feed if tolerated (see 📖 'Ongoing management', p.384) or IV normal saline (half normal if hypernatraemia).
- Replace 100% of urine output if euvolaemic.
- Restrict to 50–75% urine output if intravascularly overloaded to allow a negative fluid balance.
- There is no evidence to support the use of renal dose dopamine.

Ongoing management, the next 24–48h

After 24h an assessment can be made as to whether to proceed to dialysis or to continue to manage conservatively, although this decision needs to be reviewed on a daily basis.

Monitoring

- Frequency of measurements of weight, fluid balance, routine, and neurological observations as for the first 24h.
- U&Es, creatinine and plasma bicarbonate, Ca, PO_4, Mg, albumin, FBC (usually daily but frequency is determined by the clinical picture).
- Urinalysis daily.

Conservative management

- With careful attention to diet and fluid restriction of the euvolaemic child to an intake of insensible fluid losses and urine output, even patients with oliguria can be managed without dialysis. However it is difficult to maintain an adequate nutritional intake if the fluid allowance is very low, as catabolism (which also causes a high urea and hyperkalaemia) culminates in malnutrition.
- A suggested dietary approach is described in 📖 'Nutrition in acute kidney injury', p.390.

Indications for dialysis

- Hyperkalaemia >6.5mmol/L.
- Severe fluid overload with pulmonary oedema, which is resistant to furosemide.
- Urea >40mmol/L (>30mmol/L in a neonate).
- Severe hypo- or hypernatraemia or acidosis.
- Multi-system failure.
- Anticipation of prolonged oliguria, e.g. HUS, so that space can be made for dietary intake.

Fluids for the patient on dialysis

- A fixed fluid intake can be prescribed when dialysis is established. A suggested starting volume would be half the normal maintenance fluid allowance (see Table 17.3), which can be increased depending on efficiency of dialysis or the development of urine output.

Table 17.3 Maintenance water and electrolyte allowance for healthy children

	Weight (kg)	Daily requirement
Water	<10	100mL/kg
	11–20	1000mL plus 50mL/kg for each extra kg >10
	>20	1500mL plus 20mL/kg for each extra kg >20
Na, K, and Cl	<10	2.5mmol/kg
	11–30	2.0mmol/kg
	>30	1.5mmol/kg

Established acute kidney injury

- Monitoring of routine observations can be decreased to 4-hourly, and weight and U&Es, creatinine and plasma bicarbonate, Ca, PO_4, FBC to daily.
- A fixed fluid intake can be introduced for conservatively managed patients as urine output increases, using a regimen similar to patients on dialysis (see 📖 'Fluids for the patient on dialysis', p.385, and Table 17.3).

The recovery phase

- Polyuria may develop in the recovery phase, so during this time it may be necessary to return for twice daily weighing, hourly input-output recording, and hourly observations, including BP and monitoring of the toe-core temperature gradient.
- Urine output and insensible losses should be replaced for 24h with normal saline, then a fixed fluid intake can be set. This can start at around two-thirds of the previous day's intake, if renal function continues to improve.
- Dialysis can be stopped when the urine output is sufficient to allow an adequate nutritional intake and the creatinine starts to decline.

Management of electrolyte abnormalities in acute kidney injury before dialysis

Hyperkalaemia

- K >6.5mmol/L is an indication for emergency treatment until dialysis or urine output has been established (Table 17.4).
- Monitor for signs of toxicity on ECG (peaked T waves, prolongation of PR interval, flattening of P waves, QRS widening) (see 📖 Chapter 6, p.99).
- Toxicity of K is increased if there is hypocalcaemia.
- Only ion exchange resins remove potassium from the body, so it is important to check the serum K for rebound after 2–4h.
- Of all the ways to reduce K, the simplest is to use a salbutamol nebulizer, which is familiar to all paediatric nurses, quick to prepare and administer, and rapidly effective.

Table 17.4 Emergency management of hyperkalaemia

Effect on K	Treatment	Dose	Side effects
Reduces toxic effect of K by stabilizing the myocardium	10% calcium gluconate IV	0.5–1mL/kg over 5–10min	Bradycardia, hypercalcaemia
Shifts K into cells	Salbutamol nebulizer	2.5mg if<25kg, 5.0mg if>25kg, maximum 2-hourly	Tachycardia, hypertension
	Salbutamol IV	4micrograms/kg over 10min	
	Sodium bicarbonate 8.4% IV	1–2mmol (mL)/kg over 10–30 min	Hypernatraemia reduces ionized calcium
	Glucose and insulin IV	0.5–1.0g/kg/h glucose (2.5–5.0mL/kg/h10% glucose) and insulin 0.1–0.2U/kg as a bolus or continuous infusion of 10% glucose at 5mL/kg/h(0.5g/kg/h) with insulin 0.1U/kg/h.	Hypoglycaemia, monitor blood glucose every 15min during bolus then at least hourly
Removal of K from the body	Calcium Resonium® orally or per rectum with oral lactulose	1g/kg every4h 2.5mL<1 year; 5mL 1–5 years, 10mL >5 years	Effect is slow. Large doses can become impacted in the gut if given orally
	Resonium A® as above		

Hyponatraemia

- Mild hyponatraemia is often dilutional secondary to prior prescription of hypotonic fluids.
- A plasma Na >118mmol/L will usually correct with fluid restriction ± dialysis and fluid replacement with normal saline.
- A plasma Na <118mmol/L risks central nervous system (CNS) damage so the Na should be raised to around 125mmol/L with hypertonic saline (3 %) according to formula:

  Na dose (mmol) = (125 – measured P_{Na} × weight in kg × 0.6) and given over 2–4h

  (see 🕮 'Disorders of sodium and water: hyponatraemia', p.104).
- Severe hyponatraemia with oliguria is an indication for dialysis.

Hypernatraemia

- Much less common than hyponatraemia.
- May be caused by sodium retention or water depletion so careful assessment of fluid status is mandatory.
- Give furosemide 3–4 mg/kg IV (max 12mg/kg/day) if salt and water retention is the cause.
- Replace insensible losses as 0.45 % saline.
- Severe hypernatraemia with oliguria is an indication for dialysis.

Hyperphosphataemia

- Start treatment if plasma PO_4 >1.7mmol/L (>2.0mmol/L in a neonate).
- Treatment is by dietary phosphorus restriction and phosphate binders, which are given with oral intake.
- Calcium carbonate 250mg tablets can be dissolved in feeds, starting dose:
  - up to 2 years: 250mg qds;
  - 2–5 years: 500mg tds;
  - 5–10 years: 750mg tds;
  - over 10s: 1000mg tds.

These doses may need to be increased considerably, depending on plasma PO_4 levels.

Hypocalcaemia

- Hypocalcaemia, particularly in association with hyperkalaemia can lead to cardiac arrest; therefore, cardiac monitoring is necessary if hypocalcaemia is severe.
- Corrected calcium can be estimated from total calcium and albumin as follows:
  - corrected calcium = total plasma calcium + (36 – plasma albumin)/40
- If the corrected calcium is <1.9mmol/L or if bicarbonate therapy is required, treat with IV 10% calcium gluconate 0.1mg/kg (0.5mL/kg) over 30min to 1h.
- Hypocalcaemia will improve if hyperphosphataemia is treated.
- If acute on CKD, commence activated vitamin D (alfacalcidol or calcitriol) at a dose of 0.01micrograms/kg/day.

Acidosis

- May be severe if the respiratory system is unable to compensate. Maximum respiratory compensation may take over 24h. Correct with sodium bicarbonate if HCO_3^- <18mmol/L. If the child is unwell use IV bicarbonate.
- Calculate IV dose as: mmol $NaHCO_3$ = (18 - measured HCO_3) × 0.5 × weight in kg.
- Give over 1h.
- Oral dose is 1–2mmol/kg/day for infants and 70mmol/m^2/day for older children, to be divided into 2–4 doses.
- The ionized calcium must be checked and corrected before treatment since correction of acidosis further lowers ionized calcium.

Hypertension

- Usually due to fluid overload, although it is important to be sure that it is not due to intense vasoconstriction because of hypovolaemia.
- First treatment is furosemide, and failure to respond is an indication for dialysis, although it is usual to consider other first line agents (e.g. calcium channel blockers, labetalol if severe hypertension with signs of encephalopathy) in addition, particularly since it usually takes several hours to establish emergency dialysis.
- If dialysis is adequate but hypertension persists, nifedipine is the first choice; the starting dose is 250micrograms/kg tds. Maximal daily dose is 3mg/kg/day.

Nutrition in acute kidney injury

- Adequate nutrition will help (see Table 17.5):
  - prevent catabolism;
  - control metabolic abnormalities (particularly potassium and phosphate);
  - recovery;
  - it may delay or prevent the need for dialysis.
- The fluid restriction will limit the nutritional prescription. Dialysis allows a higher fluid intake and, therefore, better nutritional intake.
- Consider nasogastric feeding if the child is unable to meet the nutritional goals orally, e.g. due to nausea or neurological impairment.
- Parenteral nutrition should only be considered if enteral nutrition is not tolerated.
- If on prolonged peritoneal dialysis a higher protein intake may be required.

Table 17.5 Nutritional guidelines for the child with AKI

Boys and girls	Energy (EAR)	Protein (RNI)
0–6 months	95–115kcal/kg	1.5–2.1g/kg
6–12 months	95kcal/kg	1.5–1.6g/kg
1–3 years	95kcal/kg	1.1g/kg
4–6 years	90kcal/day	1.1g/kg
7–10 years	1740♀–1970♂ kcal/day	28g/day
11–14 years	1845♀–2220♂ kcal/day	42g/day
15–18 years	2110♀–2755♂ kcal/day	55g/day♂ 45g/day♀

EAR = Estimated average requirement.

RNI = Reference Nutrient Intake i.e. amount of protein needed for maintenance and growth.

Day 1

- High energy protein-free fluids using a glucose polymer, e.g. Maxijul® solution.
- Concentration depends on degree of nausea, vomiting, diarrhoea:
  - *infants:* 15% Maxijul®;
  - *1–2 years:* 20% Maxijul®;
  - *>2 years:* 25% Maxijul®.
- Full energy requirements will not be met if fluid restricted.
- Potassium and phosphate intakes may need adjusting.

Day 2

- Consider introduction of protein depending on degree of uraemia.
- If urea 30–40mmol/L start 0.5g protein/kg dry weight/day:
  - *infants*—diluted whey based infant formula e.g. Cow & Gate® 1 or SMA® 1 + Maxijul®;
  - *children*—diluted paediatric enteral feed, e.g. Nutrini® (paediatric sip feed, e.g. Paediasure® if feeding orally) + Maxijul®.
- If urea >40mmol/L continue protein-free high energy fluids for a further 24h.

Day 3

Increase/introduce protein depending on degree of uraemia:

- If urea 20–30mmol/L increase protein to 1g/kg dry weight/day.
- If urea 30–40mmol/L start 0.5g protein/kg dry weight/day (see 📖 'Day 2', p.391).
- Maximize energy intake using Maxijul® and fat emulsion, e.g. Calogen® as tolerated.

Day 4 onwards

- Normalize eating and drinking patterns as renal function improves.
- If urea 20–30mmol/L increase protein to 1g/kg dry weight/day.
- Once urea <20mmol/L ensure intake provides at least the RNI protein for height age in infants/chronological age in children.

Drug therapy

See 📖 Chapter 22, p.573:

- Correct drug doses according to GFR. The calculation for estimated GFR (see 📖 Appendix, p.599) needs to be interpreted with caution as the formula assumes a stable situation.
- Change of GFR will necessitate regular revision of drug dosages.
- Many drugs require decreased doses or a prolonged dosage interval in renal failure.
- It is preferable to avoid known nephrotoxic drugs in AKI when an alternative is available.

Dialysis

See 🕮 'Principles of peritoneal dialysis', p.466, 🕮 'Continuous renal replacement therapy', p.506, and 🕮 'Haemodialysis', pp.484–505.

Choice of dialysis

Options Peritoneal dialysis, haemodialysis or haemofiltration (Table 17.6).

- Most children requiring intensive care are managed with CRRT; see 🕮 'Continuous renal replacement therapy' (CRRT), p.506.
- Haemodialysis is the preferred option if vascular access is needed for plasma exchange. If the urea is very high, a short session (2h) with mannitol will be necessary as intracerebral disequilibrium is most likely with the first session. Thereafter, daily haemodialysis (HD) will be needed until the biochemistry improves, when it then can be weaned.
- Peritoneal dialysis can be started immediately in the child with AKI.
  - flush the catheter until the effluent is clear of blood and debris;
  - use continuous, 24h cycling, initially with 20–30-min cycles (10 min fill, 10 min dwell, 10 min drain) then varying according to response;
  - start with 10mL/kg fill volumes. This can be built up promptly if there is no leakage and the child tolerates it, to 40mL/kg;
  - it is usual to start with 1.36% dialysate, but this can be increased if fluid removal is inadequate.

Table 17.6 Advantages and disadvantages of the different types of renal replacement therapy

Dialysis modality	Benefits	Disadvantages
PD	Easy to set up Can be carried out by ward nurses Ease of access May be continued indefinitely with Tenckhoff catheter	Risk of peritonitis/leakage/drainage problems Rapid removal of a large volume of fluid is difficult so not recommended if pulmonary oedema present
HD	Gold standard solute clearance Bicarbonate is standard Can be used to rapidly remove large volumes of fluid, e.g. with pulmonary oedema	Requires haemodynamically stable patient Vascular access may be difficult
CVVH	Good ultrafiltration Solute clearance may be improved with addition of dialysis (CVVHD) Does not cause major fluid shifts and disturbances to BP and cardiac output	Requires continuous anticoagulation Vascular access may be difficult

Follow-up of acute kidney injury

Survival and renal recovery depends on the cause of the AKI. Long-term follow-up is necessary, with the exception of children with pre-renal ARF, in order to detect the development of proteinuria, hypertension and CKD.

- BP and urine albumin to creatinine ratio (Ua:Ucr, on the first urine of the morning taken on rising) should be monitored 12 months after AKI.
- Annual BP and Ua:Ucr for life.
- Check creatinine if previous measurement elevated or if proteinuria or raised BP develop.
- For treatment of proteinuria see 📖 Chapter 18, p.409 and for hypertension see 📖 Chapter 16, p.353.

Further reading

Phillips Andreoli, S. (2009). Acute kidney injury in children. *Pediatr Nephrol* **24:** 253–63.

Royle J. (2007). The kidney. In: Shaw V and Lawson M (eds) *Clinical Paediatric Dietetics*, 3rd edn. Oxford: Blackwell Sciences Ltd, pp. 203–11.

Haemolytic uraemic syndrome: definitions

Definitions

- HUS is a triad of symptoms:
  - haemolytic anaemia with fragmented erythrocytes;
  - thrombocytopenia;
  - AKI.
- There are 3 broad categories of HUS (Box 17.1):
  - typical, usually diarrhoea positive (D+) HUS;
  - atypical, usually diarrhoea negative (D–) HUS;
  - secondary HUS, secondary to drugs, malignancy, total body irradiation, transplantation, methylmalonic acidaemia (MMA) in neonates.
- *VTEC:* verotoxin producing *Escherichia coli.*
- *STEC:* shiga toxin producing *Escherichia coli.*
- *MAHA:* microangiopathic haemolytic anaemia.
- *TMA:* thrombotic microangiopathy. A microvascular occlusive disorder of capillaries, arterioles, and less frequently, arteries.
- *TTP:* thrombotic thrombocytopenic purpura. Microvascular aggregation of platelets causes ischaemic lesions mainly in the brain, and less frequently in the kidney and other organs.

The common event in HUS is endothelial injury resulting in MAHA, platelet aggregation, and local intravascular coagulation, particularly in the renal, mesenteric, and brain vasculature.

Notes on terminology

- The D+ HUS/D– HUS terminology, although simple, can mislead:
  - the terms shiga toxin and verotoxin are equivalent;
  - some patients with VTEC infection do not have diarrhoea;
  - a diarrhoeal disease may trigger HUS in a patient with a genetic predisposition to HUS;
  - thus, classifying patients only according the presence or absence of diarrhoea can lead to incorrect management.

Box 17.1 Classification of HUS[1]

Infections
- Enterohaemorrhagic *Escherichia coli* producing verotoxin (also called shiga toxin).
- *Shigella dysenteriae* type 1 producing shiga toxin.
- *Streptococcus pneumoniae* producing neuraminidase (Thomsen Friedenreich antigen ('T antigen')).
- HIV.

Inherited forms of HUS
- Complement abnormalities: see 🕮 'Haemolytic uraemic syndrome: atypical', p.400.
- Von Willebrand factor-cleaving protease constitutional deficiency.
- Defects of vitamin B12 intracellular metabolism.

Drug-associated HUS
- Ciclosporin, tacrolimus.
- Mitomycin, cytotoxic drugs, gemcitabine.
- Ticlopidine, clopidogrel.
- Oral contraceptives.
- Crack cocaine.
- Quinine.

Secondary HUS
- Bone marrow transplant-associated HUS.
- Post-renal transplantation.
- SLE and anti-phospholipid syndrome.
- Collagen type III glomerulopathy.
- Cancer-associated HUS.
- Systemic sclerosis.
- Pregnancy-associated HUS.

[1]Scheiring J, Andreoli, Zimmerhackl LB. (2008). Treatment and outcome of Shiga-toxin-associated hemolytic uremic syndrome (HUS). *Pediatr Nephrol* **23:** 1749–60.

Typical (D+) haemolytic uraemic syndrome: epidemiology and notes

- Typical (D+) HUS represents 90% of HUS in children.
- It occurs mainly in children <3 years, almost never in neonates.
- The average annual incidence of HUS for the United Kingdom and Ireland is 0.71/100,000. In Western Europe or North America, its annual incidence rate is 2–3 per 100,000 children <5 years of age.
- The incidence of exposure to VTEC has been demonstrated in many countries in about 85% of cases.
- Serotype *Escherichia coli* 0157:H7 is the most frequent (70 % of cases in the UK), but other serotypes (0111, 0103) are also associated.
- The risk of developing HUS in patients with intestinal *Escherichia coli* 0157:H7 infection is 10%.
- Cows are the main vectors of *Escherichia coli* 0157:H7, which can be present in their intestinal lumen and faeces.
- Humans are infected from contaminated undercooked ground beef, non-pasteurized raw milk, or milk products (cheese), contaminated water (well water or lake water swallowed during bathing), fruits, fruit juice, or vegetables.
- Person-to-person transmission is possible.
- Transit slowing agents and antibiotics (such as beta lactams or co-trimoxazole) increase the risk of HUS.
- D+ HUS may occur simultaneously or a few days or weeks apart in several members of a family, mainly siblings, because of contamination from the same environment.
- Epidemics are well described.
- HUS caused by *Shigella dysenteriae* is important on a worldwide basis, but is an uncommon cause of HUS in the UK.

Clinical features of typical infective haemolytic uraemic syndrome

- Diarrhoea (bloody) and vomiting (most, not all).
- Rectal prolapse, intussusception, toxic dilatation of colon, and bowel perforation.
- Hydration at the time of the diagnosis of HUS is variable—may be dehydrated or over hydrated (if anuric, but able to drink, or perhaps most commonly from inappropriate IV fluids).
- Hypovolaemic shock in 2%.
- Oligoanuria appears between 1 and 14 days after the onset of diarrhoea.
- MAHA and thrombocytopenia precede the AKI.
- Jaundice in 35%.
- Hypertension in one-third.
- The most common extra renal manifestation is central nervous system disturbance affecting up to 20%. Beware early signs such as lip-smacking:
  - seizures;
  - cranial nerve palsy;
  - cerebral oedema;

  - encephalopathy;
  - coma;
  - decerebrate posturing;
  - hindbrain herniation—causing respiratory arrest.
- Cardiomyopathy.
- Diabetes mellitus (due to necrotizing pancreatitis) affects up to 5%.
- Renal cortical necrosis:
  - due to acute cortical ischaemia;
  - mainly observed in the most severe forms of D+ HUS;
  - associated with prolonged anuria at the acute phase;
  - high risk of CKD.

Investigations

- FBC, platelets, blood film.
- Chemistry including renal and liver function, LDH, glucose, urate, lipase and amylase.
- Clotting screen.
- Group and save blood.
- Urine dipstick for blood and protein.
- Urine M,C&S.
- Ua:Ucr.
- VTEC serology.
- Verotoxin polymerase chain reaction (VT PCR).
- Stool microscopy and culture.

Selective investigations

- Direct Coomb's test (positive in T-antigen HUS–see 🕮 'Haemolytic uraemic syndrome: atypical', p.400).
- Erect CXR, abdominal X-ray (AXR).
- Renal and abdominal (to include biliary tree and pancreas) US: to exclude preceding structural renal abnormalities and other organ involvement.
- CT abdomen (if pancreatitis or suspect collection).
- ECG: if severe electrolyte disturbance or cardiac failure.
- Electroencephalogram (EEG): if seizures or altered conscious level.
- MRI brain (or CT): if seizures or altered conscious level.
- Renal biopsy very rarely required.

Treatment

General points

Early diagnosis and supportive care are of major importance. There is no specific therapy for D+ HUS.

Blood transfusion

- Packed red cell transfusion is indication for Hb <6g/dL, or if <7g/dL, but symptomatic (e.g. short of breath, shock). May worsen hyperkalaemia and volume overload.
- Platelet transfusion is rarely indicated unless invasive surgery is planned or there is intracranial haemorrhage. If given, platelets are rapidly consumed in the haemolytic process.

Antibiotics

It is generally accepted that antibiotics are not part of the routine management of typical D+ HUS caused by VTEC. Some suggest that antibiotics may make HUS worse, although this remains controversial.

Plasma exchange

Some advocate the use of plasma exchange if central nervous system signs develop in typical HUS. There are no controlled data to support this, and this recommendation remains anecdotal.

Prevention of haemolytic uraemic syndrome

- Ground beef must be cooked until the inside is no longer pink.
- Non-pasteurized products must not be given to young children.
- Children who touch cows or goats must wash their hands afterwards.
- Strict rules governing cattle slaughter to prevent contamination of meat by intestinal content.
- When *Escherichia coli* 0157:H7 infection is suspected, information and surveillance of siblings and family is necessary. Handwashing is the most effective means of preventing person-to-person spread.
- Confirmed VTEC HUS is a notifiable disease.

Prognosis

- Acute mortality rate is currently 5–10%.
- 5–10% develop CKD 5.
- After 15 years or more of follow-up, 20–60% of patients have proteinuria and/or hypertension, with up to 20% having CKD. These problems may appear after several years of apparent recovery.

Poor renal prognostic factors

- Neutrophilia >20 × 10^9/L.
- Shock during the acute phase.
- Anuria >2 weeks.
- Central nervous system involvement.
- Severe colitis and/or rectal prolapse.
- Atypical HUS.
- Cortical necrosis.
- 50% glomeruli with TMA lesions (best predictor, but biopsy is very rarely performed).

Outcome following renal transplantation for typical haemolytic uraemic syndrome

- In most retrospective series, no recurrence of HUS was observed.
- Occasional case reports of HUS recurrence in the graft are described, putting the risk at around 1%.
- Calcineurin inhibitors are not contraindicated in this setting.

Further reading

Scheiring J, Andreoli, Zimmerhackl LB. (2008). Treatment and outcome of Shiga-toxin-associated hemolytic uremic syndrome (HUS). *Pediatr Nephrol* **23:** 1749–60.

Haemolytic uraemic syndrome: atypical

Atypical HUS is due to several different aetiologies. The commonest is pneumococcal HUS, the incidence of which is increasing so that in some countries it is overtaking D+ HUS as the commonest cause.

Pneumococcal haemolytic uraemic syndrome

- *Streptococcus pneumoniae* produces neuraminidase, which cleaves N-acetylneuraminic acid from the glycoproteins on the cell membranes of red cells, platelets and glomeruli. Current thinking is that this exposes the Thomsen-Friedenreich antigen (T antigen). The exposed antigen then reacts with anti-T antibody resulting in thrombotic microangiopathy (TMA).
- The antigen-antibody reaction is called T activation and occurs more commonly in infants and young children.
- Diagnosis is by testing for red cell T-activation; and the direct Coomb's test will be positive.
- Although all *Streptococcus pneumoniae* produce neuraminidase, not all cause T cell activation. Variation is likely to be due to different strains producing different quantities of neuraminidase with different enzymatic activity, and to individual patient variation in their amount of anti-T antibody.
- Anti-T antibody may be present in transfusions and plasma so red cells and platelets should be washed before transfusion (to remove anti-T antibody) and the use of plasma avoided as far as possible. Early diagnosis may prevent ongoing activation by the use of non-washed cells.
- HUS is typically associated with severe pneumococcal infections, such as empyema or meningitis.
- Activation clears when the infection is controlled so antibiotic therapy is needed.
- Initial reports suggested increased mortality and worse renal outcome than for D+ HUS. However, much of the morbidity is due to the Pneumococcal infection (e.g. meningitis) and, more recently, it appears that renal outcome is no worse.

Other causes of atypical haemolytic uraemic syndrome

- Represent less than 10% of HUS in children.
- Any age can be affected, including newborns.
- There is usually no prodromal diarrhoea, nor seasonal predominance, although infections (including viral or bacterial gastroenteritis) may trigger an episode of atypical HUS in a susceptible individual.
- Onset may be sudden, and is relapsing and remitting over weeks or months.
- Arterial hypertension is frequent.
- Deterioration in renal function of varying severity leads to CKD in most cases (and CKD 5 in some cases), after weeks, months, or years.
- Some children have relapses of HUS, often triggered by infectious diseases, which can occur even when there is CKD 5, i.e. extrarenal disease can continue, e.g. haemolytic episodes, pancreatitis, etc.

- Some have a presentation like TTP, with predominance of central nervous system symptoms, which is the main clinical feature that differentiates TTP from HUS (although HUS can have central nervous system involvement, so this differentiation is not clear-cut).
- Atypical HUS is often familial, with autosomal recessive or autosomal dominant inheritance (see 📖 'Genetics of haemolytic uraemic syndrome', p.401).
- Histological lesions are arteriolar TMA, with intimal cell proliferation, thickening of the vessel wall and narrowed lumens of arterioles.
- Renal biopsy can be useful when diagnosis is uncertain.

Genetics of haemolytic uraemic syndrome

Central to the pathogenesis of atypical HUS is over-activation of the alternative pathway of complement (AP), and mutations have been detected in the following complement regulatory proteins:

- Complement factor H (CFH, the most important regulator of the AP), the commonest abnormality. Mutations may not result in a decrease in CFH levels.
- Complement factor I (CFI, up to 12% of cases). Again measured levels may be normal.
- Membrane cofactor protein (MCP, CD46), which protects cells from damage from complement and is present on podocytes.
- Thrombomodulin (THBD), an anticoagulant glycoprotein that plays a role in the inactivation of C3a and C5a.
- Autoantibodies to factor H (up to 10%).
- Deletions of CFHR1-5, CFH-related proteins, which are related to autoantibodies to CFH.
- Gain of function mutations of C3 and complement factor B (CFB).
- There is incomplete penetrance such that first degree relatives carrying the same mutation are often asymptomatic. Presumably, for HUS to develop there must be a combination of genetic and environmental factors.
- HUS can also be associated with deficiency of ADAMTS13 (Von Willebrand factor cleaving protease). This is the enzyme deficient in adults with TTP. Deficiency in TTP is usually due to the presence of an inhibitor, although occasionally can be due to constitutional/familial deficiency of ADAMTS13. There are a few reports of ADAMTS deficiency in paediatric patients with atypical HUS.

Specific tests to be considered for the investigation of atypical haemolytic uraemic syndrome

- Culture for verotoxin-producing *Escherichia coli* (VTEC).
- Serology for VTEC both acute and convalescent.
- Polymerase chain reaction (PCR) for VTEC.
- Liver function tests.
- Direct Coomb's test (positive in 'T antigen' associated cases).
- Thomsen-Friedenreich antigen ('T antigen') (if available).
- C3, C4, CH100, C3 nephritic factor, CFH, CFI plasma levels.
- vWF multimeric analysis.
- ADAMTS-13 enzyme activity.

- Urine for methylmalonic acidaemia and homocysteine.
- ANA, ds-DNA antibodies, ENA, anticardiolipin antibodies, lupus anticoagulant.
- HIV test.
- Renal biopsy if diagnosis unsure.
- Genetics (if pneumococcal HUS excluded): CFH, CFI, CD46, C3, CFB, and THBD for mutations and genomic disorders. Serum for CFH autoantibodies (preferably before any plasma has been given to be sure the antibodies are primary and not secondary).

Treatment

- Treatment of atypical HUS must depend on the suspected underlying cause. For example, HUS-associated with T antigen exposure in pneumococcal-associated HUS requires antibiotic therapy to treat the underlying infection. HUS associated with drugs requires removal of the offending agent.
- For idiopathic (presumed genetic) atypical HUS, therapy with plasmapheresis and/or fresh frozen plasma has been shown to be effective in some series, particularly if there is neurological involvement. Treatment is usually started daily and after 5–10 days the response assessed. Some children do not respond, whereas others become dependent on plasma therapy and need regular ongoing treatments to prevent relapse.
- Renal function may deteriorate despite plasma therapy. Preliminary trials of eculizumab, a humanized monoclonal antibody against C5, have shown it to have a high success rate, at least in the short term, even in patients who are resistant to plasma therapy, and it is likely that this will become part of the therapeutic armamentarium in the near future.

Prognosis

Overall the prognosis is poor, with 25% mortality during the initial episode. 50% of survivors need long-term dialysis. Outcome is affected by the genetic abnormalities, but even with known mutations outcome can be variable and affected by the presence of additional undefined genetic modifiers.

Overall patient outcome

- *CFH mutations is the worst:* 60–70% die or reach CKD 5 within 1 year.
- *MCP mutations is good:* with >80% remaining dialysis-independent although recurrent episodes are common.
- *CFI mutations is intermediate:* 50% die or develop CKD 5 within 2 years.
- *CFH antibodies:* <50% develop CKD 5.

Post-transplant

(See 📖 'Recurrent and *de novo* renal disease following renal transplantation', p.541.)

- MCP is corrected by an allograft bearing wild-type MCP so the recurrence rate is low.
- Overall there is a 50% chance of transplant loss due to recurrent disease.
- CFH or CFI mutations are associated with graft loss of 80% by 2 years.

Further reading

Kavanagh D, Goodship T. (2010). Genetics and complement in atypical HUS. *Pediatr Nephrol* **25:** 2431–42.

Waters AM, Licht C. (2011) aHUS caused by complement dysregulation: new therapies on the horizon. *Pediatr Nephrol* **26:** 41–57.

Rhabdomyolysis

Background

Rhabdomyolysis is the breakdown of striated muscle resulting in the release of myoglobin, which is nephrotoxic. It accounts for up to 20% of AKI. Early recognition is important as aggressive hydration may prevent AKI.

Presentation

- Approximately half present with the triad of diffuse myalgia, weakness, and dark urine.
- Calf pain or muscle swelling.
- There may be a history of trauma, loss of consciousness, and prolonged immobilization or grand mal seizures.

Causes

- There are acquired (more common) and hereditary causes.

Acquired causes

- *Excess muscle activity in normal muscles:* mechanical and thermal muscle injury and ATP depletion can occur with heat stroke, status epilepticus, status asthmaticus, myoclonus, and severe dystonia.
- *Crush injury and other trauma:* due to direct muscle injury and ischaemia reperfusion injury after prolonged ischaemia. Large numbers of cases have been reported following earthquakes.
- *Drugs and toxins:* many drugs have been reported to cause rhabdomyolysis, either via a direct toxic effect, or by inducing myositis or coma, or by excessive neuromuscular stimulation. Some toxins include snake venom and insect bites.

Hereditary causes

Disorders of muscle carbohydrate metabolism

- *McArdle's disease:* an AR disorder resulting in deficiency of myophosphorylase, and, as a result, defective generation of glucose from glycogen. Anaerobic type 2 muscle fibres are activated during vigorous exercise and are therefore particularly dependent on ATP. The rhabdomyolysis that results from ATP depletion causes muscle pain which is relieved by rest. Other inherited diseases affecting the glycolytic/ glycogenolytic pathways include phosphofructokinase deficiency (Tarui's disease), and phosphoglycerate mutase deficiency.
- *Carnitine palmitoyltransferase deficiency:* an AR disorder resulting in abnormal production of energy from long chain fatty acids. Aerobic type 1 muscle fibres are affected, so that muscle pain and rhabdomyolysis occur with prolonged exercise and inadequate energy intake. Frequent high carbohydrate meals may help.
- *Malignant hyperthermia:* an AD disorder of the calcium release channel of the sarcoplasmic reticulum resulting in high resting sarcoplasmic calcium concentrations. Exposure to halothane, succinyl choline and caffeine triggers further calcium release, resulting in muscle contraction, hyperthermia and rhabdomyolysis.

- *Neuroleptic malignant syndrome (NMS):* a central defect causing a gradual development of hyperthermia, muscle rigidity, fluctuating consciousness, autonomic instability and rhabdomyolysis. Drugs which can cause NMS include phenothiazines, butyrophenones, and other antipsychotics.

General points

- Plasma myoglobin levels rapidly rise during injury, then fall within 6h, although plasma levels are not routinely measured.
- Plasma creatine phosphokinase (CPK) levels rise 2–12h after injury, and peak 24–72h later.

Investigations

- *Myoglobinuria:*
  - *urinalysis*—stick test strongly positive for blood but no or few red cells on urine microscopy;
  - urine myoglobin positive.
- Elevated plasma CPK (MM band).
- Other plasma electrolyte disturbances:
  - hyperkalaemia;
  - hyperphosphataemia;
  - hypocalcaemia;
  - hyperuricaemia.

Management

Manage the patient on the basis of urine output and plasma electrolytes and not the plasma CPK.

- If urine output is reasonable (>0.5mL/kg/h): high fluid input = 3L/m^2/day (0.45% saline/2.5% glucose, may need adjustment: follow electrolytes regularly).
- If oligoanuric:
  - consider first a fluid challenge (5–10mL/kg);
  - possibly with furosemide to establish urine output.
- if unsuccessful =>
  - dialyse for severe electrolyte disturbance;
  - continuous veno-venous haemofiltration (CVVH) clears myoglobin reasonably well.
- Determine underlying condition. Muscle biopsy may be necessary for congenital enzyme defects.
- Outcome depends on cause, but full recovery is usual.

Further reading

Elsayed EF, Reilly RF. (2010). Rhabdomyolysis: a review, with emphasis on the pediatric population. *Pediatr Nephrol* **25:** 7–18.

Tumour lysis syndrome

Background

Tumour lysis syndrome (TLS) occurs in haematological malignancies and lymphoproliferative conditions. Rapid cell breakdown leads to hyperuricaemia (pre-TLS). The development of urate nephropathy, with AKI, hyperphosphataemia, hyperkalaemia, and hypocalcaemia indicates established TLS. Prevention is the aim of management, using high fluid intake and allopurinol or rasburicase. TLS can occur prior to chemotherapy because of autolysis of tumour cells but usually starts after induction of treatment. Duration depends on severity and supportive measures in place, but on average lasts for approximately 48h.

Factors that predispose to tumour lysis syndrome

- High cell count leukaemia (total white cell count usually in excess of 100×10^9/L).
- Burkitt's type lymphoma.
- Large tumour bulk.
- Bulky T cell lymphoma.
- Bulky lymphoproliferative disease (LPD) or post-transplant lymphoproliferative disease (PTLD).
- Evidence of renal infiltration with tumour (e.g. on US).
- Evidence of renal impairment.

Management

- Insertion of a haemodialysis catheter at the time of anaesthetic for Hickman line or bone marrow.
- Patients already in established TLS at time of admission need urgent haemodialysis.
- Disturbances of calcium and magnesium homeostasis can also occur (as a result of the hyperphosphataemia, renal impairment, changes in acid-base balance or due to the diuresis), and can lead to tetany or seizures.
- It is important that K is not added to hydration fluids.

Prevention

- Hydrate with 3L/m^2/day of 0.45% NaCl/2.5% glucose. This can be increased to 4L/m^2/day if there is no evidence of fluid overload (tachycardia, tachypnoea, gallop rhythm, desaturation, or oxygen requirement; see Fig. 17.2).
- Give allopurinol 100mg/m^2, 8-hourly by mouth if no high risk features; or rasburicase 200micrograms/kg once per day if high risk or if poor response to allopurinol, starting 12h prior to chemotherapy if possible.
- For high risk patients with rapid tumour lysis and high plasma concentration of uric acid despite receiving IV rasburicase 200micrograms/kg every 24h, consider increasing the frequency of rasburicase (e.g. once every 18-hourly) up to maximum of once every 12h for 2–3 days.

- Review the patient clinically as appropriate (but at least every 4–6h). Check for oliguria or fluid overload. Calculate the fluid balance and measure plasma biochemistry (Na, K, Ca, PO_4, TCO_2, urate, urea, and creatinine) every 4–6h. (If very high risk, monitor biochemistry 2–3-hourly). Give furosemide 1–2mg/kg if there are signs of fluid overload. Use a cardiac monitor to look for evidence of peaked T waves and dysrhythmias secondary to hyperkalaemia.
- Alkalinization of the urine is not recommended. This is because although bicarbonate may render the urate more soluble, an alkaline urine is very difficult to achieve without a dangerously high blood pH. This, along with the arrival of rasburicase, has made bicarbonate therapy unnecessary.

Treatment of established tumour lysis syndrome

HD is the preferred treatment for established TLS; haemofiltration or haemodiafiltration are less efficient in the acute phase.

Absolute indications for HD include:

- Plasma potassium >5mmol/L.
- Plasma phosphate >4mmol/L.
- Pulmonary oedema (give oxygen and consider ventilation as immediate measures).
- Anuria.

Relative indications for HD include:

- Rapid rise in potassium, phosphate, or urate.
- Oliguria unresponsive to furosemide (1–2mg/kg, but may need up to 5mg/kg).
- Urea >15mmol/L or creatinine >150µmol/L.

The rate of rise of these markers is very important—act before the patient reaches a critical state.

Management after haemodialysis

- Nearly all patients require two HD sessions; some need three or more.
- After HD there will be a rebound in biochemistry, therefore continue to review the patient every 2–4h both clinically (for oliguria and fluid overload) and biochemically (Na, K, Ca, PO_4, TCO_2, urate, urea, and creatinine).
- The indications for further HD are as previously listed.
- Some patients may benefit from going onto haemofiltration after the first HD session in an attempt to prevent the biochemical rebound. This therapy is unproven.

Further reading

Pui CH (2002). Rasburicase: a potent uricolytic agent. *Expert Opin Pharmacother* **3**: 433–42.

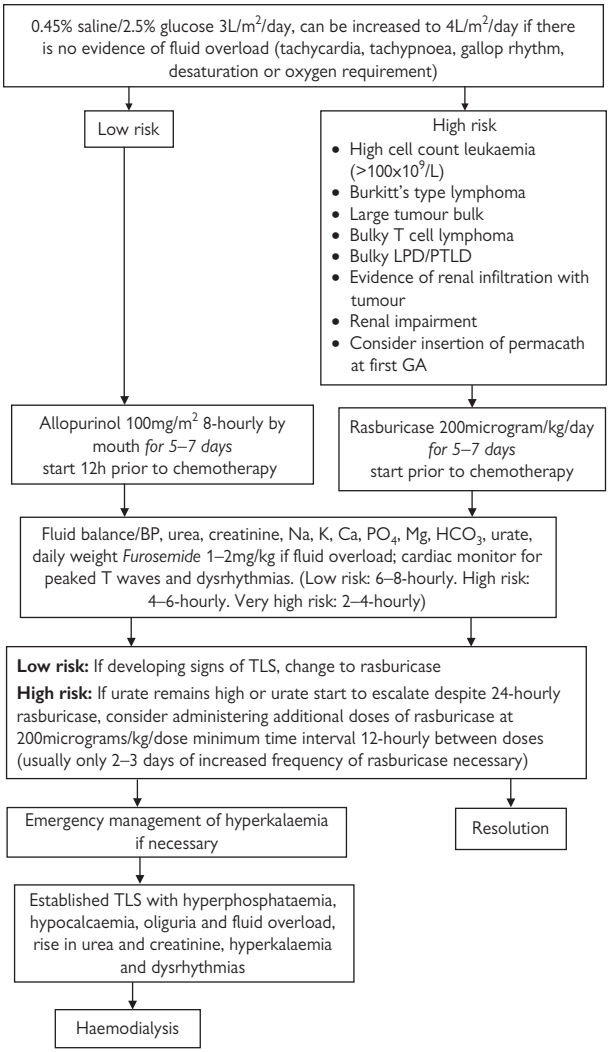

Fig. 17.2 Prevention and treatment of tumour lysis syndrome.

Chapter 18

Chronic kidney disease

Background and epidemiology

- Chronic kidney disease (CKD) occurs when there are irrecoverable, bilateral abnormalities of the renal parenchyma.
- Progressive decline in renal function to the need for renal replacement therapy (RRT, i.e. dialysis and/or transplantation) occurs in moderate to severe cases (Table 18.1), but it is not known if all milder cases progress.
- Progressive decline in glomerular filtration rate (GFR) does not happen if only one kidney is abnormal—many children, particularly those with renal dysplasia, can have stable renal function even in the worst stages of CKD for many years. Over the first 4 years of life an improvement in GFR often occurs.
- More rapid decline in GFR is often heralded by the onset or worsening of proteinuria.
- CKD is associated with a decrease in life expectancy, and even early CKD is associated with an increased risk of premature death from cardiovascular disease (CVD).
- Mortality risk increases with the severity of CKD, and has been estimated to be 1.4% higher than the age-matched population for children before RRT is needed, but much higher for children on dialysis, when lifespan is reduced by 40–60 years.

Epidemiology

The true incidence of CKD in childhood is not known. Figures quoted are underestimates because many children go undiagnosed and may not present even until adulthood. The incidence of children needing RRT is collected by national registries, and is similar at 9–10 per million child population (pmcp) per year in the UK, Australia and New Zealand, and slightly higher at 15pmcp in the United States.

Table 18.1 The probability of needing RRT at age 20 years according to GFR in early childhood

GFR in early childhood, mL/min/1.73m^2	Probability of needing RRT at age 20 years
51–75	37%
25–50	70%
<20	97%

Assessment of renal function

- Easiest way to assess renal function on a day-to-day basis is the plasma creatinine. This is produced at a constant rate from the breakdown of creatine phosphate in muscle and is excreted by filtration without reabsorption, so is a good representation of renal function.
- There is, however, some tubular secretion of creatinine, which increases with declining GFR, so the plasma creatinine can overestimate true GFR in advanced CKD.
- GFR in childhood can be calculated roughly from the formula (see 🕮 Appendix, p.599):

[Height (cm) × 40 = GFR (mL/min/1.73m^2)]/Plasma creatinine (μmol/L)

- GFR can also be calculated from the clearance of creatinine, by taking a blood sample for creatinine during a timed urine collection, and using the formula:

$$UV/P$$

where U is the urine creatinine, V is the urine volume, and P is the plasma creatinine. Given the difficulties of collecting urine in children, it is not often undertaken in childhood.

- More accurate measurement of GFR is by clearance of a substance that is filtered at the glomerulus, but not reabsorbed by the tubules, e.g. iohexol (see 🕮 Appendix, p.599).
- Milder cases of CKD may go undiagnosed in childhood because:
  - creatinine increases progressively with increasing height and muscle bulk so may not be raised in a child who is small and thin due to CKD;
  - plasma creatinine does not rise until renal function has fallen to less than half normal.

Suspect CKD in any child with:

- Plasma creatinine above the normal range for age.
- Bilateral renal defects on antenatal scans.
- Bilateral renal defects on scans e.g. for urinary tract infections (UTI).
- A family history of CKD.
- Persistent proteinuria.
- Previous acute kidney injury (AKI).
- Hypertension.

Presentation of chronic kidney disease

- Most present in the newborn period, usually following antenatal diagnosis (approximately 50% of cases), although some abnormalities may be missed without a third trimester scan.
- UTI.
- Decompensation of CKD causing AKI (precipitated by infection or dehydration).
- Polydipsia and polyuria.
- Family history.
- Poor nutritional intake and short stature.
- Pallor (anaemia), lethargy, nausea.

- Bony abnormalities from renal osteodystrophy.
- Incidental finding of proteinuria.
- Hypertension.
- Mild cases are frequently asymptomatic.

The current classification is shown in Table 18.2

Table 18.2 Staging of CKD

Stage	GFR (mL/min/1.73m^2)	Features
1	>90	Renal parenchymal disease present
2	60–90	Usually no symptoms, but may develop biochemical abnormalities at the lower end of the GFR range
3	30–60	Biochemical abnormalities and anaemia, and in addition may develop poor growth and appetite
4	15–30	Symptoms more severe
5	<15	Renal replacement therapy will be required

Causes of chronic kidney disease in children

In order of frequency:

- CAKUT.
- Renal cystic diseases.
- Nephrotic syndromes.
- Nephronophthisis (isolated or in association with syndromes).
- Glomerulonephritides.
- Vascular events.
- Atypical haemolytic uraemic syndrome (aHUS).
- Renal stone diseases.
- Familial nephropathies.
- Systemic diseases (SLE, vasculitis).
- Following AKI.

Pathogenesis

Despite these different causes of CKD, progressive destruction of renal tissue works through a common pathway. Abnormal intrarenal haemodynamics, chronic hypoxia, inflammation, cellular dysfunction, and activation of fibrogenic biochemical pathways lead to replacement of normal structures with extracellular matrix, culminating in fibrosis.

Investigation of the cause of chronic kidney disease

After the history and examination, an US and stick testing of the urine for protein may be enough to provide a diagnosis, and will guide further investigations as necessary (Table 18.3). The kidneys are usually echobright with poor corticomedullary differentiation in all causes of CKD (and AKI). Further imaging may be necessary if structural or cystic lesions or calculi are the cause and will depend on US appearances.

- Urine stick testing:
  - heavy proteinuria without significant haematuria suggests a nephrotic syndrome;
  - less protein is filtered as the GFR declines so that proteinuria may seem to improve as renal function worsens;
  - proteinuria and haematuria suggests a glomerulonephritis or familial nephropathy;
  - proteinuria may be tubular (tubulopathy), such as in Dent disease—if suspected, send urine for low molecular weight proteins, such as retinol binding protein (RBP) to creatinine ratio or β-2-microglobulin;
  - proteinuria may result from any cause of CKD because of hyperfiltration due to raised intraglomerular pressure as a result of glomerular hypertrophy, which occurs in response to decreased glomerular numbers;
  - no proteinuria may be present with cystic diseases and dysplasias.
- Complement levels, ANA, anti double stranded DNA (anti-ds-DNA), anti-neutrophil cytoplasmic and anti-glomerular basement membrane antibodies, IgA levels, ASOT/anti-DNAase if glomerulonephritis suspected.
- Plasma and urine calcium, oxalate and purines if calculi.
- Urine pH and white cell cystine if tubulopathy suspected.
- Renal biopsy may be necessary if the cause of CKD is not clear, but should be avoided in advanced CKD when the kidneys are small (<5cm bipolar length) as there is a significantly increased risk of bleeding, and histology may show end-stage kidney without being able to identify the cause.
- More and more causes of CKD can be diagnosed by looking for genetic mutations (see 🕮 'Genetic testing and antenatal diagnosis', p.38).

Table 18.3 Appearance of kidneys on renal US and guide to differential diagnosis

Cystic	Small	Normal sized	Obstruction	Calculi
Dysplasia	Dysplasia ± vesico-ureteric reflux	Glomerulo-nephritides	Dysplasia with posterior urethral valves	Recurrent UTIs ± obstruction/ reflux
Autosomal recessive polycystic kidney disease	Vascular insults (venous or arterial)	Familial nephropathies	Dysplasia with vesicoureteric junction obstruction	Calcium disorders Dent disease
Autosomal dominant polycystic kidney disease	All causes may result in small kidneys by Stage 5 CKD	Nephrotic syndromes	Dysplasia with PUJ obstruction	Hyperoxaluria
Tuberous Sclerosis		Nephronophthisis (may be cystic)	Neuropathic bladder	Purine disorders
Glomerulocystic diseases		Tubulopathies		Cystine

Management: overall aims

Aims of management of CKD

- Slow progression.
- Prevent biochemical and haematological derangements.
- Maintain normal growth and development.
- Preserve the limb vasculature—when possible avoid use of:
  - antecubital veins as they will be needed for fistula formation;
  - subclavian veins, stenosis of which would preclude creation of a fistula in that arm.

Outpatient checks in the child with CKD

- Height, weight and head circumference.
- Pubertal stage.
- BP.

Investigations at each clinic visit

- Full blood count (FBC; and ferritin if needing an erythropoiesis stimulating agent).
- Urea & electrolytes (U&Es), bicarbonate, and creatinine.
- Calcium, ionized calcium, phosphate, albumin, alkaline phosphatase, intact PTH.
- Urine protein or albumin to creatinine ratio (Up:Ucr or Ua:Ucr) measured in the first urine of the morning (to standardize measurements and reduce the orthostatic element).
- Fasting HDL and LDL, total cholesterol and triglycerides 6 monthly.

Management

- Nutrition.
- Fluid and electrolyte balance.
- Growth.
- Anaemia.
- Hypertension (HTN).
- CKD mineral and bone disorder (CKD-MBD).
- Immunizations.
- Preparation for RRT.

See individual chapters for further details.

Slowing the progression of chronic kidney disease

Proteinuria

Rate of decline of kidney function is related to the quantity of proteinuria, which in turn is related to the degree of hyperfiltration and glomerular hypertension. Proteinuria may itself be toxic to the tubulo-interstitium. The level at which to start treatment is unknown; some would suggest that any proteinuria should be treated.

- The aim is to reduce proteinuria by progressively increasing the dose of an angiotensin-converting enzyme inhibitor (ACEI; which dilates the glomerular afferent arteriole, reducing intraglomerular pressure) stopping if there are side effects or abnormal biochemistry. Usually, it is possible to reduce proteinuria by half.

- An AT1 receptor blocker can be added in if there is still proteinuria with a maximum tolerated dose of ACEI (see Table 18.4) or if there are side effects with the ACEI.
- Most centres use enalapril or captopril as their ACEI of choice. Plasma creatinine and K, and BP should be measured at each clinic visit and 4–7 days after each increase in dose.
- Check Up:Ucr or Ua:Ucr for evidence of benefit; aim for maximum reduction of proteinuria without hypotension or hyperkalaemia.
- There may be a rise in plasma creatinine as the total renal blood flow is decreased. A rise of up to 25%, if not increasing, may be acceptable.
- ACEIs carry a risk of severe hypotension, especially when other risk factors, such as nephrotic syndrome or when salt depleted (e.g. with gastroenteritis) are present. Consider stopping the ACEI during these episodes.
- ACEIs may depress erythropoiesis so watch FBC.
- Cough is a side effect of ACEIs.
- There is a risk of fetal malformations, particularly if used during the second and third trimesters. All teenage girls need to be informed of this risk.

Table 18.4 Commonly used renin angiotensin system blockers

Drug	Route	Normal starting dose	Normal dose range (to maximum)	Divided into doses/day	Preparations and comments
Captopril	Oral	50microgram/kg/dose	0.5–3mg/kg/day (maximum 6mg/kg/day)	3	Tablets 2mg, 6.25mg, Very soluble in water Caution in renal artery stenosis, hyperkalaemia and when GFR <30
Enalapril	Oral	100microgram/kg/dose	200–500 microgramkg/day (maximum 600microgram/kg/day up to 40mg/day)	1	Tablets 2.5, 5, and 10mg C/I commencing treatment in pregnancy and hyperkalaemia. Caution in renal artery stenosis and when GFR<30
Irbesartan	Oral	2mg/kg/dose	6–12 years: 75–150mg/day >13years: 150–300mg/day	1	Tablets 75, 150mg

Hypertension

Hypertension is another important contributor to the progression of CKD. The BP should be maintained within the normal range for age and height. Whether it should be just <90th centile or lower is debatable; there is some evidence that <50th centile may be beneficial.

Dyslipidaemia

- Dyslipidaemia may contribute to the progression of CKD. Increased LDL cholesterol is a particular problem for children with nephrotic syndrome. Hypertriglyceridaemia and abnormal apolipoprotein metabolism is a feature of CKD.
- Dietary intervention may be necessary, and some children (particularly those with nephrotic syndrome) may need lipid lowering agents. The recent SHARP study has reported a reduction in cardiovascular events in adult CKD patients treated with statins. No comparable data exist in children.

Low protein diet

There is no evidence that a low protein diet is beneficial in children and this is not recommended.

Treatment of anaemia

Anaemia and subsequent tissue hypoxia may contribute to the progression of CKD. Increasing oxygen delivery to tubular cells may decrease tubular damage and protect against nephron loss induced by tubular injury (see 📖 'Management: anaemia', p.446).

Management: fluid and electrolytes

Background

- Many children with structural renal diseases are Na, bicarbonate, and water-losers, and need salt and bicarbonate supplementation, and free access to water.
- A low K diet may be necessary when the GFR falls to <10% normal.
- Ca absorption is poor and vitamin D may be needed to improve this.
- Phosphate retention needs early dietary intervention.

Table 18.5 gives the recommended nutrient guidelines for populations of healthy children. They are not, however, always appropriate for the individual child with CKD, and should not be considered as nutritional targets.

Sodium, bicarbonate, and water

Requirements for salt, water and bicarbonate vary with the type of renal disease. Children with dysplasia and structural renal diseases are usually Na, bicarbonate, and water losers. This is because the predominant effect is on the renal tubule, so that reabsorption of Na, bicarbonate, and water from the glomerular filtrate is inadequate. Therefore, these children are often polyuric and polydipsic, and are prone to episodes of decompensation with hypovolaemia and AKI, unless they have salt and bicarbonate supplementation and free access to water.

Sodium

- Requirements can be very high in early CKD, but fall as the glomerular disease progresses such that by stage 4–5 CKD, salt restriction may become necessary.
- The heaviest electrolyte losers are those with tubulopathies, in particular cystinosis; replacement of adequate Na and bicarbonate may be difficult.
- Salt depletion contributes to poor growth.
- Children with CKD due to predominantly glomerular disease may retain salt and water and develop hypertension. Such children should be managed with a 'no added salt' diet (avoidance of foods particularly high in salt and no salt added to food in cooking or at the table).
- Many infants on peritoneal dialysis (PD) lose excessive amounts of Na and need supplementation.

Bicarbonate

As well as urinary bicarbonate losses there may be an inability to acidify, and bicarbonate replacement, starting dose 1mmol/kg/day in 2–4 divided doses, may be needed.

Water

Children who are unable to concentrate their urine require free access to water.

Table 18.5 Recommended nutrient intake (RNI) for Ca, Na, K, and P

Age	RNI for Ca (mmol/day)	RNI for sodium (mmol/day)	RNI for K (mmol/day)	RNI for phosphorus (mmol/day)
0–3 months	13.1	9	20	13.1
4–6 months	13.1	12	22	13.1
7–9 months	13.1	14	18	13.1
10–12 months	13.1	15	18	13.1
1–3 years	8.8	22	20	8.8
4–6 years	11.3	30	28	11.3
7–10 years	13.8	50	50	13.8
11–18 years	25 ♂ 20 ♀	70	80 (11–14 years) ♂ 90 (15–18 years) ♀	25♂, 20♀

Potassium

- CKD can be associated with K retention, but hyperkalaemia does not usually occur until the GFR is <10% normal.
- Possible causes of hyperkalaemia include:
  - inadequate energy intake;
  - anti-hypertensive and K sparing drugs, e.g. captopril and spironolactone;
  - high dietary intake of K;
  - acidosis.
- Adequate control of plasma K can usually be achieved by improving energy intake, avoiding foods that are very high in K, whilst allowing foods containing moderate amounts of K.
- Furosemide may be of benefit, but must be used with care as the change in circulating blood volume can destabilize renal function in severe CKD.

Calcium and phosphate

See 🕮 'Management: mineral and bone disorder', p.434.

Further reading

Department of Health Report on Health and Social Subjects (1991). *Dietary Reference Values for Food, Energy and Nutrients for the United Kingdom*, No. 41. London: Stationery Office.

Royle J. (2007). The kidney. In: Shaw V, Lawson M (eds) *Clinical Paediatric Dietetics*, 3rd edn. Oxford: Blackwell Sciences Ltd, pp. 211–26.

Management: growth

Background

- Growth retardation occurs in up to 50% of children with moderate to severe CKD (GFR <50mL/min/1.73m^2).
- Children with congenital nephropathies are particularly severely affected, because growth in the first 2 years of life is principally dependent on nutrition, which is very difficult to maintain because the infant with CKD is anorexic and frequently vomits.
- After this age, when the role of growth hormone (GH) becomes more important, the rate of growth can be normal.
- Growth may also be adversely affected at the time of puberty, which may be delayed, with an abnormal pubertal growth spurt.
- Growth retardation increases with CKD stage, but it has to be remembered that many children have associated syndromes that in themselves affect growth.
- Successful renal transplantation can normalize growth in some children, but may be counteracted by corticosteroid therapy used as immunosuppression.

Important points

- Length and weight must be measured at each clinic visit, and head circumference and pubertal stage when appropriate. Results should be plotted on growth charts. This enables calculation of rate of growth, decline requiring urgent action.
- The most important cause of poor growth is inadequate intake of calories and protein leading to malnutrition. Water, electrolyte and acid-base imbalances, bone disease, and GH resistance are also important.
- Many children need dietary supplements orally or enterally.
- Gastrostomy feeding delivered overnight by enteral feeding pump is associated with reduced vomiting.
- Vomiting needs evaluation for gastro-oesophageal reflux; anti-reflux medications may help. If not, Nissen fundoplication may be necessary.
- Correction of biochemical abnormalities is necessary for normal growth.
- Many children are salt losers and need salt supplementation.
- Children who fail to respond to all these measures may benefit from recombinant human GH (rhGH).
- Steroid therapy, particularly if daily, is an important cause of poor growth post-transplantation.

Investigations

- Dietary assessment of calorie and protein intake.
- Assessment of salt and water intake.
- In infants with a history of vomiting, barium swallow for reflux and malrotation, and gastro-oesophageal pH studies.
- Bicarbonate, parathyroid hormone (PTH) and thyroid function tests.

Management

- Act on any decline in rate of growth by addition of dietary supplements, either orally or enterally, via nasogastric (NG) tube or gastrostomy, if anorexic.
- Gastrostomy may be placed percutaneously except for the child on PD, when an open gastrostomy is necessary to reduce the risk of peritonitis (see 📖 'Management: nutrition', p.422 and 📖 'Management: enteral feeding', p.430).
- Salt supplementation may be necessary in children with renal dysplasia, which is predominantly a tubular lesion.
- Correct acidosis, hyperparathyroidism (see 📖 'Management: mineral and bone disorder', p.434), and abnormal thyroid function.
- Vomiting can be a very big problem for infants. It may be so severe that nutritional intake is compromised. It is usual to start with ranitidine and then to add in domperidone if no improvement (see Table 18.6).
- Vomiting is usually less with a gastrostomy than a NG tube.
- If vomiting persists despite oral medication and there is gastro-oesophageal reflux, Nissen fundoplication is indicated.
- rhGH can be offered to the child whose growth has failed to respond to all these measures (see 📖 'Management: growth', p.420).

Table 18.6 Use of ranitidine and domperidone in CKD

Age	Dose	Frequency	Adjustment for CKD (all ages)	
Ranitidine			Cr clearance (mL/min/1.73m^2)	Dosage as % normal
<6 months	1mg/kg	3 × daily	10–50	75%
6 months to 8 years	2mg/kg	Twice daily	<10	50%
Over 8 years	up to 150mg	Twice daily (300mg/day)		
Domperidone			Side effects	
All ages	200–400 micrograms/kg	3–4 × daily	Caution in neonates (prolonged QT interval) and young children (extrapyramidal signs)	

Further reading

KDOQI Work Group (2009). KDOQI Clinical Practice Guideline for Nutrition in Children with Chronic Kidney Disease: 2008 Update. *Am J Kidney Dis* **53:** S11–104. Available at: 🔗 http://www.kidney.org/professionals/KDOQI/

Rees L, Shaw V. (2007). Nutrition in children with CRF and on dialysis. *Pediatr Nephrol* **22:** 1689–702.

Management: nutrition

Background

Ensuring adequate nutrition is one of the most important aspects of care of the child with CKD. Involvement of the paediatric renal dietitian is crucial to:

- Control symptoms and prevent complications, particularly uraemia and renal bone disease (thereby delaying the need for dialysis).
- Promote optimum growth.
- Preserve residual renal function.

Causes of poor nutritional intake

Anorexia and vomiting are characteristic of CKD.

- Poor appetite may be due to abnormal taste sensation, the requirement for multiple medications, the preference for water in the polyuric child, and elevated circulating cytokines such as leptin, tumour necrosis factor (TNF)-α and IL-1 and -6, which act through the hypothalamus to affect appetite and satiety.
- Vomiting may result from gastro-oesophageal reflux and delayed gastric emptying in association with decreased clearance of polypeptide hormones.
- Insufficient intake may be due to episodes of fasting surrounding surgical procedures and episodes of sepsis.
- Many children with CKD have associated co-morbidities that influence feeding (and growth) in their own right.

Important general points

Energy

- Inadequate energy from non-protein sources will result in the use of dietary protein for energy, rather than growth, and also result in increased plasma urea and K levels.
- Oral supplements and/or enteral feeding may be necessary to achieve optimum energy intake.
- Enteral feeding is indicated in both infants and children when oral intake is inadequate to maintain growth and should be considered as soon as the growth rate falls below normal.
- Children on PD having glucose-containing dialysate will absorb glucose during the dwell time (average 10kcal/kg body weight/day).

Protein

- Protein intake above the reference nutrient intake (RNI) is recommended to ensure adequate intake for growth.
- Protein intake often needs adjustment to nearer the RNI when GFR <25mL/min/1.73m^2 (see Table 18.7). Kidney Disease Outcomes Quality Initiative (KDOQI) recommends 100–140% dietary reference intake (DRI; CKD stage 3); 100–120%DRI (CKD stage 4-5).
- Aim for plasma urea levels <20mmol/L in infants and children under 10 years and < 30mmol/L in older children (over 10 years) with a normal serum albumin.
- The blood urea level is a reflection of protein intake, unless there is a catabolic state, when it reflects tissue breakdown.

- Symptoms of nausea and anorexia increase when the urea starts to climb over 20 mmol/L.
- A very low urea suggests protein malnutrition.
- Dietary protein intake is rarely inadequate in CKD stages 1–4 as it is easily achieved from the diet.
- Protein intakes on dialysis are 100% RNI with an allowance to replace dialysate losses (see Table 18.8)—these are greatest in infants and after peritonitis.

Table 18.7 Guidelines for energy intake and protein requirements in children with conservatively managed CKD

Age	Energy*	Protein† (use height age for infants and children <2nd centile for height)
Preterm	120–180kcal/kg	2.5–3.0g/kg
0–3 months	115–150kcal/kg	2.1g/kg
4–6 months	95–150kcal/kg	1.6g/kg
7–12 months	95–150kcal/kg	1.5g/kg
1–3 years	95–125kcal/kg	1.1g/kg
4–6 years	90–110kcal/kg	1.1g/kg
7–10 years	1740♀–1970♂kcal/day	28g/day
11–14 years	1845♀–2220♂kcal/day	42g/day

*Depending on losses through vomiting and underlying diagnosis; †Reference nutrient intake (except for preterm).

Table 18.8 Guidelines on protein intake for children on peritoneal and haemodialysis

	Peritoneal dialysis*	Haemodialysis†
Boys and girls	Protein (g/kg/day; use height age for infants and children <2nd centile for height)	Protein (g/kg/day; use height age for infants and children <2nd centile for height)
Preterm	3.0–4.0	3.0
0–3 months	≥2.4	≥2.2
4–6 months	≥1.9	≥1.7
7–12 months	≥1.8	≥1.6
1–6 years	≥1.4	≥1.2
7–14 years	≥1.3	≥1.1
15–18 years	≥1.2	≥1.0

*RNI + 0.3g/kg/day to compensate for peritoneal losses; † RNI + 0.1g/kg/day to compensate for dialytic losses.

Vitamins and minerals

See Table 18.9.

Table 18.9 Selected micronutrient content of vitamin and mineral preparations

Vitamin and minerals	Paediatric Dialyvit®	Ketovite® tablets (3)	Ketovite® liquid (5mL)	Abidec® (0.6mL)	Dalivit® (0.6mL)
Vitamin A (microgram)			750	400	1500
Pyridoxine (mg)	2	1		0.8	1
Folic acid (microgram)	1000	750			
Vitamin C (mg)	40	50		40	50
Vitamin D (microgram)			10	10	10
Iron (mg)					
Zinc (mg)	8				
Suitable in CKD?	✓ All children on PD	✓ All children on PD	× Caution vitamin A	× Caution vitamin A	×Caution vitamin A

- Few data are available on the micronutrient requirements of children with CKD.
- Vitamin supplements should not be routinely prescribed, as most contain vitamin A (e.g. Abidec®, Dalivit®). Renal excretion of vitamin A metabolites is impaired in CKD and high plasma levels can be associated with hypercalcaemia, anaemia, and hyperlipidaemia.
- Intake from diet, infant formula, enteral feeds, or nutritional supplements and any 'self-prescribed' micronutrient supplement must be considered before any supplement is prescribed.
- In patients with CKD not requiring RRT and those on HD the aim is to achieve RNI for all micronutrients except vitamin A.
- Children on PD require supplements of vitamin C, pyridoxine and folic acid to offset dialysate losses, e.g. Dialyvit® Paediatric (½ capsule <5 years of age; 1 capsule >5 years of age) or 3 Ketovite® tablets daily, adjusted after assessment of the individual's intake of micronutrients. Ketovite® liquid is not appropriate as this provides high doses of vitamin A.
- If an iron (Fe) preparation is prescribed this should ideally be given in 2–3 divided doses and taken in the absence of food, antacids and phosphate binders. Iron preparations available include:
  - sodium feredetate (Sytron®) (55mg Fe in 10mL);
  - ferrous sulphate 200mg (65mg Fe);
  - ferrous fumarate 210mg (68mg Fe).

- *Nutritional vitamin D (25(OH)D):* a very large proportion of patients with CKD are deficient. The daily requirement in children with CKD is unknown, but supplementation is recommended, to a maximum maintenance dose of 1000 IU/day in infants and 2000 IU/day in older children.

Practical management of feeding

There are various types of supplements, with different ratios of calories and protein. In the young child with vomiting it is possible to increase the feed concentration and therefore decrease the feed volume. However, the vomiting may worsen and diarrhoea can occur with increasing feed density so changes should be introduced gradually.

Diet in infancy

- Breast milk or whey based infant milk (e.g. SMA® 1 or Cow & Gate® 1) are best as they have a low renal solute load.
- Infants with uncontrolled plasma urea levels may need a higher energy feed. Infant formula can be supplemented with glucose polymer (e.g. Maxijul®) and/or fat emulsion (e.g. Calogen®).
- If the urea level remains raised despite optimizing energy intake then protein intake should be reduced in 0.2g/kg increments towards the RNI.
- Raised plasma K levels (>6.0mmol/L) are most often due to inadequate energy; energy intake should therefore be optimized.
- If hyperkalaemia is more severe (>6.5mmol/L) or persistent, Renastart® or Kindergen® (low K, low phosphate formula) can be used to replace part of the standard infant formula base of the feed.
- If hypercalcaemia is persistent Locasol® (low Ca formula) can be useful, although consideration of reduced doses of activated vitamin D and/or Ca containing phosphate binders may be warranted first.

Weaning solids

- These should be low in protein and phosphate to start, i.e. baby rice, pureed fruits and vegetables.
- As the infant takes more protein from solids, protein intake from the milk should be adjusted as needed.
- Cows milk and cows milk products may need to be restricted to prevent plasma phosphate levels increasing.

Diet in children

- The diet will normally be high in energy and restricted in phosphate.
- Protein and K may need to be restricted, particularly in CKD stage 4 and 5.

Protein

- Requirements are based on chronological age. If <2nd centile for height, requirements are based on height age (i.e. the age at which the child's height would be on the 50th centile) to ensure adequate protein intake.
- About 70% of protein intake should be from high biological value sources e.g. meat, fish, cheese, eggs, or milk (NB. phosphate content may limit use of these foods).

- The remaining protein is given as lower biological value sources, e.g. bread, rice, potatoes, pasta, and biscuits. These foods are usually allowed freely.
- Strict protein restriction is not necessary, and simple dietary advice about reducing the size of protein portions in meals and limiting protein to 2 meals/day is usually adequate to keep the urea at an acceptable level. A small number of patients will require specific protein portion advice if urea levels cannot be controlled.
- On the other hand, sufficient protein intake may be difficult to achieve in the child on dialysis. Protein supplements over and above the normal reference nutrient intake for protein for age are usually needed, as protein in PD and amino acids in HD are lost in the dialysate effluent.

Energy

- High energy foods/diet are recommended.
- High energy drinks are encouraged (e.g. flavoured Vitajoule® or Maxijul® water, sugar containing squashes and fizzy drinks such as Lucozade® High Energy.
- Children with poor appetites can benefit from nutritional supplements (a paediatric sip feed, e.g. Paediasure®, Fortini®, Paediasure Plus Juce®; older children may have an adult sip feed e.g. Fresubin®, Fortisip®, Ensure Plus Juce®, ProvideXtra®).
- For children on enteral feeds, infant formula is changed to a paediatric enteral feed, e.g. Nutrini® or Paediasure® between 1 and 2 years of age (greater energy and protein density).
- For children on a fluid restriction, HD, PD, or for those who need a more energy and protein dense feed Nepro® or Suplena® are available (also low in K and phosphate). Renilon® 7.5 is an alternative oral high energy and protein supplement (although not nutritionally complete).

Further reading

KDOQI Clinical Practice Guideline for Nutrition in Children with Chronic Kidney Disease (2009). Update. *Am J Kidney Dis* **53**(Suppl. 2)**:** pS1–124. Available at: http://www.kidney.org/professionals/KDOQI

Management: use of recombinant human growth hormone

Background

The Cochrane review of the use of recombinant human growth hormone (rhGH) in children with CKD or post-transplant has shown that a dose of 28IU or 10mg/m^2/week results in a significant increase in height standard deviation score (SDS) at 1 year, but no further increase in height indices during the second year of administration, and concluded that it is not certain if final adult height will be increased. There was no increase in the frequency of reported side effects of rhGH compared with controls. RhGH should only be considered when growth has failed to respond to correction of inadequate diet and biochemical abnormalities, and optimization of dialysis. For children on steroid therapy, the dose of steroids should be reduced to the lowest possible.

Important points

- There is GH resistance in CKD as circulating GH are levels are high and bioavailability of insulin-like growth factor 1 (IGF-1) is low.
- rhGH is licensed in prepubertal children whose GFR is reduced by 50% and in children after 1 year post-transplant.
- rhGH has the most beneficial effect in the youngest, most growth retarded patients. Children with less severe CKD do better than those on dialysis. Post-transplant, those with the best renal function, on low doses of steroids have the greatest response to rhGH.
- Some children are small and have CKD as part of a syndromic diagnosis. These children respond poorly to rhGH.

Indications for the use of recombinant human growth hormone

Children with CKD (including post-transplant) of all ages who have a height (Ht) SDS <–2SD and a Ht velocity SDS <–1SD below the mean, but only after adequate nutrition has been established, metabolic abnormalities have been corrected, dialysis adequacy ensured, and steroid therapy reduced to a minimum.

Investigations

- Assessment of Ht SDS, height velocity and Ht velocity SDS over the previous year.
- Assessment of pubertal staging.
- Dietary review to ensure adequate calorie and protein intake.
- Parental heights should be measured and the target height calculated (95% of children will have a final height within 8.5cm on either side of the mid-parental height).
- Fundoscopy, as benign intracranial hypertension is a recognized side effect.

Investigations at start of therapy
- Fasting plasma glucose and insulin levels.
- Fasting triglycerides and cholesterol.
- Thyroid function tests.
- IGF-1.
- Bone age.

Follow-up and further investigations
- Fundoscopy 3-monthly.
- Calculation of Ht SDS and Ht velocity 6-monthly and Ht velocity SDS after 1 year.
- Pubertal staging 6-monthly.
- Fasting plasma glucose and insulin, triglycerides, and cholesterol 6-monthly.
- IGF-1 and bone age annually.

Management

The recommended dose of rhGH is 45–50microgram/kg *or* 1.4mg/m^2 daily by subcutaneous injection. Higher doses may be needed and can be adjusted if necessary after 6 months.

Do not commence treatment if:
- Within 1 year post-transplant (as spontaneous catch-up may occur).
- Inadequate dietary intake.
- The PTH is more than twice the upper limit of normal, as the extra demands for Ca may worsen osteodystrophy. There is an increased incidence of avascular necrosis of the hip, which may be related to high PTH levels.
- Post-transplant the prednisolone has not been reduced to the minimum possible dose.
- Post-transplant there have been rejection episodes within the preceding year, as there is an association with continuing rejection in patients treated with rhGH.
- Dialysis adequacy is not optimized.
- There is X-ray evidence of epiphyseal fusion (i.e. growth is complete).

rhGH should be stopped when:
- The child receives a renal transplant (to assess growth in the first year post-transplant) unless the child has GH deficiency.
- There are side effects.
- There is no increase in Ht SDS or Ht velocity after 1 year.

Consideration should be given to stopping rhGH when:
- There is non-compliance.
- The increase in Ht velocity is <50% from baseline in the first year of treatment.
- After the first year if the Ht velocity falls to the pre-rhGH value. However, Ht velocity SDS may be more useful than Ht velocity during puberty, when a spontaneous increase in Ht velocity would be expected.
- When the target height is approached and Ht Velocity is <2cm/year.

Factors that increase the chances of a response to rhGH

- Young age.
- More growth retarded.
- Less severe CKD, including post-transplant.
- Post-transplant, on low doses of steroids.

Side effects

There should be regular surveillance for efficacy and side effects

- Avascular necrosis of the femoral head and slipped femoral epiphysis, particularly if there is CKD-MBD.
- Intracranial hypertension post-transplant and in children on dialysis.
- There is a possible slight increase in the risk of transplant rejection in patients who have had previous rejection episodes.
- There have previously been concerns about using rhGH post-transplant for fear of inducing malignancy. However, the consensus view is that the risk of this is negligible.
- Any potential side effects must be reported.

Further reading

Vimalachandra D, Craig JC, Cowell C, Knight JF. (2005). Growth hormone for children with chronic renal failure. *Cochrane Database of System Rev* Issue 4.

Management: enteral feeding

Background

- Enteral feeding is indicated when calorie or protein intake is inadequate, or when struggling with oral intake in an anorexic child causes intolerable strains within the family.
- Although a NG tube is acceptable for a short time, most families prefer the placement of a gastrostomy, which cannot be seen beneath clothing.
- Vomiting may improve following insertion of a gastrostomy, but in children with persistent vomiting a Nissen fundoplication may also be indicated.
- Although it is customary to undertake a barium swallow before a Nissen, it is not uncommon for this to be negative, and most would proceed with a Nissen despite this if vomiting is profuse.

Nasogastric tubes

Advantages

- The method of choice in the infant weighing <4kg.
- Placement is simple and easily taught to families.
- There is no risk of peritonitis in children on PD.

Disadvantages

- The trauma of frequent replacement is considerable, for the child and family.
- They may inhibit the development of oromotor skills causing subsequent problems with speech and swallowing.
- Appearance is altered, giving the obvious demonstration of a 'sick child'.
- Rarely, may result in oesophageal or gastric perforation.
- Increased risk of gastro-oesophageal reflux, vomiting, and aspiration because the tube stents open the lower oesophageal sphincter.

Transpyloric tubes

It is possible to advance the feeding tube beyond the stomach, either into the duodenum or jejunum, to try to reduce vomiting. However:

- They are easily displaced and require interventional radiology for insertion and replacement, with frequent radiation exposure.
- They cannot be used for bolus feeds, only continuous feeds.

Gastrostomies

Insertion of a gastrostomy may be percutaneous endoscopic (PEG), percutaneous radiological or percutaneous laparoscopic. It may also be 'open', of which the commonest type is the Stamm. Whatever the type of placement, the gastrostomy tube exit site is limited to the left upper quadrant (LUQ) of the abdomen or the midline because of the anatomy of the stomach. As a result, PD catheters should not be placed in the LUQ in children who may subsequently need gastrostomy placement.

Perioperative management

- All types require perioperative antibiotic cover.
- Stop medications that reduce gastric acid production as patients on these drugs may have bacteria in their stomachs.

- Leave unused, with the tube to gravity drainage, for 24–48h before starting feeds.
- Start with clear fluids administered continuously over 24h by pump, changing to the appropriate feed when this is tolerated.

Techniques of insertion

Percutaneous endoscopic gastrostomy

The 'pull technique':

- An endoscope is introduced into the stomach and the stomach is insufflated.
- An IV catheter is inserted percutaneously and a wire is passed into the stomach.
- The wire is grabbed and pulled out through the mouth, and the wire is used to pull the gastrostomy tube from the mouth into the stomach and through the abdominal wall.
- The PEG is secured by rigid phalanges inside and outside the abdominal wall.

The 'push technique':

- The wire is passed into the stomach, and used to pass dilators and then the gastrostomy tube.
- Interventional radiological placement uses the push technique:
  - barium sulphate suspension is given the night before the procedure for colonic opacification;
  - NG tube is used to insufflate the stomach and screening is used to check that the bowel is satisfactorily displaced;
  - the stomach bubble is identified on fluoroscopy or ultrasound, and a needle is introduced and used to pass dilators for the gastrostomy tube.
- Percutaneous laparoscopic procedures use the push technique, but are done under direct vision using a laparoscope. It is difficult to combine with an endoscopic approach due to insufflation inside and outside the stomach.

Open gastrostomy

- A small incision is made and the greater curvature of the stomach is pulled out of the peritoneal cavity.
- A purse string suture (or two) is placed in the stomach.
- A hole is made in the middle of the purse string and a tube (latex tube such as a Malecot) or a button is placed through purse string, which is then tied.
- The stomach is sewn onto abdominal wall, usually with at least 4 separate sutures.
- If a latex tube is used, it can be replaced by a button after 3–4 weeks.
- There are different types of button, e.g. Mic-Key, Bard, or mini. The principle is the same—they all have a 'stalk' to insert through the abdominal wall and something to hold the distal (intragastric) portion in the stomach. The internal fixing device can vary, although usually it is a water-filled balloon.
- All buttons have a valve in the lumen to prevent leaking of stomach contents from the lumen of the tube.

Complications

Are reported to be minor in 10–15%, major in 3–5%, and the mortality is up to 1%.

Specific to percutaneous endoscopic gastrostomy

- Intra-abdominal leakage because the tube is held against the abdominal wall with no suturing. Peritonitis can develop in the child on PD.
- Tube blockage.
- Gastrocolic fistula, due to accidental snaring of the colon between the stomach and abdominal wall—the child may present with stools that look like the feed and weight loss.
- Routine replacement is needed every 2 years under general anaesthetic due to the rigid intragastric portion of the tube. Alternatively, some physicians cut this off and allow it to pass through the GI tract.

Specific to open gastrostomies

- *Balloon rupture:* if the balloon has burst or is leaking, the button needs to be replaced. Parents can be taught to replace the button at home. A smaller lumen tube should be provided in case the button cannot be reinserted by the family.
- *Tube displacement:* if displacement occurs within 2 weeks of surgery, the tract will not be well formed, and forcing a tube may disrupt the stomach from the abdominal wall. The tube should, therefore, be replaced under radiological cover.
- *Closure of the tract:* this can happen very quickly or can take time. In general, the longer the feeding gastrostomy has been in place, the longer the time for the tract to spontaneously close. It is important, therefore, that parents are taught to come to the hospital straight away should there be problems.
- *Tract too large:* the button can be taken out for progressively more hours to allow the tract to shrink.

Of both percutaneous endoscopic and open gastrostomies

- *Leakage around the gastrostomy exit site:* do not put in a bigger tube, pull the balloon tight to the abdominal wall or blow up the balloon more. Wait for the tract to epithelialize, keep the skin in good condition and cauterize any granulomas.
- *Skin irritation and itching, particularly if there is leakage:* the skin should be kept clean and dry, a barrier cream used, and *Candida* treated if necessary. Skin irritation may progress to 'gastrostomy dermatitis'. The skin should be cleansed each day with soap and water only, avoiding hydrogen peroxide, alcohol, betadine, and other lotions. Occlusive dressings should not be used.
- *Exit site infection:* swab and use topical antibiotic cream and oral antibiotics if severe. Granulomas can be treated with application of silver nitrate twice a week.
- Failure of the tract to close after tube removal, resulting in a permanent gastrocutaneous fistula, which needs to be surgically closed.
- *Haemorrhage:* most commonly, this is due to bleeding from a granuloma, but can also be due to trauma, or rarely, GI bleeding. It is, therefore, important to differentiate bleeding through the lumen of the tube (GI bleeding) from bleeding around the tube (skin irritation or granulation tissue).

- *Exacerbation of reflux due to distortion of gastric anatomy (rare):* this may be counteracted by the use of a gastrojejunal tube, entering via the gastrostomy site. Many of these patients may need a subsequent fundoplication.

Open gastrostomy

Indicated in:

- Children who have had previous abdominal surgery.
- Children on PD as there is a risk of PEG formation causing peritonitis. Peritoneal dialysis should be withheld for a few days after the procedure.
- Children undergoing Nissen fundoplication.

Management of a gastrostomy button

- The button is held in place by a water-filled balloon. Parents are taught to test whether the balloon is intact by withdrawing the water from it each week. If the balloon has burst, the button needs to be replaced.
- Parents can be taught to replace the button at home. If they prefer not to, they should be provided with a NG tube in case the button falls out. This should be inserted 1 inch into the gastrostomy and strapped in place to keep the tract open until they get to the hospital. Closure of the tract can happen very quickly or may take time. It is important, therefore that parents are taught to contact the hospital straight away should there be problems.
- If there are no complications, the life of the button depends on the make, but some can last for up to 3 years.

Timing of gastrostomy insertion in the child who is about to start or on peritoneal dialysis

- It is better to insert a gastrostomy prior to commencement of PD in order to decrease the risks of peritonitis, because placement of a PEG leads to a small leak of stomach contents into the peritoneal cavity. Dialysate, due to its high dextrose content, will encourage any organisms to rapidly multiply and result in peritonitis.
- The open procedure limits contamination of the peritoneal cavity by entering the gastric lumen outside of the abdomen and by securing the stomach to the abdominal wall with sutures.
- There is no evidence that there is an increased risk of peritonitis in children on PD with an established gastrostomy.

Post-transplant management

In the majority of children, appetite improves post-transplant so that the gastrostomy can be removed, although some continue to need it for the administration of fluids and medications. Its continued use will also be affected by the success of the transplant.

- Assess dietary intake 4–6 weeks post-transplant.
- Proportionately decrease feed as oral intake increases.
- Remove gastrostomy when diet, growth, fluids, and medication intake satisfactory, if the transplant is functioning well.

Further reading

Rees L, Brandt ML. (2010). Tube feeding in children with CKD: technical and practical issues. *Pediatr Nephrol* **25**(4)**:** 699–704.

Management: mineral and bone disorder

CKD leads to abnormal vitamin D, Ca, phosphate, FGF23, and PTH metabolism as follows:

- ↓ *Plasma 25(OH)D:* due to dietary restrictions, decreased manufacture in skin because of reduced activity and sun exposure in children with CKD, and urinary losses of vitamin D binding protein if proteinuria.
- ↓ Ca intake due to dietary restrictions.
- ↑ Fibroblast growth factor 23 (FGF23) and ↓ of its co-receptor Klotho in response to an increased phosphate load, resulting in phosphaturia, and maintaining a normal plasma phosphate in early CKD.
- ↑ Plasma phosphate (when ↑FGF23 can no longer compensate) due to decreased clearance and increased gastrointestinal absorption if the active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) is prescribed.
- ↓1α hydroxylation of 25(OH)D to the active form, $1,25(OH)_2D$.
- ↓ Ca absorption due to ↓$1,25(OH)_2D$.
- ↑ PTH due to low plasma Ca, high phosphate, and low $1,25(OH)_2D$.

Untreated, CKD-MBD results, which is a constellation of:

- Disordered bone turnover, mineralization, volume, and strength.
- Bone pain and fractures.
- Abnormal growth.
- Vascular and soft tissue calcification.
- Increased mortality from cardiovascular disease.

The term CKD-MBD is now used to encompass all these abnormalities; renal osteodystrophy should be reserved for the bony abnormalities that are seen on histology.

Sequence of the events that cause chronic kidney disease mineral bone disorders

Early CKD

See Fig. 18.1.

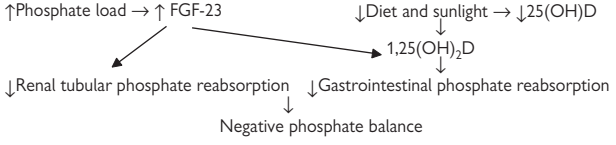

Fig. 18.1 Phosphate balance in early CKD.

- ↓Plasma 25(OH)D results in ↓$1,25(OH)_2D$.
- ↓$1,25(OH)_2D$ leads to low Ca absorption and (beneficially) low phosphate absorption.
- Low dietary Ca intake along with low absorption lead to low plasma Ca.
- The decrease in GFR and renal tubular phosphate excretion would be expected to cause hyperphosphataemia early in CKD. However, this is prevented by the FGF23-Klotho axis.

Fibroblast growth factor 23 (FGF23)

- Acts with its co-receptor Klotho, expression of which is decreased in early CKD.
- Requires Klotho to activate FGF signalling.
- Increased in early CKD in response to a high phosphate load.
- Produced by osteocytes and acts on the renal tubules to decrease phosphate reabsorption.
- Able to maintain plasma phosphate in the normal range in early CKD.
- Suppresses the renal 1-α hydroxylase receptor, thereby reducing the synthesis of $1,25(OH)_2D$ and therefore GI phosphate absorption (and, adversely, Ca).
- Significantly linked with cardiovascular mortality.

CKD progression

- FGF-23 is no longer able to compensate for the decreased glomerular filtration of phosphate and the plasma phosphate rises.
- The high plasma phosphate stimulates the secretion of PTH, which is also a phosphaturic hormone.
- ↓Renal 1α hydroxylase activity results in ↓ conversion of 25(OH)D to $1,25(OH)_2D$.
- ↓$1,25(OH)_2D$ levels stimulate PTH secretion via the vitamin D receptors (VDR) in the PTH gland.
- ↓Plasma Ca stimulates PTH via the Ca sensing receptors (CaSR).

See Fig. 18.2.

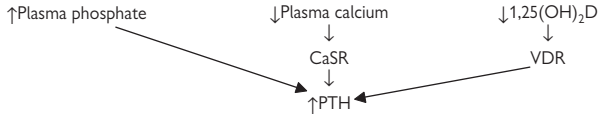

Fig. 18.2. Factors that stimulate PTH production.

CaSR

- Vital to the minute-to-minute control that maintains the plasma ionized Ca within a narrow physiological range.
- If there is a small fall in ionized Ca, the PTH increases steeply, resulting in normalization of the serum Ca.
- In contrast, a rise in ionized Ca acts via the CaSR to shut off PTH secretion.
- Present in high concentrations on parathyroid cells and is also on bone cells and along the nephron.
- Stimulated by magnesium (to suppress PTH).

All the actions of PTH are to increase the plasma Ca (see Fig. 18.3) by:

- Increasing renal tubular reabsorption of Ca.
- Increasing GI Ca absorption by increasing 1 α hydroxylation of 25(OH) D to $1,25(OH)_2D$.
- Increasing bone turnover and, therefore, efflux of Ca from bone and decreasing renal tubular reabsorption of phosphate.

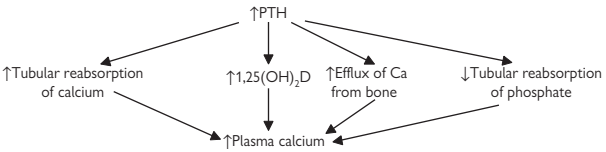

Fig. 18.3 Effects of PTH.

However, this creates a vicious circle of ongoing PTH stimulation, because:

- The increase in $1,25(OH)_2D$ augments phosphate absorption (alongside Ca), which in turn, stimulates PTH secretion further.
- CKD decreases the expression of the CaSR in the parathyroid glands so that Ca sensing is altered so that there is an increase in the set point for Ca (the Ca level at which there is a 50% reduction in PTH) and a change in the degree of suppression by Ca throughout the Ca sensitive range.
- High plasma phosphate levels also increase the set point for Ca.

Persistent stimulation of the parathyroid glands leads to PTH resistance (Fig. 18.4). The logic, therefore, has to be that prevention of the process starting by early dietary intervention with phosphate restriction, and the use of phosphate binders and vitamin D as soon as metabolic derangements are detected, must be beneficial.

Persistent parathyroid stimulation
↓ Half-life of parathyroid cells is 30 years
Parathyroid hyperplasia
↓
Reduced VDR and CaSR expression
↓
Less suppression of PTH by $1,25(OH)_2D$ and calcium
↓
Nodular hyperplasia
↓
Need for parathyroidectomy

Fig. 18.4 The evolution of resistance to PTH.

Renal osteodystrophy

Normal bone turnover

During normal bone turnover:

- Osteoblasts form a layer at the site of new bone formation. Some become trapped in new bone and become osteocytes.
- Osteocytes enable metabolic exchange between the tissue fluids and bone, and withdraw or deposit minerals.
- Osteoclasts lie on bone surfaces at the sites of reabsorption. They organize the architecture of bone structure. Their activity is increased by PTH.
- Bone tissue is formed by osteoblasts, maintained by osteocytes and resorbed by osteoclasts.

- These cells originate from mesenchymal cells that are capable of differentiating into fibroblasts, bone, or cartilage cells.

The effect of PTH on the skeleton is to increase the activity of osteoclasts and osteoblasts:

- High PTH levels cause high bone turnover (osteitis fibrosa) with:
  - increased osteoclasts and bone resorption;
  - increased osteoblasts and bone formation, with increased osteoid and non-lamellar bone;
  - marrow fibrosis.
- Low PTH levels cause low turnover (adynamic) bone disease:
  - normal or reduced osteoid;
  - low or diminished numbers of osteoclasts and osteoblasts.

Both low and high bone turnover lead to bone pain, fractures, deformities and growth problems, and contribute to CVD.

Radiological changes

Radiological changes of CKD-MBD include rickets, hyperparathyroidism and osteosclerosis, with:

- Periosteal erosions.
- Elevation and widening of the zone of provisional calcification with a coarse trabecular pattern.
- Vertebral collapse, alternating with areas of osteosclerosis, giving the appearance called rugger jersey spine.

Radiological changes occur late and bone X-rays may be normal even with moderate hyperparathyroidism.

Vascular calcification

Cardiovascular disease (CVD) is the major cause of mortality in patients with CKD. Risk is increased 30-fold in comparison with the age-matched population, and much more in patients on dialysis. Calcification of the vascular media is characteristic of CKD.

- The most important factor contributing to this is the plasma phosphate.
- Plasma phosphate is an independent predictor of mortality in adults with CKD.
- Hyperphosphataemia causes osteoblastic differentiation of vascular smooth muscle cells that leads to vascular calcification.
- Resultant stiffening of the blood vessels causes diastolic dysfunction, hypertension and increased cardiac work.
- Ca × phosphate product, PTH and FGF-23 also contribute to CVD in CKD-MBD.
- Vitamin D levels both above and below the normal range are associated with vascular calcification.

Aims of management of chronic kidney disease mineral bone disorders

- To maintain normal bone turnover and therefore prevent symptoms of bone pain and fractures.
- To allow normal growth.
- To prevent CVD and soft tissue calcification.

It is important to intervene early in the course of CKD to prevent escape of the parathyroid glands from normal control mechanisms.

Phosphate control

Phosphate has probably the best described spectrum of toxicity of all molecules that circulate in excess in CKD:

- Decreased renal phosphate excretion plays a major role in the onset of hyperparathyroidism.
- Plasma phosphate levels are positively and independently correlated with an increasing risk of death from CVD: as phosphate levels increase above 5.6mg/dL (=1.8mmol/L), the hazards ratio for mortality increases by 6% for every 1mg/dL (=0.3mmol/L) increase in serum phosphate.
- Phosphate causes vascular calcification, which leads to diastolic dysfunction, hypertension and increased cardiac work.

What phosphate level should we aim for?

- There is an association between phosphate levels and coronary artery calcification even in young adults without kidney disease.
- In patients with CKD, rising phosphate levels within the normal range are associated with a greater prevalence of vascular and valvular calcification.
- There are no clinical trials addressing the issue of plasma phosphate levels and mortality, although one study has demonstrated that the use of any type of phosphate binder, even with phosphate levels in the normal range, is associated with decreased mortality in patients on haemodialysis.
- Plasma phosphate varies throughout childhood, falling steeply from birth until the age of 1–2 years, then continuing to fall more slowly until the age of seven years (Fig. 18.5).
- The optimum target is not clear, but a plasma phosphate level that is persistently at the upper limit of normal implies that there are times when it is above normal. It makes sense, therefore, to try to keep the plasma phosphate around the 50th centile.

Dietary phosphate is principally in protein containing foods, and dairy products in particular. Processed foods contain phosphate in significant quantities as it is a component of moisture and flavour enhancers.

- A normal adult diet contains around 800–1500mg of phosphate, of which 50–70% is absorbed, depending on serum phosphate and vitamin D levels.
- $1,25(OH)_2D$ increases phosphate absorption to as much as 80–90%.
- In early CKD, dietary restriction may be sufficient to control plasma phosphate levels.
- Table 18.10 shows a suggested weight related daily dietary phosphate intake for children with CKD.
- Because restriction of dietary phosphate has its principal effects after meals, there may be no change in the morning plasma phosphate levels, so plasma values obtained in the afternoon are more useful in monitoring the effect of phosphate restriction or phosphate binders.
- The problem with dietary intervention is that foods high in phosphate are also usually high in Ca and vitamin D, so that nutritional 25(OH)D and Ca deficiency is common.

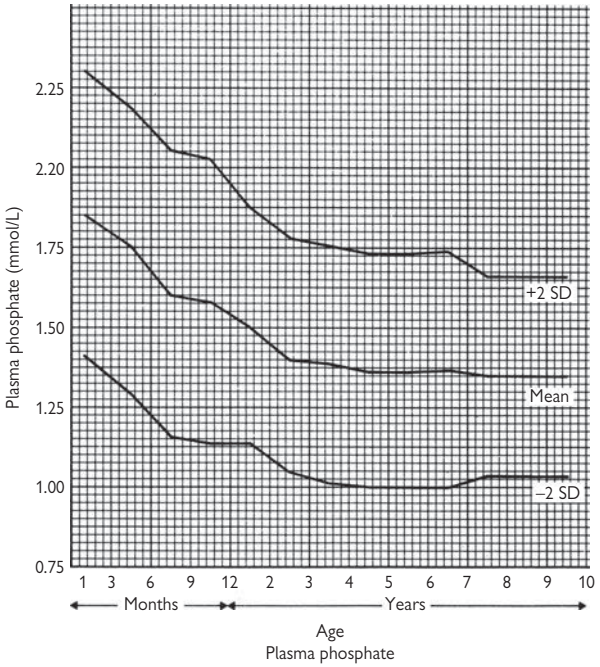

Fig. 18.5 Phosphate centiles according to age. Dietary control of phosphate. Reproduced with permission from Clayton BE, Jenkins P, Round JM, (eds). (1980). *Paediatric Chemical Pathology: Clinical tests and reference ranges*. Oxford: Wiley Blackwell.

Table 18.10 Weight-related suggested daily dietary phosphate intake for children with CKD

Body weight (kg)	Phosphate allowance (mg)
<10	<400
10–20	<600
20–40	<800
>40	<1000

Phosphate binders

As CKD progresses, the majority of patients need a phosphate binder to reduce phosphate absorption. Phosphate binders are divided into Ca containing and non-Ca containing:

- Ca-containing preparations have been used the longest and are by far the most widely used phosphate binder, but have fallen out of favour because of their theoretical link with soft tissue calcification; the fear of ectopic calcification with excess Ca intake has lead to a switch to newer non-Ca containing drugs.
- Currently there is no Ca-free phosphate binder that is licensed for use in children.
- Phosphate binders must be given with food and must not be given at the same time as Fe preparations as they form insoluble compounds in the gut. All the phosphate binders may have GI side effects. Preparations and cost of commonly used phosphate binders are shown in Table 18.11.

Table 18.11 Preparations and cost of commonly used phosphate binders

Preparation	Cost per tablet/capsule
Ca-containing preparations	
$CaCO_3$ 250mg dispersible (special) -disperse in water	21p
$CaCO_3$ 1.25g (Calcichew®)	9p
$CaCO_3$ 2.5g (Calcichew® Forte)	22p
$CaCO_3$ 1.5g (Adcal®)	7p
Calcium acetate 1g (Phosex®)	11p
Calcium acetate 500mg (Phosex®): this strength not licensed (swallow whole, can be crushed—NB calcium acetate 1g has 'approx 2 × binding capacity of Calcichew® 1.25g')	9p
Non-Ca preparations	
$MgCO_3$ 500mg (special) (5mmol Mg per capsule)	35p
Licensed in adults on dialysis	
Sevelamer tablets 800mg (Renagel®) Swallow whole.	66p
Lanthanum carbonate 500mg tablets (Fosrenol®): to be chewed	£1.27

Calcium-containing phosphate binders

- Dissociation of $CaCO_3$ is maximal below a pH of 5, whereas maximal binding of Ca to phosphate is at a higher pH. It is not, therefore, as effective when given with H2-blockers or proton pump inhibitors.
- Ca acetate has better solubility over a wider range of pH. This means that Ca acetate has a greater binding capacity for the same elemental Ca content so that less Ca is absorbed (Table 18.12).
- Ca absorption is greater if the binder is taken between meals, when it acts as a Ca supplement.
- Absorption varies with plasma $1,25(OH)_2D$ levels, being as low as 3% in deficiency to presumably higher than the expected normal range in patients who are prescribed activated vitamin D, when hypercalcaemia may occur.
- The main issue with Ca-containing binders is the risk of absorption of Ca that cannot be excreted if urine production is reduced, resulting in hypercalcaemia and a risk of ectopic calcification.

Table 18.12 Ca-containing phosphate binders

	Elemental Ca content %	% Ca absorbed	Phosphate (mg) bound per mg Ca absorbed	Phosphate (mg) bound by 1g
Calcium carbonate	40%	20–30%	1mg P per 8mg Ca	39mg
Calcium acetate	25%	20% with meals, 40% between meals	1mg P per 1–3mg Ca	45mg

Non-Ca-containing phosphate binders

Magnesium carbonate

- $MgCO_3$ is not commonly used, due to its propensity to cause diarrhoea.
- It is less effective than Ca salts.
- It may be a problem for children on dialysis, who are often already hypermagnesaemic.

Sevelamer hydrochloride

- Sevelamer is a non-absorbable polymer of allyamine hydrochloride.
- It functions best at pH 6–7 in the small intestine.
- It acts like an exchange resin; organic anions, and in particular phosphate, bind to cationic amine groups, displacing the chloride moiety. For this reason an associated metabolic acidosis is common. Sevelamer is now available as the carbonate, which may remove this side effect.
- As well as phosphate, sevelamer binds bile salts, thereby exerting a beneficial effect on plasma total and low density cholesterol, but on the other hand, sevelamer also binds fat soluble vitamins.
- The tablets need to be swallowed, and are difficult to use in children who are dependent on tube feeds because they form a gel that swells inside the tube causing tube blockage.

- Hypercalcaemia is less common, but many children need Ca supplements.
- Sevelamer may attenuate the progress of coronary and aortic calcification when it is already established, probably through its effects on blood lipids, but there is no proven benefit over other binders in its prevention in patients in whom calcification has not started.
- Sevelamer is of benefit in patients who have a high dietary Ca intake. However, children on a low phosphate diet who are not receiving a Ca-containing phosphate binder probably do not have a positive Ca balance when they are on maintenance dialysis.
- KDOQI recommends that in children exclusively on sevelamer, a higher dialysate Ca concentration and/or Ca supplementation with a Ca-containing phosphate binder is used.

Lanthanum carbonate

- Lanthanum is a trivalent cation that binds phosphate ionically and is active over a wide pH.
- Concerns centre around its safety because of the potential for its accumulation in the body, particularly in bone and liver, but absorption is low; less than 0.0013% is absorbed and is then excreted in bile.
- Studies in adults show that binding is similar to other calcium binders, and there is less hypercalcaemia and a similar incidence of hypocalcaemia to sevelamer.
- Lanthanum has now been used for 6 years with no evidence of significant side effects. There are no studies in children.

Case for and against calcium-containing phosphate binders

Recently, there has been a swing away from Ca-containing phosphate binders towards the routine use of sevelamer. The concern is that with the large doses of Ca from Ca-containing phosphate binders, coupled with decreased urinary excretion of Ca, particularly in the face of low bone turnover, hypercalcaemia will occur and cause soft tissue calcification. Although this is a theoretical possibility, evidence of an improvement in survival in patients taking sevelamer is lacking.

Evidence for the use of calcium containing phosphate binders in children

- Vascular calcification in paediatric patients is not a new phenomenon, and was seen at a time when aluminum hydroxide was the only commonly used phosphate binder.
- Coronary artery abnormalities were identified at post-mortem in 12 children who had been on haemodialysis in the 1970s, and soft tissue calcification was present in 60% of autopsies undertaken in 120 children with uraemia, dialysis, or renal transplants who died between 1960 and 1983.
- Most studies are in adults, but there are dangers in extrapolating adult data to children, in whom there is the added dimension of a need for a positive Ca balance in the growing skeleton.
- It has to be remembered that not all hypercalcaemia is due to intestinal Ca absorption, and that high bone turnover itself can do this by increasing the efflux of calcium from bone. Indeed, hypercalcaemia is described with both sevelamer, and lanthanum and vascular calcification is seen in adult pre-dialysis CKD patients who are not prescribed any phosphate binder.

Evidence against calcium containing phosphate binders in children

- Some, but not all paediatric studies have identified a relationship between Ca-containing phosphate binder intake and cardiac calcification, left ventricular mass (LVM) and/or carotid intima media thickness (CIMT).
- The serum Ca level does not reflect the total body calcium load.
- It is likely that episodes of hypercalcaemia in patients on dialysis, in whom calcification inhibitors are compromised, will worsen vascular calcification, particularly in association with high plasma phosphate.

Calcium

Of the total body calcium, 99% is in the skeleton, 0.6% in soft tissues, and 0.1% in extracellular fluid. Total skeletal calcium increases from approximately 25g at birth to 900 and 1200g in adult females and males, respectively.

- At low dietary Ca intakes a greater proportion is absorbed (≈34%), and is proportional to circulating 25(OH)D levels.
- At higher dietary intakes there is less influence of vitamin D on calcium absorption, and less calcium is absorbed (≈29%), i.e. there is adaptation to low 25(OH)D levels and dietary calcium intake.
- The amount of Ca incorporated into the skeleton increases up to a threshold dietary intake, above which no further bone accumulation occurs. This threshold is influenced by age such that during periods of rapid growth, i.e. infancy and adolescence, Ca balance is at its highest. These high Ca requirements are in comparison with the much lower values in adults (Table 18.13).
- The normal range for calcium parallels that of phosphate throughout childhood (Fig. 18.6).
- A low phosphate diet is by definition also low in Ca (and 25(OH)D), and many children may be relying on their phosphate binder to provide adequate Ca intake.
- KDOQI recommends intake of 100% of the DRI (dietary reference intake) for calcium, and limitation of the calcium intake from binders and dialysate solutions to < 2 × DRI or <2500mg elemental Ca.
- Ca balance is difficult in oliguric patients on dialysis. Dialysate Ca concentration of 1.75mmol/L provides an influx of around 800mg; 1.25mmol/L will maintain neutral calcium balance.

Table 18.13 The Ca intake above which no further incorporation of calcium into bone occurs and the Ca balance per day at different ages

Age, years	Ca threshold (mg/day)	Balance per day (mg/day)
0–1	1090	503 ± 91
2–8	1390	246 ± 126
9–17	1480	396 ± 164
18–30	957	114 ± 133

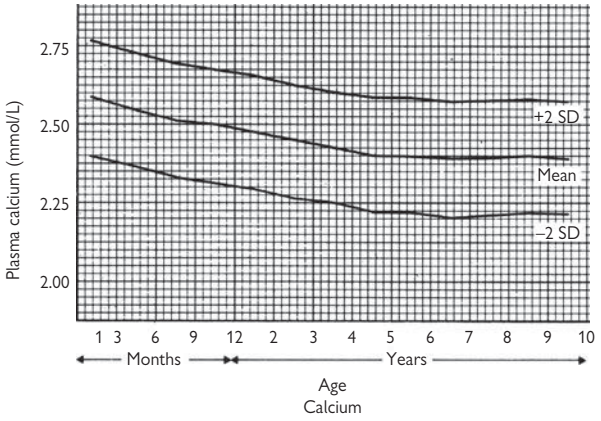

Fig. 18.6 Calcium centiles according to age. Reproduced with permission from Clayton BE, Jenkins P, Round JM, (eds). (1980). *Paediatric Chemical Pathology: Clinical tests and reference ranges*. Oxford: Wiley Blackwell.

Vitamin D

Evidence is emerging that the benefits of vitamin D extend beyond its effect on bone:

- It has anti-inflammatory properties and beneficial effects on the cardiovascular system.
- This has to be balanced against the risks of increased Ca and phosphate absorption, and hypercalcaemia and hyperphosphataemia.
- If it is possible to measure 25(OH)D, and this proves to be low, replacement doses of ergo or colecalciferol should be prescribed. Maintenance doses can be safely prescribed without routine measurement of levels.
- If the PTH is high despite 25(OH)D supplementation and phosphate control, the smallest possible dose of $1,25(OH)_2D$ to suppress the PTH (0.01microgram/kg/day) can be introduced and then the dose titrated against the PTH level. The lowest possible dose is used to prevent its depressant effect on osteoblasts and hypercalcaemia.
- If hypercalcaemia develops, the $1,25(OH)_2D$ should be stopped.
- New vitamin D analogues may suppress hyperparathyroidism without inducing hypercalcaemia.

PTH

Guidelines for the management of CKD-MBD hinge on the need to keep the PTH level within a fixed range, which is one that maintains normal bone turnover. Current guidelines were written as our understanding of the interplay with CVD was emerging, are largely opinion-based as they are extrapolated from adult studies and a small number of paediatric studies, and are largely out-of-date. The area is controversial, but there is a swing away from currently recommend very high levels in dialysis patients towards levels that are up to twice the upper limit of normal.

- European guidelines recommend maintaining the PTH in the normal range until dialysis, when up to 3 × the upper limit of normal (ULN) is acceptable.
- KDOQI recommends the normal range until CKD 4, when 1 to 2 × ULN is recommended and then 3 to 5 × ULN for patients on dialysis.
- When hyperparathyroidism becomes tertiary, with persistent hypercalcaemia, radiological changes, and no response to treatment, parathyroidectomies may become necessary.
- Ca sensing receptor blockers (e.g. cinacalcet) are effective in reducing plasma Ca, phosphate and PTH, and may be useful to try in the treatment of tertiary hyperparathyroidism before considering parathyroidectomy.

PTH assays

- PTH consists of 84 amino acids, 1–84PTH.
- Fragments of 1–84PTH circulate in CKD.
- Actions of the fragments depend on the presence of the amino or C terminal.
- 7–84PTH is the most important quantitatively in CKD. It antagonizes 1–84 PTH, acts at a specific C-terminal PTH receptor and is present in the parathyroid gland.
- Current 'intact' immunoradiometric assays (IRMA) measure 1–84PTH and also its fragments. The term 'intact' is therefore a misnomer.
- Newer assays (CAP-IRMA) measure only 1–84 PTH, but their use is not yet fully validated.
- The proportion of circulating PTH fragments can be calculated by subtracting the PTH level as measured by the new assay from the PTH level measured by the 'intact' assay. It increases with severity of CKD and with PTH levels outside the normal range (either high or low). The newer assays may, therefore, be useful in evaluating extreme PTH levels.

Further reading

Rees L, Shroff R. (2010). Phosphate binders: chalking out the differences. *Pediatr Nephrol* **25**(3)**:** 385–94.

Rees L. (2008). What parathyroid hormone levels should we aim for in children with stage 5 chronic kidney disease; what is the evidence? *Pediatr Nephrol* **23**(2)**:** 179–84.

Management: anaemia

Background

The anaemia of CKD begins when the GFR falls below 35mL/min/1.73m^2. It is a normochromic, normocytic anaemia, with a low reticulocyte count. Causes are:

- Decreased production of erythropoietin.
- Decreased red cell survival.
- Bone marrow inhibition due to uraemia or chronic inflammation.
- Iron, B12 or folate deficiency.
- Osteitis fibrosa.
- ACEIs.
- Blood loss during haemodialysis, from the GI tract or from repeated blood sampling.
- Aluminium toxicity.

Important general points

- Erythropoiesis stimulating agents (ESAs) are effective in improving the anaemia of CKD and the failing renal transplant.
- The requirement relative to body weight decreases with age, being highest in infants.
- Dosage intervals can be determined by response and vary with the product.
- Erythropoietin is conventionally given weekly subcutaneously and more frequently in HD patients when it is given IV up to 3 times per week.
- Darbepoetin alfa has a longer half-life than erythropoietin, and is usually given every 2–4 weeks subcutaneously in pre-dialysis patients, every 1–2 weeks SC in PD patients and weekly IV in HD patients. Pain at the injection site has been reported.
- Newer products being tested in children may enable administration as infrequently as monthly.
- Iron supplementation (oral or IV) is required.
- Oral Fe must be separated from phosphate binders and food by 2h before or an hour after. Proton pump inhibitors decrease absorption.
- All children should achieve a haemoglobin above the lower limit of the normal range for age, but the upper limit is not known. An increase in cardiovascular events in adults with higher haemoglobins has lead to a non-evidence-based recommendation of 10–12g/dL for children.
- The normal range for haemoglobin for age and the level at which to begin evaluation for anaemia (when the haemoglobin is approaching the lower end of the normal range) by the measurement of Fe and folic acid levels and commencement of Fe therapy are shown in Table 18.14.

Assessment of iron stores

As well as absolute Fe deficiency, functional deficiency occurs when there is a need for a greater amount of Fe to support haemoglobin synthesis than can be released from Fe stores.

- High Fe availability is required to maximize the response to ESAs.
- Serum ferritin reflects body Fe stores and needs to be kept between 100 and 500micrograms/L. However, it is an acute phase reactant

so results may be difficult to interpret in the infected child, and CRP should be measured at the same time.

- Transferrin saturation is a marker of the amount of Fe available for incorporation into haemoglobin and should be >20%.

Management

See Fig. 18.7.

Table 18.14 Normal range for haemoglobin throughout childhood

Age range (years)	Mean haemoglobin level (g/dL)		Range or SD	5th percentile	
	Boys	Girls		Boys	Girls
0–0.5	11.5		9.5–13.5	9.5	
0.5–1	12.0		10.5–13.5	10.5	
1–2	12.0	12.0	±0.8	10.7	10.8
3–5	12.4	12.4	±0.8	11.2	11.1
6–8	12.9	12.8	±0.8	11.2	11.5
9–11	13.3	13.1	±0.8	12.0	11.9
12–14	14.1	13.3	±1.1	12.4	11.7
15–19	15.1	13.2	±1.0	13.5	11.5

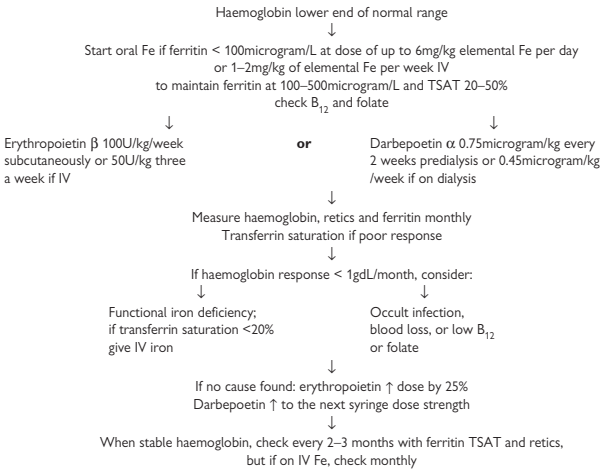

Fig. 18.7 Commencement of an ESA.

Darbepoetin α

- Darbepoetin α is a hyperglycosylated derivative of erythropoietin with a longer half-life.
- Darbepoetin α is available in the following strengths—20, 40, 60, 80, 100, 150, 300, and 500microgram as prefilled syringes or a prefilled disposable injection pen device (pen not advised if <25kg as easy bruising).
- The complete vial always needs to be used; due to the unpredictability of mixing of the active drug in its suspension, incomplete use of the total dose will lead to administration of an unknown quantity of darbepoetin. Therefore, an increase in dose can only be according to the strengths available.
- The withdrawal of some preparations of erythropoietin β (cartridges for use with the recopen and prefilled syringes 1000U) necessitates a change to darbepoetin for most children excluding infants.
- Darbepoetin α is approved for correction of anaemia and maintenance of a normal Hb in children age >11 years and Hb maintenance if age >1 year and converting from stable doses of erythropoietin. It can be used off license for anaemia correction at age 3–11 years. There is minimal information on the use of darbepoetin α in infants age <1 year who should be treated with erythropoietin β and then remain on erythropoietin β or converted to darbepoetin α age >1 year.
- Starting dose for children not previously receiving an ESA:
  - *pre-dialysis:* 0.75microgram/kg SC every 2 weeks;
  - *peritoneal dialysis:* 0.45microgram/kg SC weekly;
  - *haemodialysis:* 0.45microgram/kg IV weekly.
- Check the haemoglobin 2 weeks after starting darbepoetin α. If the haemoglobin has risen >1g/dL withhold the dose for a week and then give the next smallest dose strength, e.g. if receiving 40microgram go to 30microgram.
- If the haemoglobin increase is <1g/dL after 2 weeks do not change dose. However, if after 4 weeks the increase is still <1g/dL, increase the dose to the next syringe strength. Do not increase dose more frequently than every 4 weeks.
- Continue until the target haemoglobin is reached.
- *Maintenance dose when target Hb achieved:* decrease the frequency of injections for predialysis or PD and increase proportionately the total dose at each injection: e.g. predialysis patient (25kg) requiring 20microgram darbepoetin α every 2 weeks will need 40microgram every 4 weeks:
  - *pre-dialysis:* SC every 3–4 weeks;
  - *peritoneal dialysis:* SC every 2–3 weeks;
  - *haemodialysis:* IV every 1–2 weeks.
- *Conversion from erythropoietin β:*

Weekly EPO dose (U) ÷ 240 = weekly darbepoetin α dose (microgram)

  - i.e. PD patient maintained on 5000u EPO β weekly will need 20microgram darbepoetin α weekly or 40microgram every 2 weeks (note adjustments of dose to correlate with prefilled syringe doses available);
  - children must be on a minimum weekly EPO β dose of 1200U (approx) to convert to an equivalent minimum available dose of darbepoetin α, i.e. 10microgram every 2 weeks.

Table 18.15 Dose of IV Fe according to ferritin and TSAT levels

	Ferritin (microgram/L)	TSAT	Dose	Maximum single dose
Maintenance dose	>100 and <500	>20%	2mg/kg/dose given every 2 weeks	100mg
Accelerated dose	<100	<20%	7mg/kg/dose × 1 dose for first week then 2mg/kg/dose given once every 2 weeks	200mg 100mg
No treatment	>500	>50%		

Maintenance intravenous iron therapy for children on haemodialysis

All IV Fe formulations may be associated with immune-mediated reactions that may lead to anaphylaxis (more common with Fe dextran formulations) and the release of bioactive and partially unbound Fe into the circulation by the Fe agent, causing oxidative stress and hypotension (non-dextran forms). Most centres now use Fe sucrose, which carries less risk:

- Fe substitution is critical for optimal response to ESAs. Oral Fe may be poorly absorbed and may not be able to keep pace with the requirements of the marrow.
- IV Fe can be easily given to children on haemodialysis.
- Children on maintenance IV Fe therapy do not need oral supplements.
- The serum ferritin (microgram/L) should be measured monthly. Fe (μmol/L) and transferrin (μmol/L) should be measured if response to the ESA is poor.
- Transferrin saturation (TSAT) can be calculated as follows:

$$\text{TSAT} = \text{Fe (μmol/L)}/2 \times \text{transferrin (μmol/L)}\ (\%)$$

- Treatment depends on the results of the serum ferritin and TSAT (Table 18.15).

Administration of IV iron

Iron (III)-hydroxide sucrose complex (Venofer®)—'off label' use in children

- Venofer® must only be administered by the IV route, either by slow IV injection at a rate of 1mL undiluted solution/min (i.e. 5min/100mg ampoule), or by IV infusion.
- Extravasation of IV iron causes a painful tissue reaction; secure IV access must be obtained prior to administration.
- Before administering the first dose to a new patient, a test dose of Venofer® must be given as follows:
  - *IV injection*: 0.5–1mL (10–20mg,) should be injected slowly over a period of 1–2min. If no adverse events occur within 15min of completing the test dose, then the remaining portion of the injection may be given;

  - *intravenous infusion:* preferred route for patients not on haemodialysis. Dilute 5ml Venofer® (100mg Fe) in 100mL 0.9% NaCl. No other solution should be used. Infuse the first 25mg iron (i.e. 25mL solution) as a test dose IV over a period of 15min; if no adverse reactions occur during this time then the remaining portion of the infusion may be given at a rate of not more than 50mL in 15min. (Suggested infusion rate = 2mg iron (2mL solution) per min.)
- Facilities for cardiopulmonary resuscitation must be available because allergic or anaphylactoid reactions, and hypotensive episodes may occur.
- Venofer® may be administered during the middle of the haemodialysis session directly into the venous limb of the dialyser under the same procedure as for IV administration.

Contraindications to IV iron

- Fe overload or disturbances in utilization of Fe.
- History of hypersensitivity to parenteral Fe preparations.
- History of asthma, eczema, or other allergic disorders or anaphylactic reactions.
- Clinical or biochemical evidence of liver damage.
- Acute or chronic infection.

Side effects of IV iron

- Very rarely, anaphylaxis or other allergic reactions can occur—if so, discontinue promptly. Allergic reactions have been more commonly observed when the recommended dosage is exceeded.
- Occasionally, metallic taste, headache, nausea, vomiting.
- Hypotension may occur if the injection is administered too rapidly.
- Less frequently, abdominal disorders, paraesthesia, muscular pain, fever, urticaria, flushing, oedema of the extremities, phlebitis, and venous spasm at site of injection.

Pure red cell aplasia with anti-erythropoeitin antibodies

- Consider diagnosis if escalating dose of ESA or epoetin dose >350units/kg/darbepoetin α > 1.5microgram/kg/week.
- Occurred particularly in association with epoetin alfa (Eprex®), mostly if given subcutaneously. The incidence has decreased since the method by which Eprex® is stored and reconstituted was changed.
- Has also been reported rarely with epoetin beta and darbepoetin.
- Usually recovers, but may need immunosuppression.

Benefits of treatment of anaemia

- Anaemia may contribute to decreasing progression of CKD.
- Amelioration of left ventricular hypertrophy (LVH).
- Improved quality of life and decreased hospitalization.
- Reduced need for transfusion, with its risks of infection and HLA sensitization.

Further reading

Koshy SM, Geary DF. (2008). Anemia in children with chronic kidney disease. *Pediatr Nephrol* **23:** 209–19.

Management: immunization schedule for infants and children

Background

All children must complete all routine childhood vaccines. Bacille Calmette-Guérin (BCG), Varicella, pneumococcal polysaccharide (PPV) and hepatitis B vaccines must be added in children approaching RRT. Immunizations must begin as soon as possible in the child born with severe CKD (including infants with congenital nephrotic syndrome) as the schedule can rarely be completed before 16 months of age. Only in exceptional circumstances can transplantation occur without completing the full vaccination schedule (see Table 18.6 for pre-transplantation immunization schedule).

Table 18.16 Pre-transplantation immunization schedule

Vaccine	Dose	Date given
BCG SSI (see requirements for tuberculin skin test)	1	
Dip, Tet, aPertussis, Inactivated polio, *Haemophilus Influenza* B. (Pediacel ®)	1	
	2	
	3	
HIB vaccine (without DtaP/IPV)	1	
Menigococcal Group C conjugate	1	
	2	
	3	
Pneumococcal Conjugate(PCV) (Prevenar® 13) Do not give if >5-years	1	
	2	
	3	
OR if not previously immunized Aged 13-months–5-years (2 doses only)	1	
	2	
Pneumococcal Polysaccharide (PPV) (Pneumovax® II) for additional Pneumococcal cover >2-years	1	
Hepatitis B	1	
	2	
	3	
Booster dose	4	

(Continued)

Table 18.16 (*Contd.*)

Vaccine	Dose	Date given
Measles, Mumps & Rubella (MMR)	1	
(at the same time as Hib/Men C and Prevenar® 13)	2	
Varicella vaccine	1	
	2	
Dip, Tet, aPertussis, Inactivated polio	1	
(Infanrix-IPV®) at school entry		
Influenza vaccine <13-years (2 doses if not previously vaccinated)	1	
	2 then annually	
Diphtheria (low dose), Tet, Inactivated polio (Revaxis®) at 13–18-years	1	
Human Papilloma Virus (HPV) vaccine	1	
For girls age 12–13-years. (do not mix brands)	2	
	3	

Important general points

- Routine immunization in the first year of life with the following vaccines: diphtheria, tetanus, acellular pertussis, inactivated polio, *Haemophilus influenza* type b conjugate (Hib) as (Pediacel®); pneumococcal conjugate vaccine (PCV) as (Prevenar® 13) and meningococcal group C conjugate.
- Before school or nursery school entrance (but preferably 1 year after completing the primary course) a booster of diphtheria, tetanus, acellular pertussis and inactivated polio (Infanrix-IPV ®)should be given.
- Mumps, measles and Rubella (MMR) may be given at 12 and 15 months in the infant on or approaching RRT.
- Over 10 years of age, give a booster dose of low dose diphtheria, tetanus and inactivated polio (Revaxis ®), and MMR.
- Girls age 12–13 years should be offered human papilloma virus (HPV) vaccine.
- Influenza vaccine should be given annually plus H1N1 during pandemics or as part of seasonal flu vaccine.

Bacille Calmette-Guérin, Statens Serum Institut

May be given to some newborns routinely. BCG can be given to children up to the age of 6 years without a prior Mantoux test, unless they were born in or had visited (>1 month) a high-incidence country. Over the age of 6 years give only if tuberculin skin test (Mantoux) negative. (NB. Tuberculin testing should not be carried out within 3 weeks of receiving a live vaccine as response may be falsely negative).

Bacille Calmette-Guérin dose

- *Dose:* <12 months 0.05mL by intradermal injection.
- *12 months and older:* 0.1mL by intradermal injection.
- BCG may be given simultaneously with another live vaccine, but if not given at the same time, allow an interval of at least 3 weeks. In neonates the vaccine must be given intradermally into the upper arm only (preferably the left deltoid region).
- Do not use same arm for further immunization for 3 months.
- Delay transplantation for 3 months.

Hepatitis B

- All patients who will need RRT (Table 18.17) should be immunized against hepatitis B, preferably pre-emptively, whilst the GFR remains relatively high.
- Vaccine can be given at any age at intervals of 0, 1, and 6 months.
- An accelerated course can be used so that the third dose is given 2 months after the first dose (i.e. doses at 0, 1, and 3 months, and a booster dose at 6–12 months.
- The anterolateral thigh (IM) is the preferred site in infants and young children. The deltoid muscle is the preferred site in older children. It should not be injected into the buttock as vaccine efficacy is reduced.

For pre-dialysis patients

- *Engerix B®(Glaxo Smith Kline) by intramuscular injection:*
  - 1 month to 15 years; 3 doses of 0.5mL (10microgram);
  - age 16–18 years; 3 doses of 1mL (20microgram).
- *HBVax Pro® brands (Aventis Pasteur):*
  - HBVax Pro Paediatric ® 1 month to 15 years; 3 doses of 0.5mL (5microgram);
  - HBVax Pro® age 16–18 years; 3 doses of 1mL (10microgram).

For dialysis patients

Doses are doubled and 4 doses are given at 0, 1, 2, and 6 months.

- *HBVax Pro® (Aventis Pasteur):*
  - 1 month to 15 years; 4 doses of 10microgram;
  - 16 years; 4 doses of 20microgram.

If HBVax Pro® is not available the following doses of Engerix B should be given:

- Age 1 month to 15 years; 4 doses of (0.5mL)10microgram.
- Age 16–18 years; 4 doses of (2mL) 40microgram.

Check anti-HBsAg antibodies 2–3 months after the third dose. Dialysis patients should be monitored annually and revaccinated if necessary.

- *>100IU/L:* protective, give booster every 5 years.
- *10–100IU/L:* poor responder, give booster at 1 and 5 years.
- *<10IU/L non-responder:* repeat course of vaccine.

Table 18.17 Immunization schedule for infants with CKD in whom renal replacement therapy (RRT) is imminent

AGE (months)- can be varied	BCG SSI *see notes for dose *Intradermal*	Diphtheria, Tetanus, acellular Pertussis, *Haemophilus influenza* type b-Hib and Inactivated Polio (Pediacel®) *Deep SC or IM*	7- valent Pneumococcal conjugated vaccine (Prevenar®) *IM*	Meningococcal Group C conjugate *Deep SC or IM*	Hepatitis B * see notes for accelerated immunization schedule *IM*	MMR (Measles, Mumps & Rubella) *deep SC or IM*	*Varicella-Zoster* Vaccine *SC*	Influenza Vaccine Given each autumn for patients age >6 months *IM*
0	√							
2	Or at any time up to age 6 years with no skin test required unless born in or visited (>1 month) a high incidence country	√	√					
3		√		√				
4		√	√	√				
6					√ (0.5mL)			
7					√ (0.5mL)			
12		√ (Hib no DtaP/IPV)	√	√	√ (0.5mL)	√		

13	After age 6 years only if negative skin test Do not test within 4 weeks of giving MMR vaccine Delay transplant for 3 months	If not previously immunized: at age >1 year–10 years give 1 dose Hib (but for full cover should have had 3 doses of Pediacel®)	<u>If not previously immunized</u>: Children 12 months–5 years: 2 doses separated by an interval of 2 months. (>5 years Conjugate vaccine is *not* given)		Booster doses may be required	If not predicted for RRT can have 2nd dose with pre-school booster	√
14							√
15						√	

After 2nd birthday, single dose of 23-valent pneumococcal polysaccharide vaccine (Pneumovax II®).

Before school or nursery school entry if not on transplant waiting list: booster doses of diphtheria, tetanus, acellular pertussis, inactivated polio (Infanrix-IPV®, Repevax®).

Over 10 years of age: booster dose of low dose diphtheria, tetanus, and inactivated polio (Revaxis®).

If schedule followed at 16 months, proceed to transplant.

Measles, mumps and Rubella (MMR) vaccine

- Give at 12 months (0.5mL by deep SC or by IM injection) at the same time as Hib/Men C and Prevenar® 13. If RRT not imminent, 2nd MMR can be given with pre-school booster. If in CKD stage 5, 2nd MMR can be given at 15 months of age (interval of at least 3 months after 1st vaccine).
- Children <4 years old with a GFR <30mL/min/1.73m^2 should have their pre-school/nursery school booster (2nd MMR) brought forward.
- Older children: a 2nd MMR is advised unless there is definite serological evidence of immunity.
- If administering at the same time as other injections, use a separate syringe and needle; give MMR first as it is less painful, and use a different limb—alternatively, a second appointment can be made.
- Live vaccines may either be performed on the same day or at least 3 weeks later.
- Check measles antibody response 2–4 weeks after completing MMR course.
- An initial negative or equivocal antibody result should be repeated. In vaccinated children who have had a previously positive measles IgG, but are found to be negative/equivocal on retesting, the conventional wisdom is that primed memory cells will respond to a measles challenge.
- If blood or blood products have been given 3 months prior to the test the measles IgG may be transiently positive and a retest will be required.
- Delay transplantation for 1 month after MMR course.

Varicella vaccine (Varilrix® or Varivax®)

- Can be given with, or 4 weeks after, MMR vaccine if non-immune (check titres).
- Ensure lymphocyte count >1.2 – 10^9/L.
- Delay for 5 months if patient has received immunoglobulin or a blood transfusion because of likelihood of vaccine failure due to passively acquired Varicella antibodies.
- Salicylates should be avoided for 6 weeks after Varicella vaccination as Reye's syndrome has been reported following the use of salicylates during natural Varicella infection.
- If a measles-containing vaccine is not given at the same time as the Varicella vaccine, an interval of at least 1 month must elapse between vaccines. Measles vaccination may lead to short-lived suppression of the cell-mediated response.

Dose

- From the age of 12 months, 2 doses (0.5mL) by deep subcutaneous injection (anterolateral area of thigh in younger children and deltoid region in older children) with an interval between doses of 4–8 weeks.
- Check titres (ELISA) after 2–3 months.
- Delay transplantation for 1 month after vaccination course if seroconversion demonstrated.

Pneumococcal vaccines

Pneumococcal polysaccharide conjugated vaccine-13 valent (Prevenar® 13)

Recommended for all children aged 2 months to 5 years. It is not necessary in children over 5 years of age.

- 3 single doses (0.5mL) by intramuscular injection, one each at 2 and 4 months of age, and one after the first birthday.
- Children aged 12 months to 5 years: 2 doses (0.5mL) with an interval of at least 2 months between doses.

Pneumococcal polysaccharide vaccine-23 valent (Pneumovax® II)

All children over 2 years of age who have received the conjugate vaccine (PVC) need a single dose (0.5mL) of 23 valent vaccine (PPV) to provide protection against the serotypes of *S. pneumoniae* not covered in the conjugate vaccine.

- Leave an interval of at least 2 months between the two vaccines.
- Children over the age of 10 years can be revaccinated if high risk (e.g. nephrotic syndrome).

Human papilloma virus vaccine

Offered to all girls aged 12–13 years and a catch-up programme is under way.

Dose

- 3 doses of 0.5mL by IM injection into the deltoid region. The 2nd and 3rd doses are given 1–2 and 6 months after the first dose. All 3 doses should be given within a 12-month period. If the course is interrupted it should be resumed, but not repeated.
- There are 2 brands of vaccine: Cervarix®, Gardasil® with differing dosage schedules. The vaccines are *not* interchangeable.
- Injection-site reactions are very common. Other side effects include GI disturbances, dizziness, headache.

Influenza vaccine

- Annual vaccination is recommended from the age of 6 months.
- In children the dose should be repeated after 4–6 weeks if not previously vaccinated.

Further reading

Department of Health (2006). *Immunization against infectious diseases*, 'Green book' and updates from the Department of Health. Available at: www.dh.gov.uk/greenbook

Update from DH: Gateway ref number: 15014 (vaccinations at 12 & 13 months of age JCVI meeting October 2010.

Preparation for renal replacement therapy

Background

The general principle is that transplantation should be the ultimate aim for the overwhelming majority of children with CKD stage 5 in whom active treatment is felt appropriate. Preferably transplantation should be performed within the 6-month period prior to the need for dialysis (pre-emptive transplantation). Children should prepared for a living or deceased donor transplant once the GFR is <15mL/min/1.73m^2 and it is clear that they are likely to require dialysis in the near future and/or are experiencing significant complications of their CKD, including growth failure. In this way dialysis may be avoided.

It is preferable to avoid dialysis because:

- Dialysis is disruptive to family lifestyle, schooling, and social interactions, and places huge demands on the family.
- Dietary and fluid restrictions are necessary on dialysis.
- Mortality is higher on dialysis than post-transplant.
- Avoidance of dialysis preserves vascular and peritoneal access sites for future use.
- Dialysis is associated with vascular calcification and risk of cardiovascular events.
- Well-being, growth, and development are improved post-transplant.

Discussions on choice of modality of RRT should begin at least 1 year before the anticipated date of starting. This enables:

- Preparation of child and family for RRT.
- Preparation of a relative as a living donor.
- Pre-emptive transplantation.

Preparation for transplantation

Investigations and procedures that need to be completed before transplantation (Table 18.18) are:

- Blood group and tissue typing.
- Is this to be a deceased donor or living related donor (LRD) transplant?
- If LRD, blood group potential donors and tissue type those with compatible blood group (Group O is the universal donor, group AB the universal recipient).
- ABO incompatible transplant can be considered; check ABO antibody titres.
- Check immunity to hepatitis B and C, measles, mumps, Varicella, HIV, cytomegalovirus (CMV), and Epstein–Barr virus (EBV).
- Ensure immunizations are complete (see 📖 this Chapter, 'Management: immunization schedule for infants and children', p.455).

Table 18.18 A suggested pre-transplant assessment check list

	Date	Comment/ result
Previous transplants		
LRD/cadaveric		
Blood group		
Tissue typing		
Cross-match (LRD)		
Immunization history		Separate sheet
Antibody results	Varicella	
	Measles	
	CMV repeat every 3 months if negative	
	EBV repeat every 3 months if negative	
	Hepatitis B	
	Hepatitis C	
	HIV	
US of aorta, IVC, and iliac vessels		
MRV/MRA (if previous femoral lines, transplant or child with VATER)		
Coagulation and procoagulation screen		
Bladder US		
Urodynamics		
Transplant ureter to be transplanted into		
Dental review		
Dialysis access		
Details of previous abdominal surgery		
Detailed interview with nephrology consultant		
Detailed interview with transplant surgeon		
Detailed interview with transplant sister		
Psychosocial assessment		

- Ensure bladder is safe for transplantation:
  - if there is complete bladder emptying on US it is likely to be satisfactory;
  - urodynamics will be necessary in children with structural renal anomalies that involve the bladder (e.g. severe VUR, posterior urethral valves, neuropathic bladder);
  - decide where the transplant ureter will be anastomosed.
- If there have been previous lines into iliac vessels, or a previous transplant, US and magnetic resonance angiography (MRA) and venography (MRV) to ensure vessel patency.
- Children with VATER (vertebral defects, anal atresia, trachea-oesophageal fistula with eosophageal atresia, renal defects, and radial dysplasia) may have a high dividing aorta and need MRA and MRV.
- Human leucocyte antigen (HLA) antibody measurement.
- Dental review, particularly looking for infection.
- Ensure that parents and child are fully informed.
- Ensure that the family and child have been offered a psycho-social assessment.

Coagulation and thrombosis screening prior to renal transplantation

Most important is the patient and family history.

Abnormalities of coagulation

- Is there a history of bleeding? e.g. delayed separation of the umbilical stump, bleeding post-Guthrie, severe/recurrent nosebleeds, surgical bleeding, easy bruising, menorrhagia.
- Is there a history of bleeding in family members?
- Has the child had previous invasive procedures without bleeding complications?

Management

- All patients should have a coagulation screen.
- In the absence of a personal or family history of bleeding, a child with a normal coagulation screen does not require further coagulation testing pre-surgery (including renal biopsy)—a normal activated prothrombin time (APPT) will exclude any factor deficiency (and abnormal lupus anticoagulant or anticardiolipin antibodies).
- If the APPT has been normal on a previous screen, then it is not possible for the patient to have a factor deficiency. If the APPT is acquired it is usually due to vitamin K deficiency or heparin contamination.
- In the event of an abnormal coagulation screen follow Fig. 18.8.

Thrombotic abnormalities

- Does the patient have nephrotic syndrome?
- Is there a history of clotting?
- Is there a history of multiple miscarriages in the mother?
- Is there a history of clotting in family members?
- Is there a history of deep vein thrombosis in any relative aged <40 years?
- Is there a personal or family history of autoimmune disease?

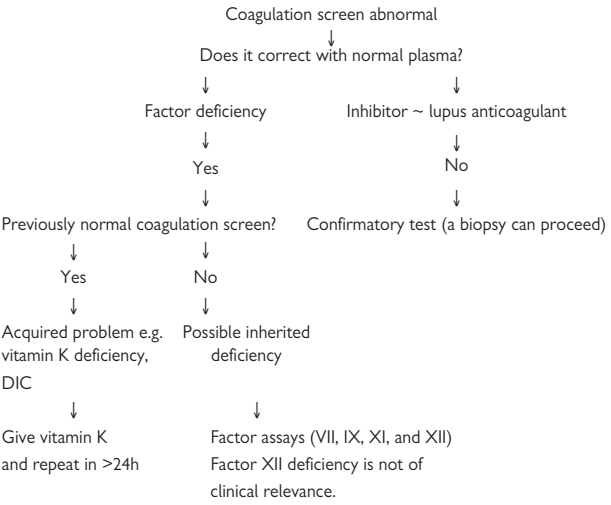

Fig. 18.8 Procedure if the coagulation screen is abnormal.

Management

If any of the thrombotic abnormalities responses are positive, check a thrombophilia screen (ThS).

- This screens for thrombotic tendency and for lupus anticoagulant (LA), which is an acquired abnormality.
- A positive LA is a common finding in children with renal disease and is not always clinically significant. If it is positive, follow Fig. 18.9.
- Inherited thrombophilias are rare:
  - deficiencies of protein C, protein S, and antithrombin III, and the prothrombotic polymorphisms factor V G1691A and factor II G20210A predispose to venous thromboembolism;
  - factor V Leiden (FVL) and the G20210A mutation, along with antiphospholipid antibodies (APA), lupus anticoagulant, and anticardiolipin antibody increase the risk of renal allograft thrombosis. It is not known whether other hypercoagulable states, such as hyperhomocystinaemia or the C677T polymorphism of the methylenetetrahydrofolate reductase gene affect risk;
  - anticoagulation has to be balanced against risk of bleeding; in patients with an identified thrombophilic risk factor, previous thrombosis or SLE, a plan for peri-operative heparin until the graft is well functioning and the child is mobile should be considered.
- Aspirin 1mg/kg body weight/24h as a single daily dose (maximum 75mg) is recommended for all children at the time of transplant and continued for 4 weeks post-transplant.
- Families should be fully informed about the risks of transplantation. A suggested check-list is given in Box 18.1.

Box 18.1 Information for parents of children going forward for renal transplantation

Patient survival

- Transplant survival for:
  - living donor;
  - deceased donor;
  - effect of HLA matching;
  - effect of donor age.
- Risks post-surgery:
  - fluid overload and the risk of need for ventilation;
  - hypertension, insulin-requiring (diabetes mellitus) and fits (convulsions/seizures);
  - the routine use of aspirin and renal venous thrombosis;
  - post-operative bleeding (from transplant surgery or gut) and lymphocoele;
  - primary non-function, delayed graft function and the need for dialysis;
  - management of disease recurrence and bacterial infection;
  - the need for scans/biopsies and the occasional need for return to theatre;
  - other complications (including increased co-morbidity).

Complications that may occur, usually not post-operative

- Acute rejection, drugs used to treat it, and the use of transplant biopsy.
- Chronic transplant loss (UTIs, chronic rejection, recurrent disease).
- Bacterial infection (line, UTI).
- Viral infection (chickenpox, CMV, EBV, and PTLD).
- Transplant artery stenosis.
- Urological complications needing surgery or intervention by a radiologist.
- Malignancy (including care with sun exposure).

Immunosuppressive drugs used and their side effects:

- Steroids.
- Azathioprine.
- Tacrolimus.
- MMF.
- Basiliximab.
- Antilymocyte globulin (ATG).
- Sirolimus.
- Ciclosporin.

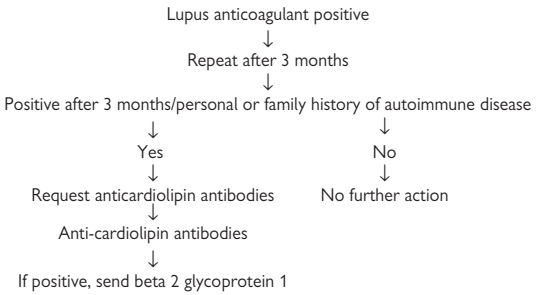

Fig. 18.9 Procedure if lupus anticoagulant positive.

Preparation for dialysis

Background and principles

If a pre-emptive transplant is not possible, the type of dialysis to be used must be discussed with the family. At any time around 20% of children on RRT are dialysed. Choice of dialysis modality varies around the world; PD is usually the first choice in Europe, whereas in the US HD is more common. There are some universal rules:

- Avoidance of HD in the infant due to difficulties with vascular access.
- Intra-abdominal pathology, social difficulties, or technique failure may preclude PD.

When should dialysis be started?

There is no absolute GFR when dialysis should be started. The need should be considered when the GFR falls to <15mL/min/1.73m^2. However, some children with maintained urine output can do well with very low GFRs if there is good nutritional management. Indications for dialysis are:

- Fluid overload.
- Uraemic symptoms (nausea, anorexia, lethargy, itching).
- Biochemistry cannot be controlled.
- Growth rate is decelerating.

Points to discuss when considering dialysis

- Will the dialysis be at home? If yes, a home visit is necessary to see if the housing is suitable.
- If HD, is the child of a size for a fistula? Will this be home HD or, if in a centre, standard or haemodiafiltration (HDF).
- For preparation for dialysis access see 📖 Chapter 19, p.465 and 📖 'Dialysis', p.393.

Effectiveness of types of dialysis

Only a well-functioning renal transplant can restore renal function, although most transplants do not maintain a normal GFR.

- Home nocturnal HD can deliver the equivalent to 50% normal renal function.
- HDF is the next most effective type of dialysis.
- Short daily HD delivers the equivalent of 25% of normal renal function.
- Conventional HD (4h × 3 per week) and PD deliver about 15% of normal renal function.

This page intentionally left blank

Chronic peritoneal dialysis

Principles of peritoneal dialysis

- Solute moves down the concentration gradient across the peritoneal membrane by diffusion and water by osmosis (ultrafiltration, UF).
- UF causes movement of solutes by convection, so that solutes may be carried across the membrane (solvent drag) even in the absence of a concentration gradient.

The efficiency of peritoneal dialysis is affected by:

- The peritoneal membrane.
- The peritoneal microcirculation.
- The dialysis compartment (type and volume of solution).

Insertion of the peritoneal dialysis catheter

The surgical technique

- Screen for nasal carriage of *Staphylococcus aureus* with a nasal swab. If positive check carers and use mupirocin 2% ointment to each nostril for 5 days and then for 5 days per month each month. Follow-up swabs should be taken at least 2 weeks post-treatment.
- IV antibiotic cover pre-operatively: one choice would be amikacin 10mg/kg (maximum 500mg) and teicoplanin 10mg/kg (maximum 400mg) one dose of each IV.
- Catheters with 2 cuffs (to prevent tracking of organisms from the exit site down the tunnel) and a downward pointing exit site (to prevent collection of debris) are preferable.
- A catheter that spirals at the intraperitoneal end reduces the risk of blockage of the catheter by bowel or omentum.
- Omentectomy will also reduce the chances of catheter blockage.
- A swan-neck tunnel reduces the risk of catheter displacement.
- The tip of the catheter should be in the lowest part of the pelvis without bending.
- The distal cuff should be 2cm from the exit site and the proximal cuff embedded in fascia.
- Any hernia should be repaired at the time of catheter placement.
- The exit site should be as small as possible, above the nappy in young children, and away from other stoma, e.g. gastrostomy, ureterostomy, etc.
- The catheter drainage should be checked before leaving theatre.
- The catheter should be flushed continuously with 10mL/kg dialysate until the dialysate is clear, then capped off with heparinized saline. Thereafter, the catheter can be flushed weekly until use.
- The catheter must be securely fixed to prevent movement at the exit site and dressings should not be removed for the first week as movement of the catheter within the tunnel prevents healing and results in leaks, exit site infection (ESI) and granulomas.
- Thereafter, the exit site should be cleaned once a week for the first 3 weeks (see 📖 'Care of the exit site and exit site infection', p.467).
- It is preferable to leave the catheter for 3 weeks to allow healing of the tunnel before use.

Complications of peritoneal dialysis catheters

- ESI and tunnel infections will result from inadequate catheter immobilization post-insertion (see 📖 'Care of the exit site and exit site infection', p.467). They can lead to peritonitis by tracking of infection down the tunnel. A new catheter cannot be inserted until the abdominal wall is free from infection.
- Post-surgical leakage of fluid may be due to a subcutaneous tunnel that is too large, a perpendicular tunnel, fluid retention and abdominal wall oedema, catheter blockage (peritoneal dialysis (PD) fluid will flow along the path of least resistance), or early commencement of dialysis. This can be treated by suspending dialysis and immobilizing the catheter. When dialysis is started low volumes should be used and if leakage persists the catheter should be replaced.
- Leakage after dialysis has been established is often due to catheter blockage.
- Catheter migration due to:
  - torque placed on catheter at the time of insertion which causes it to try to undo the bend inflicted on it;
  - too acute an angle of entry of the catheter to the peritoneal cavity;
  - the shallow pelvis of infants;
  - constipation;
  - adhesions or sclerosing peritonitis.
- The catheter can be repositioned laparoscopically and can be sutured if there is not too much torque. If there is, however, the catheter needs to be replaced.
- Cuff extrusion may also be caused by torque, by placement of the catheter cuff too near the exit site or by ESI or tunnel infection. The cuff may be shaved if there is no infection, but the catheter must be replaced if there is infection.
- Poor catheter drainage may be due to blockage by omentum. Many surgeons undertake routine omentectomy at the time of catheter insertion. If blocked, a laparoscopic approach can be taken to unblock it.

Care of the exit site and exit site infection

Catheter-related infections (exit site or tunnel) with subsequent peritonitis account for up to 20% of transfers to haemodialysis (HD). These infections are strongly linked to the nasal carriage of *Staphylococcus aureus*:

- The most important way to prevent infection and granuloma formation is immobilization of the catheter (Fig. 19.1).
- Screen 3-monthly for nasal carriage of *Staphylococcus aureus* and treat with mupirocin 2% ointment (and swab carer) if positive (see 📖 'The surgical technique', p.466).
- The exit site should be cleaned every other day, or daily if there is colonization or infection. A strict aseptic technique should be used. Aqueous chlorhexidine 0.05% is used until the exit site is clean and the chlorhexidine is then removed with sterile water.
- The exit site should be swabbed monthly on a routine basis or if there are signs of infection.
- If the exit site is positive for *Staphylococcus aureus*, but no clinical signs of infection (i.e. colonized), apply mupirocin 2% ointment to the exit site for 4 weeks and eradicate nasal carriage if present.

- If the exit site looks infected (red, tender, swollen, discharge, or granuloma) an ultrasound scan (US) can determine whether there is extension of infection down the tunnel. Topical mupirocin, oral antibiotics (usually flucloxacillin or ciprofloxacillin if a history of *Pseudomonas*) and an antifungal (usually nystatin orally) should be prescribed. Granuloma can be treated with silver nitrate sticks daily for 5 days.
- Flucloxacillin dose for PD patients:
  - 62.5mg three times a day age <1 year;
  - 125mg three times a day age 1–5 years;
  - 250mg three times a day age 5–10 years;
  - 250mg three times a day to 500mg age >10 years.
- Ciprofloxacin dose for PD patients:
  - 2.5–3.5mg/kg twice a day age 4 weeks to 1 year;
  - 5mg/kg twice a day age 1–18 years.
- If there is tunnel infection beyond the external cuff, consider removal of the catheter.
- If there is no response at 4 weeks repeat the tunnel US. If no tunnel infection, treat for a further 2 weeks and then consider removal if there is treatment failure.
- If there is no response at 4 weeks and tunnel infection, consider removal of the catheter.

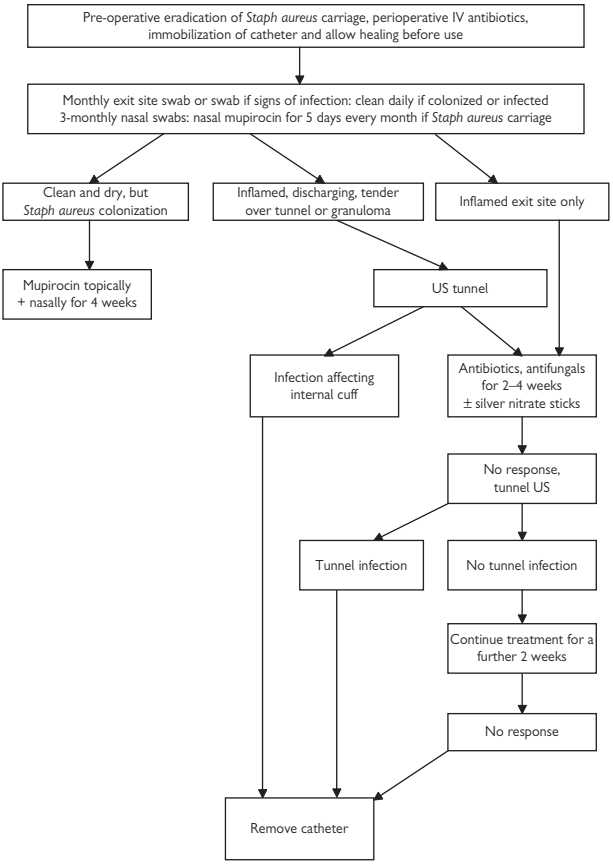

Fig. 19.1 Prevention and treatment of ESI in peritoneal dialysis.

Peritoneal dialysis solutions

- Dialysate solutions contain an osmotic agent, which is usually glucose. Osmotic UF can be increased by increasing the concentration of glucose (common concentrations are 1.36, 2.27, and 3.86%). The rate of absorption of glucose from the peritoneum varies; this affects the length of time for which the gradient remains effective.
- Exposure of the peritoneum to glucose containing dialysate results in an initial increase in the vascular surface area, which causes an increase in the peritoneal transport rates of small solutes and UF failure. This can be treated with short dwells and icodextrin. However, subsequent membrane thickening and scarring of blood vessels causes irreversible membrane failure and failure of the technique. Sclerosing-encapsulating peritonitis can also occur (see 📖 'Sclerosing peritonitis', p.481).
- Damage and pain can occur at filling because of the acid pH, which, in combination with lactate, is toxic to peritoneal cells; and because of the high osmolality. The pain usually settles as equilibrium occurs.
- Long-term toxicity results from glucose degradation products (GDPs), which develop during sterilization of dialysate if the pH is >3.5, and attach to the proteins of the mesothelial cells of the peritoneal membrane. GDPs may also contribute systemically to the pro-oxidative state of chronic kidney disease stage 5 (CKD 5).
- High glucose solutions should not be used more than is necessary because of this toxicity and also because the calories from the glucose contribute to obesity, hyperinsulinism, and dyslipidaemia.
- Icodextrin can be used for sustained high osmotic pressure. It consists of glucose polymers that are too large to diffuse across the peritoneal membrane, but are absorbed into the lymphatics. In the blood it is hydrolysed to maltose. It contains less GDPs. It is useful as a daytime dwell (last bag fill) in children on overnight CCPD. Sodium removal is relatively greater with icodextrin, so care must be taken to not induce hyponatraemia.
- Bicarbonate in peritoneal dialysate will cause precipitation of magnesium and calcium carbonate so that lactate, which is metabolized to bicarbonate in the liver, is commonly used. Disadvantages are that:
  - the pH of these solutions is 5.5–6.5, which may contribute to abdominal pain on filling;
  - lactate may contribute to peritoneal fibrosis.
- New solutions use separate bags so that the glucose can be sterilized at low pH and, therefore, GDPs do not form. Also, the bicarbonate can be mixed at inflow so that lactate is not necessary and the pH of the mixed solution is physiological. This results in less abdominal pain and less injury to the peritoneum.
- Amino acids can also be used as osmotic acids, and have the advantage of no GDPs and also providing a source of nutrition. However, they may increase plasma urea and acidosis.
- Na in dialysate is usually 132–134mmol/L. Most sodium is lost by convection (solvent drag), unless short exchanges are used, when free water removal increases relative to Na. Children (especially infants) may need Na supplementation, particularly if there are ongoing renal tubular salt losses or diarrhoea.

- Dialysate may contain calcium at 1.75mmol/L, when the ionized calcium is higher than blood, or 1.25mmol/L, which can be used to remove Ca if the child is on large doses of Ca-containing phosphate binders.

Types of peritoneal dialysis regimens

- *Continuous ambulatory peritoneal dialysis (CAPD):* fluid is instilled manually into the peritoneal cavity, and drained and replaced, usually four times a day. This type of dialysis may be better for the adolescent who wants to socialize in the evening. There is a higher rate of peritonitis due to more frequent catheter access. The risk of herniae and PD leaks is also higher.
- *Dialysis machines* for use at home can be programmed to deliver the correct regimen using computer technology. Information can be obtained retrospectively from the computer chip about all aspects of the dialysis at home, e.g. compliance, lost dwell times, catheter flow rates, etc. Fill volumes as low as 60mL can be delivered and can change by 10mL increments if necessary.
- *Automated PD (APD):* usually administered as continuous cycling overnight. This is usually the method of choice because:
  - life is not interrupted by dialysis procedures in the day;
  - the ability of APD to deliver short cycles, high dialysate flow rates and high intraperitoneal volumes make it particularly good for the high fluid intake of the infant diet;
  - fluid can be left in the abdomen during the day (last bag fill). This increases the dialysis prescription, UF, and clearance of middle molecules considerably; this is called continuous cycling peritoneal dialysis (CCPD), but the volume selected may be limited by the occurrence of abdominal symptoms that may affect nutritional intake or by the induction of abdominal hernias;
  - if the child is on PD overnight and the abdomen is left empty during the daytime, this is called nightly intermittent peritoneal dialysis (NIPD);
  - the clearance of both large and small molecules may be reduced by as much as one-third, but the occurrence of herniae is reduced;
  - another possible advantage is that the peritoneal cells and immunoglobulins may be reconstituted during the dry phase;
  - assessment of membrane transport (see 📖 'Peritoneal equilibrium test', p.473 (PET)) characteristics enables calculation of the optimum dialysis regimen, for which there are computer programmes available;
  - it is possible to add in an extra cycle (usually undertaken on return from school) using the dialysis machine;
  - tidal PD is overnight CCPD, but only a fixed proportion of the fill volume is drained at each cycle;
  - the optimum percentage drain can be calculated by observing the drainage flow rate and using the point at which this declines;
  - a complete drain can be programmed for the middle of the night; it is useful when there is abdominal pain on draining; when there are lost dwell times due to repeated alarms because of poor returns (due either to catheter problems or in the polyuric child who absorbs dialysate); and for clearance of larger molecules such as phosphorus.

Factors affecting the effectiveness of peritoneal dialysis

- Number of hours overnight on dialysis: this needs to be balanced against interfering with schooling or social life. Intensive dialysis programmes may increase protein losses in the peritoneal dialysate.
- Number of cycles and dialysate dwell time.

A suggested schema to start PD would be as shown in Table 19.1.

Table 19.1 Suggested schema to start PD

	Hours	Ratio of cycles to hours
Infant	12–14	1:1 or more
Polyuric child	Up to 12	2:3
Oliguric/anuric child	Up to 12	1:1

This can be adjusted according to results of the PEqT, in conjunction with weight, BP and UF.

- The fill volume. It is usual to start with a fill volume 800mL/m^2 in infants and 1100mL/m^2 after infancy, but up to 1000mL/m^2 and 1400mL/m^2, respectively, can be used when the child is lying (intra-abdominal pressure is less in the prone position); above this, intra-abdominal pressure starts to rise, which will decrease UF.
- Intraperitoneal pressure should be 7–14cmH_2O; maximum tolerated is 18cm H_2O.
- It is usual to leave dialysate in the abdomen at the end of the overnight session (last bag fill). The volume is 600–800mL/m^2. A daytime dwell significantly increases clearance of small and large molecules.
- If there is poor return on the initial drain when starting back on overnight PD (<two-thirds of the last bag fill), Icodextrin can be used.
- The rate of UF will affect solute removal. UF can be increased by increasing the glucose concentration or by increasing the number of cycles.
- Peritoneal blood flow will be affected by the cardiac output.
- Peritoneal membrane characteristics (surface area, permeability) (see 🕮 'Peritoneal equilibrium test', p.473).

Programming the dialysis machine

For example with the Baxter Homechoice machine:

- Recirculation may occur in infants with low fill volumes, so 'low recirculation volume' lines can be used which reduce the volume of effluent that is returned to the infant from 44 to 17mL. There is a 'no flow' alarm of 12mL/min and 'slow flow' of 50mL/min. These rates can be altered in infants who have low volume lines to 3 and 15mL/min, respectively.
- Minimum drain volume is set at 85% of fill volume, but this can be adjusted.
- Minimal drain time is used for low fill volumes and is usually set to 10–15min.

Peritoneal equilibrium test

The PET gives 2 measures of membrane function during a 4-h dwell:

- *Small solute transport:*
  - how easily does creatinine cross from the blood to the peritoneal cavity?
  - ratio of dialysate to plasma creatinine.
- *Ultrafiltration:*
  - how easily does glucose cross from the peritoneal cavity to the blood?
  - ratio of dialysate glucose at 4h to dialysate glucose at time 0.
- *The 'leakier' the peritoneal membrane:*
  - higher D/P creatinine;
  - lower D4/Do glucose.

Solute transport varies between individuals and affects the dialysis prescription. It can change with time and is the commonest cause of UF failure.

The procedure

- Measures the rate at which creatinine and glucose reach equilibrium between the blood and dialysate. Patients are divided into high (rapid movement of creatinine into the peritoneum and elimination of glucose), high and low average, and low transporters.
- The patient must empty the peritoneal cavity as completely as possible before the test dwell.
- The peritoneum is filled with 1100mL/m^2 of 2.5% dextrose dialysate. Dialysate and plasma samples are obtained at 0, 2, and 4h into the exchange.
- There are standard curves available for the ratio of dialysate to plasma for creatinine and glucose against time. These can be used for comparison to determine if a child is a high, high average, low average, or low transporter for creatinine and glucose.
- Roughly, the dialysate/plasma creatinine (D/Pcr) ratio at the end of 4-h dwell grades the patient's transport status as high if >0.77, high average if >0.64, low average if >0.51, and low if <0.5.
- Those with a very high or high average transport (high D/Pcr) have a rapid decline in dialysate glucose concentration and less UF, whereas those with average low and low transport (low D/Pcr) have a high 4-h dialysate glucose level and normal to high UF.
- UF failure may be due to excessive salt and water ingestion, excessive fluid absorption during the long dwell exchange, non-compliance with dialysis prescription, after recurrent peritonitis, and peritoneal sclerosis and/or adhesions.

Importance of transporter status

Although, ideally, a PET will guide the prescription, in most cases PD will start without this information. High or high average transporters have a rapid transfer of creatinine and urea into the dialysate, and the decline in intraperitoneal glucose means that fluid removal rapidly ceases so that short cycles are therefore better. However, this must be balanced against a relative reduction in dwell time as a greater proportion of the cycle will be spent filling and draining, and dialysis time will be lost. Longer dwells may be suitable for low or low average transporters, when the glucose osmotic force remains present for longer so that UF is maintained.

Peritoneal membrane changes over time

Anatomical changes

- ↑ Thickness of the mesothelial layer.
- Local vasculopathy with neoangiogenesis (↑ vascular endothelial growth factor).
- Impaired host defences (↓ phagocytosis and bactericidal activity).

These changes result in fibrosis → sclerosis → calcification. Around 50% of children have peritoneal sclerosis after 5 years on PD.

Functional changes

- ↑ Glucose absorption.
- ↓ Net UF.
- ↑ Small solute clearance.

  = Change to high transporter status.

High transporter status is associated with:

- Increased dialysate protein losses.
- Rapid progression to peritoneal membrane failure.
- Greater risk of sclerosing peritonitis.
- Increased mortality:
  - low albumin;
  - increased prevalence of vascular disease.

Transporter status may increase after peritonitis and with time on PD.

Delivered dialysis dose (clearance of creatinine and urea)

One of the most important factors influencing adequacy is residual renal function, which can decrease with time.

Clearance

Creatinine clearance is obtained from 24-h collections of dialysate (D) and urine (U), normalized to 1.73m^2 body surface area (BSA). The average of renal creatinine and urea N clearance (since at lower glomerular filtration rate (GFR) creatinine clearance over estimates GFR because it is secreted by the tubules) is added to the peritoneal clearance. Creatinine clearance can be calculated by measuring the plasma (P) creatinine at the midpoint of a timed dialysate collection by:

Clearance of creatinine (Cr) =
(Cr in dialysate × drained dialysis flow rate)/Cr in the blood

Weekly creatinine clearance (C_{cr}) =
(D_{cr} × D volume × 1.73 × 7)/(P_{cr} × BSA)

It has been suggested that values should be >40L/week/1.73m^2 in infants, >50L/week/1.73m^2 in 12–24-month-olds and >60L/week/1.73m^2 in those over 2 years of age. It is easier to achieve creatinine clearance targets in high transporters, although these patients may have unsatisfactory UF.

Kt/V urea

The clearance of urea nitrogen divided by the urea distribution volume (V) is termed *Kt/V*. The ratio determines the adequacy of dialysis:

$$K = \{[\text{dialysate } (D) \text{ urea}] \times (\text{24-h volume})\}/\text{plasma } (P) \text{ urea}$$

where K is the peritoneal clearance of urea, T is the number of dialysis days per week, and V is the volume of distribution (0.6 × body weight in kg). In patients with urine output, a urea nitrogen clearance is added to the peritoneal clearance to make it a total clearance per week:

$$\text{Weekly } Kt/V = \{[(D_{ur} \times V_d) + (U_{ur} \times V_u)]/(P_{ur} \times V)\} \times 7$$

where D_{ur}, U_{ur} and P_{ur} are the dialysate, urine, and plasma urea concentrations, V_u is the urine flow rate, V_d is the volume of dialysate, and V is the volume of distribution of urea. The minimum weekly goal for adult patients is a Kt/V urea of 2.1 (including contributions by residual renal function) and it is likely that the dose for children should at least equal this.

Kt/V and C_{cr} may not correlate

This is because urea is cleared better in low transporters so that Kt/V may be higher than in high transporters, whereas high transporters with high convective clearance and high UF have better C_{cr}.

Complications

- Exit site infections.
- Peritonitis (see 📖 'Peritonitis in patients on chronic peritoneal dialysis', p.476).
- Sclerosing peritonitis (see 📖 'Sclerosing peritonitis', p.481).
- Testicular fluid accumulation due to patent processus vaginalis.
- Hernias are common. As well as the uncovering of congenital hernias there may be new hernias in the abdominal wall due to the raised abdominal pressure when dialysis fluid is in the abdominal cavity.
- Pleuro-peritoneal fistula may allow the passage of dialysate into the pleural cavity. Diagnosis can be made by the instillation of radioisotope into the peritoneal cavity. A significant leak will need repair or pleuradhesis, or a switch to haemodialysis.
- Intra-abdominal adhesions.
- High intake of glucose may lead to insulin resistance and hyperlipidaemia.
- Parental/carer stress and burn out.

Peritonitis in patients on chronic peritoneal dialysis

Background

The peritoneum can be infected by skin organisms at the time of connection/disconnection to the dialysis bag or cycler, by damage to the line, or via the Tenckhoff tunnel if the exit site is infected. *Staphylococcus aureus* and *epidermidis*, and *Pseudomonas aeruguinosa* are the most common causative bacteria. They may adhere to the catheter (biofilm) making eradication difficult, predisposing to recurrent infection. More rarely, organisms from the bowel may cause peritonitis.

Important general points

- Symptoms and outcome are usually worse with *Staphylococcus aureus* and Gram positive infections and fungi.
- Prolonged use of antibiotics may result in fungal peritonitis.
- Treatment should be aimed at preservation of the peritoneal membrane, rather than the catheter.
- UK Renal Association standards state that units should not have more than 1 episode of peritonitis per 14 patient months averaged over 3 years.

Clinical presentation

- Cloudy dialysate fluid: needs urgent dialysate microscopy (menstruating girls may develop cloudy or blood-stained PD fluid).
- Abdominal pain.
- Fever.
- History of line break/contamination.
- Septic shock.

Assessment

May present either as a local infection with minor systemic signs or associated severe systemic illness.

- Send 50–100mL of PD fluid effluent for cell count and differential, Gram stain and culture (microscopy, culture, and sensitivity (MC&S)).
- White blood cells (WBC) and differential, C-reactive protein (CRP).
- Blood cultures.

Diagnosis

- Treatment should be initiated if there are >100 WBC × 10^6/L PD effluent, or if there are 50–100 WBC × 10^6/L and symptoms/signs are suggestive of peritonitis.
- If between 50 and 100 WBC × 10^6/L and the patient is asymptomatic, hold dialysis and repeat a specimen in 4–6h.
- The WBCs are usually >50% neutrophils. If the cell count is persistently high, but the differential is predominantly lymphocytes or mononuclear cells, fungal peritonitis should be considered.
- Polymorphonuclear leucocytes may also be associated with visceral inflammation, such as appendicitis; monocytes are associated with gastroenteritis and icodextrin use; and eosinophils may be associated with allergy.

- Most laboratories report the total polymorphonuclear leucocyte count, without distinguishing between neutrophils and eosinophils in response to a request for routine microscopy of peritoneal dialysate effluent. If there is a possibility of eosinophilic peritonitis, an eosinophil count must be specifically requested.
- Organisms may be seen on Gram stain, although this may only be positive in 30% of cases.
- A positive PD fluid culture usually develops within 24h, and in the majority (75%) the diagnosis can be established within 72h.
- No growth from PD fluid in the presence of other evidence of peritonitis (culture negative peritonitis) should only occur in <15% of cases (UK Renal Association standards). It may be due to culture methods of low sensitivity, small culture volume, causative micro-organisms that need special culture methods, patients already on antibiotics and non-infectious peritonitis. Culturing a large volume of dialysate improves the accuracy of diagnosis. Most methods presently use concentration methods, filtration or centrifugation.

Eosinophilic peritonitis

Eosinophilic peritonitis is a response of the peritoneum to foreign substances (e.g. a component of the dialysis system, air, the dialysate (particularly icodextrin), intraperitoneal medications). It presents with cloudy dialysate, and may be missed because not all laboratories report the eosinophil count, giving only the total polymorphonuclear cells.

- It should be considered if there is culture negative peritonitis.
- It is defined as >100 WBC/mL of PD effluent, of which eosinophils constitute more than 10% of the total white cell count.
- There may also be a peripheral blood eosinophilia.
- It occurs most often after catheter insertion or during the treatment phase of peritonitis.
- It is more common in the very young.
- Rarely, it may occur in association with fungal and parasitic infections.
- It may be persistent and may mask genuine infection.
- Usually no treatment is necessary, but anthistamines or intraperitoneal hydrocortisone may be helpful.
- It is benign and usually resolves spontaneously over 2–6 weeks, although occasionally it may be so severe that catheter obstruction occurs due to fibrin, particularly in infants.
- It may occur post-surgery.

Post-surgical peritonitis (within 2 weeks of procedure)

- A raised PD fluid white cell count is often found following placement of PD catheter or other intraperitoneal procedures, or even post nephrectomy, but symptomatic peritonitis is uncommon.
- The white cells may be eosinophils.
- The operative procedure should be covered with IV antibiotics (amikacin 10mg/kg and teicoplanin 10mg/kg stat). The catheter is flushed frequently until the dialysate is clear and then capped off.
- The catheter is flushed weekly before use, but a PD fluid sample should only be sent for microscopy and culture if the child is symptomatic. Treatment will be indicated in a symptomatic child with a rising WBC on serial PD fluid samples.

Line break/contamination of catheter

- Obtain 50–100mL of PD fluid; if less than 100 WBC × 10^6/L present add vancomycin and ciprofloxacin to dialysis bags for 48h, but continue usual dialysis regimen. If more than 100 WBC × 10^6/L noted then treat as peritonitis.

If line break or contamination occurs before PD has commenced:

- Perform a line change.
- Give IV antibiotics for 48h and continue as clinically indicated.

General management

- Intraperitoneal antibiotics with broad spectrum gram positive and gram negative cover should be given until cultures are available. An example of an antibiotic regimen is shown in 📖 'Antibiotics', p.478.
- IV antibiotics may be necessary if there is severe systemic involvement or if the child is immunosuppressed.
- Continuous cycling (CCPD) should be started for 48h and continued until the dialysate WBC, which should be checked daily, is <100 × 10^6/L, then the usual regimen can be reinstated, with antibiotics into the dialysis bags.
- The usual total therapy volume but with a total therapy time of 24h can be used for CCPD. This will give the same number of cycles per day, but with increased dwell times and should be continued for 2 days. Intraperitoneal antibiotics and heparin should be added to all of the dialysis fluid bags.
- Close observations of fluid balance and plasma potassium levels are necessary.
- Oral antifungal therapy such as nystatin 100,000U qds should be given while on antibiotics.
- Samples of PD fluid effluent should be sent daily for microscopy and culture to monitor treatment response. Allow at least 2h between the last exchange and sampling.
- If the WBC is <100 × 10^6/L after 48h continue on the usual dialysis regimen adding antibiotics to PD fluid (including last bag fill if on CCPD).
- If the WBC is >100 × 10^6/L after 48h continue cycling regimen.
- In most cases the child can go home after 48h to continue treatment.
- Continue for a minimum of 2 weeks, depending on the organism. Four weeks of treatment may be necessary for *Staphylococcus aureus*.

Antibiotics

See 📖 'Drug prescribing', p.573.

- If there is only minor systemic illness, treatment can be intraperitoneal without IV antibiotics. Some centres use an intraperitoneal loading dose. Initially use both intraperitoneal vancomycin and ciprofloxacin until Gram stain/culture of PD fluid is available. Then modify treatment accordingly:

  Gram positive organisms = vancomycin (15mg/L) intraperitoneally (IP)
  Gram negative organisms = ciprofloxacin (20mg/L) IP

No organisms seen but >100 WBC × 10^6/L = vancomycin (15mg/L) + ciprofloxacin (20mg/l) IP

+ heparin 200u/L (for 48h cycling and continue as clinically indicated)
+ nystatin oral suspension 100,000U qds, while on antibiotics.

- If there is severe systemic illness or the child is immunocompromised, IV and intraperitoneal therapy is recommended. Initially use both IV vancomycin and ciprofloxacin until Gram stain/culture of PDF available. Then modify treatment accordingly:

Gram positive organisms = vancomycin 10mg/kg stat IV. If the 24h level is <10mg/L give further dose

Gram negative organisms = ciprofloxacin 5mg/kg dose 12-hourly IV (max dose 400mg 12-hourly)

No organisms seen but >100 WBC × 10^6/L = vancomycin 10mg/kg stat IV (if 24h level <10mg/L give further dose) + ciprofloxacin 5mg/kg dose 12-hourly IV (max dose 400mg 12-hourly)

+ heparin 200u/L IP (for 48h cycling and continue as clinically indicated)
+ nystatin oral suspension 100,000U qds while on antibiotics.

Review after 24–48h with the blood culture and PD fluid results. If blood culture negative change to intraperitoneal treatment. If blood culture positive continue IV antibiotics according to sensitivities, and consider adding intraperitoneal antibiotics.

Continuing antibiotic therapy can be modified according to the identity and sensitivity of the organisms cultured. Flucloxacillin 50mg/L can be substituted for sensitive gram positive organisms if there is concern about the development of resistance to vancomycin; and gentamicin 5mg/L or amikacin 25mg/L can be substituted for possible ciprofloxacin resistance. When no bacteria are isolated both antibiotics are continued.

Indications for removal of the catheter

- Fungal peritonitis.
- Severe intra-abdominal sepsis and septicaemic shock.
- Exit site or tunnel infection due to the same organism as that causing the peritonitis.
- This is a recurrence with the same organism within 4 weeks of stopping therapy (i.e. relapsing peritonitis).
- Persistently raised WCC after 3–4 days if infection severe, or 7 days if infection mild.
- Child remains symptomatic after 3–4 days.

After the catheter has been removed:

- Antibiotics should be continued for another 5–7 days.
- A new catheter can be inserted at a minimum of 1 week after all clinical evidence of peritonitis has subsided, providing *Staphylococcus aureus* carriage has been eliminated and any infection in the Tenckhoff tunnel has resolved.

Fungal peritonitis

Children at risk

- Frequent broad-spectrum antibiotic usage.
- Immunosuppressed post-transplant with PD catheter *in situ*.
- Gastrostomy.

Treatment

- Start treatment with liposomal amphotericin B—1mg/kg as a daily dose IV changing if possible after 48h (following fluconazole sensitivity testing and identification) to fluconazole 12mg/kg IV as a daily dose for 48h decreasing to 6mg/kg/day (max dose 200mg daily) for a total of at least 2 weeks.
- If the child has a functioning renal transplant, the dose must be adjusted based on renal function (remember that fluconazole increases calcineurin inhibitor levels). Then continue with oral fluconazole for further 4 weeks. Most *Candida albicans* (germ tube positive yeasts) are sensitive to fluconazole.
- Catheter removal as soon as possible as adhesions precluding future PD develop rapidly.
- Re-initiation of PD is common following successful early treatment of fungal peritonitis as long as it is treated promptly. However, it is wise to rest the peritoneum for 3 months if possible.

Complications of peritonitis

- Catheter removal and haemodialysis.
- Loss of ultrafiltration.
- Malnourishment due to catabolism, poor nutritional intake and high dialysate protein losses.
- Fungal peritonitis.
- Persistent intra-abdominal sepsis requiring laparotomy.
- Adhesions and failure of future peritoneal dialysis.
- Ileus and pancreatitis.
- Death.

Further reading

Warady B, Schaefer F, Holloway M, *et al* (2000). *International Society for Peritoneal Dialysis Guidelines/Recommendations. Consensus Guidelines for the Treatment of Peritonitis in Pediatric Patients Receiving Peritoneal Dialysis Peritoneal Dialysis International.* **20**: 610–20.

Sclerosing peritonitis

The peritoneum becomes thickened and fibrosed, affecting gut peristalsis, and leading to gut obstruction and malnutrition.

Causes

- Prolonged period on PD.
- Recurrent peritonitis.
- Prolonged use of peritoneal dialysate fluid with high glucose concentrations.

Presentation

- Episodes of sterile peritonitis, fever, abdominal pain, high CRP and/or ascites (which can be haemorrhagic).
- Poor ultrafiltration and decreasing small solute clearance.
- Adhesions may cause gut obstruction.
- Adhesions may cause the dialysis catheter to move out of the pelvis, resulting in poor drainage.

Diagnosis

- No absolute test (other than biopsy) so a high index of suspicion is necessary.
- Thickened bowel loops may be seen on US.
- Peritoneal calcification may be present.
- Diagnosis is ultimately dependent on biopsy of the peritoneum.

Treatment

- Transfer to haemodialysis (although the process may continue).
- Immunosuppression has been used, but there is only limited evidence of efficacy.
- Surgery to remove the thickened membrane if gut obstruction occurs.
- Total parenteral nutrition may be necessary.
- Tamoxifen has been used in adults, but there is no published experience in children; the concomitant administration of steroids in many trials makes the specific effect of tamoxifen difficult to ascertain.

Outcome

- Mortality is high due to the complications of surgery and malnutrition.
- Intraperitoneal transplantation, if necessary, is technically difficult.

This page intentionally left blank

Chapter 20

Extracorporeal treatment

Haemodialysis: principles

- A semi-permeable membrane allows the passage of water and small molecular weight molecules, and inhibits the movement of larger molecules.
- Solute transfer occurs by diffusion and convection.
- Water is removed by ultrafiltration.

Diffusion is movement down a concentration gradient and is affected by:

- Membrane permeability.
- Membrane surface area.
- Solute molecular weight.
- Solute charge.
- Transmembrane concentration gradient is therefore maximized by high flow rates of blood and dialysate in opposite directions (countercurrent).
- Temperature of the dialysate.

Convection (solute drag)

- Passive movement of solute 'dragged' by water moving down an osmotic or pressure gradient.
- It is independent of the concentration gradient but dependent on the ultrafiltration (UF) rate and the dialyser.

Ultrafiltration

- The process whereby water is moved across the membrane by the convective flow of water down a pressure gradient, which is created by generating a transmembrane pressure within the dialysate compartment by the dialysis effluent pump. Large molecular weight molecules are removed better by convection than diffusion.
- The net rate of UF is affected by the surface area, structure, and thickness of the dialyser, and the transmembrane hydrostatic pressure and osmotic pressure.

Diafiltration

The combination of dialysis and UF.

Mass transfer

- Toxins in the intravascular space will be rapidly removed.
- Intracellular toxins need time to move into the intravascular space as concentration gradients change, so are removed more slowly.
- Molecular size will also affect removal (Table 20.1).
- Large numbers of biochemically active, potentially toxic 'middle molecules' have been identified: e.g. peptides that may contribute to poor appetite, anaemia, inflammation, and cardiovascular disease.
- The best known is β2-microglobulin, which causes dialysis-related amyloid.
- Some protein-bound middle molecules may also be toxic, e.g. leptin, and are particularly difficult to remove by any dialysis technique.

Table 20.1 Uraemic retention solutes by molecular weight (MW), and their method of removal during haemodialysis (HD)

Solute	MW	Example (MW)	Method of removal
Small solutes	<500	Urea (60), creatinine (113)	Diffusion
Middle molecules	300–5000	Vitamin B12 (1355)	Diffusion/convection
Low molecular weight proteins	5000–50,000	β2-microglobulin (11,800)	Diffusion/convection
Large proteins	>50,000	Albumin (60,000)	Convection

Haemodialysis: the machine, dialysate, and water

There are two circuits—for blood and dialysate, which run in opposite directions, separated by the semi-permeable membrane of the dialyser. Fig. 20.1 illustrates the important elements of a HD circuit.

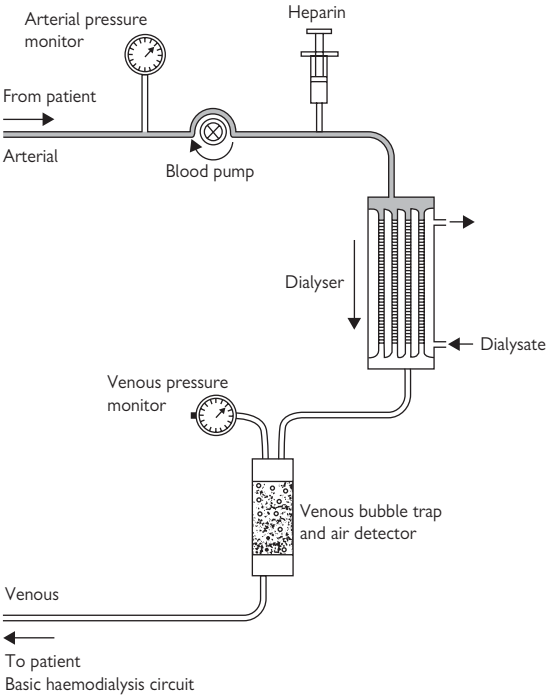

Fig. 20.1 The important elements of a haemodialysis circuit.

A paediatric HD machine needs:

- A volumetric fluid removal system, i.e. one where the in- and outflow volumes from the dialyser are measured so that UF volume is measured directly.
- The ability to measure and remove very small amounts of fluid.
- To be capable of low blood flow speeds.
- To be able to use lines of varying blood volumes.
- To have a bicarbonate dialysate delivery system.

Dialysate

- Is a solution of purified water, Na, K, Mg, Ca, Cl, dextrose, and bicarbonate.
- Electrolytes are mixed and proportionated by the dialysis machine.
- Bicarbonate is the dialysate buffer: the dialysis solution contains acetic or citric acid, which lower the pH of the final mixture and prevent precipitation of Ca and Mg carbonate. Bicarbonate is added by a second proportionating pump.
- The dialysis machine monitors the electrical conductivity of the dialysis solution to ensure the correct proportion of water to concentrate is occurring.
- Standard dialysate flow is 500mL/min (range 300–800mL/min).
- Dialysate is warmed to 35–37.5°C.

Water

- A system of progressively smaller filters, activated carbon and water softeners, culminating in a reverse osmosis unit in the machine, purify water so it is of a quality suitable for dialysate production by removing particulates, dissolved inorganic and organic substances, micro-organisms and toxins.
- Water quality standards (bacterial, endotoxin and chemical content) should be checked monthly (see http://www.edtna-erca.org and http://www.ndt-educational.org/images/Hemodialysis%201%20Section%20IV.pdf).
- Ultra-pure water is ideal and essential for haemodiafiltration.
- Even very low levels of endotoxin in the water can cause cytokine-mediated inflammation that, in turn, may contribute to the increased risk for cardiovascular disease seen in patients on dialysis (Table 20.2).

Table 20.2 European Pharmacopoeia definitions for the upper limit of water quality

	Bacterial growth (cfu/mL)	Endotoxin (EU/mL)	Cytokine induction
Mains water	200	5	+
Regular water	100	0.25	+
Ultra-pure	0.01	0.03	–
Sterile	10^{-6}	0.03	–

Further reading

European Renal Association–European Dialysis and Transplant Association. (2002). Recommendations of the European Pharmacopoeia. *Nephrol Dial Transplant* **17**(Suppl 7)**:** 45–62. Available at: http://www.ndt-educational.org/images/Hemodialysis%201%20Section%20IV.pdf.

Haemodialysis: factors affecting the prescription

The extracorporeal circuit

- The extracorporeal circuit is composed of an arterial (red) line and a venous (blue) line. The 'A' line carries blood out of the child to the haemodialyser, while the 'V' line takes dialysed blood back to the child.
- Pressures are monitored in the arterial and venous segments. Low pressure alarms indicate insufficient blood flow ('sucking'). High venous pressure alarms indicate reduced return of blood to the patient. If an alarm activates, the blood pump is stopped and the lines are clamped.
- Sample ports in either side of the circuit allow blood samples to be obtained while the child is on the machine.
- The lines and the haemodialyser are selected on the basis that the child can tolerate 8% (up to a maximum of 10%) of their total blood volume (80mL/kg estimated dry weight) in the extracorporeal circuit.

Example: A child weighing 10kg has a total blood volume (TBV) of 800mL (10 × 80mL); therefore, the extracorporeal circuit is 64–80mL. Therefore, the total volume of the lines and haemodialyser must not exceed 64–80mL. There are lines that are made in a variety of sizes (Gambro; Kimal for neonatal) by different companies. Some examples are shown in Table 20.3.

- Lines are primed with saline.
- If it is necessary to exceed the safe extracorporeal volume because the smallest available circuit volume is still greater than 10% of the child's circulating volume, then the circuit must be primed with blood. The blood is not washed back into the child at the completion of dialysis to prevent haemoconcentration.

Table 20.3 Volumes of HD lines

	Venous (mL)	Arterial (mL)	Total (mL)
Mini-neonatal (<6kg)	21	8	29
Neonatal (6–12kg)	22	18	40
Paediatric	42	30	72
Adult	70	62	132

The haemodialyser

- The haemodialyser is composed of two compartments, one for blood and one for dialysate, which are separated by the semi-permeable membrane. A hollow fibre configuration achieves the maximal membrane surface area over which blood and dialysate make contact.
- The membrane can be modified cellulose or a synthetic material. Unmodified cellulose membranes are the least biocompatible, and may cause activation of complement and leucocytes, or a severe allergic reaction within minutes of starting dialysis. Sterilizing solutions (e.g. ethylene oxide) may also cause allergic reactions.

- The dialyser size is selected on the basis of its surface area and the priming volume. Roughly, the surface area should be equal to, but not exceed that of the child's. At present, haemodialyser surface areas range from 0.25m^2 up to 1.7m^2 and above. The greater the surface area, the greater the clearance of water and solutes.
- The ultrafiltration coefficient, KUf, describes the dialyser's ability to remove water. For example, a KUf of 2.0 means that 2mL/h of UF will occur for each mmHg of trans-membrane pressure (TMP).
- Dialysers with KUf's of less than 10 are referred to as low-flux and those with a rate of 15–60mL/h/mmHg are called high flux. Synthetic membranes tend to be high-flux.
- Solute transport properties of dialysate membranes are expressed as the mass transfer-area coefficient (KoA).
- Dialysers of usual efficiency (for removal of small solutes) have a KoA of 300–500; high-efficiency dialysers may have a KoA of more than 700.
- Clearance of creatinine, urea, vitamin B_{12}, and phosphate are given for all dialysers. Refer to the specific manufacturer specification sheet for precise clearance values.
- Some molecular weights (Da): urea 60, creatinine 113, vitamin B12 1355, albumin 60,000.
- Dialysers may be sterilized with irradiation, steam, or ethylene oxide. Priming the circuit with 1–2L of saline to expel air and prepare the capillaries for use will also help flush out remaining ethylene oxide and other soluble compounds in the circuit, which may be toxic or cause allergic reactions at the commencement of dialysis.

Types of haemodialysis

- Conventional HD uses a low flux (small pore size) membrane and solute removal is primarily by diffusion.
- High efficiency hemodialysis uses a low flux membrane with a high efficiency (KoA) for removal of small solutes. It is also achieved by using a larger surface area membrane and a high blood flow.
- High flux HD utilizes high flux membranes. It is more efficient in removing solutes that are substantially larger than urea (middle and large molecules such as vitamin B_{12} and ß-2 microglobulin respectively), but may not be more efficient than conventional HD in removing small solutes.
- Because conventional HD is principally diffusive based, even when using high flux dialysers it is limited in clearing middle-sized molecules (MW 200–20,000), which are better removed by convection.
- Haemodiafiltration (HDF) superimposes convection upon standard diffusive blood purification. It is possible to use a high flux haemofilter to ultrafilter up to 30% of the blood volume passing through it. The desired volume of replacement fluid is then infused into the blood circuit. Better clearance of β2-microglobulin may reduce the risk of amyloidosis. Ultrapure dialysate is necessary. Care must be taken that excess fluid removal does not occur.
- High flux dialysers or HDF should be considered in larger children, particularly if they are likely to be on HD for an unpredictable time, and those showing evidence of amyloidosis.

Length of session

- 4h is standard for chronic HD.
- Shorter sessions will adversely affect clearance of large molecules.
- Long (or frequent short) sessions (e.g. overnight) improve fluid balance and phosphate clearance, both of which have a positive effect on mortality.
- Increasing the number of hours per week on dialysis is the most important factor that can improve outcome.
- For acute dialysis:
  - if the plasma urea is greater than 30mmol/L then the session;
  - should last no more than 1–2h;
  - patients with tumour lysis syndrome may need a very long session;
  - for acute correction of hyperkalaemia 1–1.5h may be sufficient.

Frequency of sessions

- Chronic HD is conventionally performed three times a week.
- More intensified regimens are beneficial to growth, bone health, quality of life, and life expectancy. Such regimens may be daily for 3h or slow overnight. New technology is now making home HD a feasible option for children.
- Acute HD is performed as often as necessary (usually daily), but with an aim to achieve a target of three times a week.

Blood pump speeds

The speed at which the blood is pumped out of the child and around the circuit is equivalent to their extracorporeal volume total, i.e. up to body wt (kg) × 8mL/min. Thus, the 10-kg child, with an extracorporeal circuit of 64–80mL can have blood speeds of up to 80mL/min.

Estimation of target weight

- In chronic HD, the aim is to end the session with the child at their target/desired weight, i.e. the weight below which the child will become symptomatically hypotensive.
- Target weight can only be determined by careful, persistent fluid removal to achieve normal blood pressure (BP) after dialysis.
- Target weight needs to be reassessed at least monthly, more often in very small children.
- The child who is always hypertensive is likely to be above their target weight; antihypertensives can usually be discarded when this is achieved.
- However, attainment of target weight with conventional three times a week dialysis can be difficult in the child who has high interdialytic weight gains requiring large UF volumes. Much better results have been obtained with daily dialysis, with most children no longer needing antihypertensives at all.

Fluid removal

- The fluid loss required is calculated by the interdialytic weight gain, the volume of saline required for the 'wash back', and any drinks consumed during the session. The HD machine will adjust the TMP accordingly, depending on the time (in hours), and the venous pressure (affected by the blood speed and peripheral resistance), to give an hourly UF rate.

- The greater the TMP that is set, the greater the amount of fluid that will be removed from the child, and the more likely that the child will feel unwell.
- High UF rates whilst diffusion is occurring are not well tolerated. To counteract this, isolated UF can be performed, in which the flow of dialysate is halted, therefore diffusion and hence dialysis ceases. This allows more fluid to be removed more quickly from the child, and is useful when there are large volumes for UF.
- The amount each child will tolerate losing per hour varies, but 10mL/kg/h is a safe starting point. Up to 600mL/h can be removed in children 40kg plus, who are consistently volume overloaded.
- No more than 5% of body weight should be removed in one session, or 0.2mL/kg/min.
- Fluid loss (UF) can only be achieved if the fluid is in the vascular space. As the vascular space empties, refilling must occur from the other compartments, to allow UF to continue. The child will show signs of hypovolaemia if UF (from HD or isolated UF) continues unchecked.
- If hypovolaemia occurs, the UF rate should be decreased and the child given a drink or bolus of saline to correct hypotension, if necessary:
  - many patients collapse having had no prior warning of feeling unwell, therefore close monitoring of BP and other observations (including peripheral temperatures) is important during isolated UF;
  - chronic HD children are often able to recognize the early warning signs and can prevent such episodes.
- A child undergoing acute HD should be treated with caution, as their target weight will not have been established and their response to extracorporeal treatments unknown.
- As dialysis does not occur during isolated UF, the length of time on the dialysis machine will increase.

Anticoagulation

- Heparin is given at a rate of 5–50U/kg/h through the arterial side of the circuit to prevent the blood clotting. For the child with acute kidney injury (AKI) with no bleeding disorders a rate of 10U/kg/h can be given.
- Low molecular weight heparin is an alternative, given as a bolus of 1mg/kg at the beginning of the session.
- The heparin infusion should stop 30 min prior to the end of dialysis if a fistula is being used, to prevent bleeding after the needles have been removed.
- The formation of clots, particularly in the bubble trap, should be monitored. A bolus of 50–100mL of saline flushed through the circuit with the arterial lines clamped may reveal clot formation. UF will need to be increased to remove the extra saline. The heparin dose may be increased and/or a bolus of heparin given. The venous side of the blood circuit can be changed during the session to prevent total clotting.
- The heparin dose will need to be adjusted in the patient with abnormal clotting or low platelets. Heparin-free dialysis can be used; the circuit can be primed with heparinized saline (3000–5000U/L) (and then flushed) as this will bind to the dialyser. The dialyser must be checked regularly for signs of clotting. High blood flow will help prevent clotting.
- Heparin may induce thrombocytopenia in some patients, which resolves on stopping treatment.

Clots will form when there is:
- Slow blood flow because of access flow problems.
- Inadequate heparinization.
- A raised haematocrit.
- A long period of ultrafiltration, as the warmed dialysate flow is lost, and the haematocrit is raised as fluid is removed.
- If a circuit clots off completely, the blood in the lines is lost. This will not have a detrimental effect on the child, providing the extracorporeal rules have been observed.
- If clotting problems persist, aspirin and/or dipyridamole or warfarin or treatment may be considered.

Biochemistry
- *Na:* the dialysate Na must be within 10mmol of the child's plasma Na to avoid disequilibrium. The Na dialysate concentrate level can be altered on the machine within preset parameters (see discussion of Na ramping in 📖 'Haemodialysis: complications', p.494).
- *K:* as the usual concentration of K in dialysate is 1–2mmol/L, adjustment may be needed for children with low plasma K levels or in those requiring a long dialysis session, when a dialysate K of 3–3.5mmol/L can be used; if the child has a very high K, a zero-K dialysate can be used for a short period of time, before reverting to the normal K dialysate. There is a danger of severe hypokalaemia if a zero-K is used for too long. The use of plasma K monitoring equipment (ionometer) is recommended to facilitate management of hyperkalaemia. Although immediately post-HD K levels are very low, they rebound rapidly.
- *Bicarbonate:* the dialysate level can be adjusted on the machine, within preset limits. The level is usually around 35mmol/L.
- *Urea:* a rapid reduction in serum urea, usually if over 40mmol/L for chronic patients and 30mmol/L for acute patients, can result in disequilibrium syndrome (see 📖 'Haemodialysis: complications', p.494). Mannitol can be infused (1g/kg), during HD, through the bubble trap to counteract this. The best way to avoid disequilibrium is to keep the dialysis session short, less than 2h.
- *Creatinine:* will fall rapidly during the session as there is none in the dialysate, but it will rebound and rise rapidly following the end of dialysis.
- *Ca:* the standard dialysate level is 1.75mmol/L. This is equivalent to the blood-ionized Ca, so results in an influx of Ca into the patient and a rise in serum Ca post-dialysis. Dialysates containing Ca concentrations from 1.25mmol/L (which is equivalent to the blood in the normal child) are available, and can be used in hypercalcaemia, in order to remove Ca from the patient.
- *Phosphate:* after an initial fall in the first 1–2h, movement from the intracellular compartment is slow; therefore, long dialysis sessions (e.g. overnight) result in the best phosphate clearance.

Administration of blood products

- *Albumin:* low serum albumin will result in oedema and difficulty in removing excess fluid:
  - if the child is oligoanuric 20% albumin should only be given when on dialysis, as the resultant fluid shifts can cause pulmonary oedema;
  - it must be given in small boluses through the arterial infusion port at the beginning of the session, to allow time for movement of fluid into the intravascular compartment.
- *Blood:* should only be required to prime the lines if the dialyser and lines volume exceeds the safe extracorporeal circuit volume, i.e. in infants. This blood prime is not washed back into the child at the end of the session.
- If blood is required for the treatment of anaemia, the calculation for number of millilitres of blood required = weight (kg) × 3 × number of g that the Hb is to be raised.
- The blood is infused in small boluses at the beginning of dialysis, through the arterial infusion port, so that K will be dialysed out. Resulting fluid shifts may lead to the need for ultrafiltration towards the end of the session.

Haemodialysis: complications

Common complications

- Nausea, vomiting, itching, pains, and cramps.
- Intradialytic hypotension due to:
  - intravascular volume depletion due to slow refilling from the extravascular space;
  - shifting of fluid from the extracellular to intracellular space due to a decrease in serum osmolality due to urea removal and use of a dialysate Na lower then plasma, as this leads to hyponatraemia in blood returning to the patient;
  - excessive UF requirements because of a high interdialytic salt and water intake;
  - impaired sympathetic activity;
  - vasodilation in response to warm dialysate;
  - splanchnic pooling of blood while eating during dialysis;
  - use of anti-hypertensive agents.

Treatment of intradialytic hypotension

- Acutely, normal saline 5mL/kg and cessation of UF.
- The daily fluid allowance and target weight must be reassessed.
- UF separate from dialysis.
- Na ramping: the machine can be programmed to deliver a Na concentration higher than that of the plasma at the beginning of the session so that Na diffuses into the plasma and balances the change in osmolality caused by diffusive urea removal. The Na concentration in the dialysate is then progressively reduced. Although this technique helps intradialytic hypotension, the danger is that there is inadequate Na removal, hence contributing to chronic fluid overload and hypertension.
- Newer machines are able to monitor circulating blood volume by determining changes in haematocrit. A decrease in blood volume of >8% in the first 90min or >4% thereafter is likely to lead to hypovolaemia.

Less common complications

- *Disequilibrium:* due to the plasma urea concentration falling more rapidly than brain cell urea concentration, with the resultant movement of water into brain cells by osmosis:
  - it can present with headache, nausea, and dizziness, and progress to disorientation, seizures, and coma;
  - symptoms resolve spontaneously, but if severe can be treated with IV mannitol using 1 g/10% of body weight;
  - mannitol can also be used prophylactically when initiating HD in someone with a high urea.
- *Haemolysis:* may present with pains and nausea, and a dark appearance to venous blood. It may be due to overheating, contamination or hypotonicity of dialysate, kinking of the lines, or a malfunctioning pump. Dialysis should be stopped and the K must be checked immediately. Haemolysis may continue for some hours.

- *Urticaria:* can be treated with an antihistamine or hydrocortisone if severe.
- *Air embolism:* rare as air detectors will clamp the return lines. 1mL/kg may be fatal:
  - presents with fitting or coma in the upright patient, and chest symptoms if recumbent;
  - treatment is to clamp the lines, stop the pump, put the patient head down in the left lateral position, give 100% oxygen (to enhance nitrogen diffusion out of air bubbles) and resuscitation as necessary;
  - air may need to be aspirated from the ventricle.
- *An anaphylactic reaction to the dialyser:* can occur at any time and necessitates a change of dialyser:
  - 'first use syndrome' occurs soon after the start of dialysis and disappears with dialyser reuse and predialysis rinsing or can occur at any time. Both cause hypotension (sometimes hypertension), angioedema, pulmonary symptoms, chest and abdominal pain, vomiting, fever, urticaria, and pruritus;
  - reactions can result from activation of plasma complement or kinin systems by the dialysis membrane; or the release of noxious materials as contamination of the dialyser may have occurred during manufacture or the sterilization process (e.g. with ethylene oxide);
  - dialysis must be stopped and blood should not be returned to the patient;
  - normal saline for hypotension, adrenaline SC or IM (1:1000 concentration) and/or hydrocortisone may be necessary.
- *Dialysis-related amyloidosis:* symptoms are typically first reported after 7–10 years of dialysis:
  - a disabling, progressive condition caused by the polymerization within tendons, synovium, and other tissues of β-2-microglobulin, a large (MW 11,600) molecule, released into the circulation as a result of normal cell turnover;
  - clearance is improved by longer dialysis sessions and HDF.

Haemodialysis: adequacy

The clearance of urea is used as the basis for all calculations of dialysis adequacy, and is the minimum urea clearance and nutritional intake that prevents adverse outcomes. However, it has to be remembered that:

- Urea clearance represents small molecule clearance.
- Does not measure clearance of larger and more important molecules that move more slowly.
- Clearance figures for optimal dialysis have not been established.
- Studies in adults suggest that residual renal function is more important for survival than measured 'adequacy'.

Assessment of dialysis adequacy should include:

- Height and weight gain (nutrition).
- Control of anaemia, acidosis, and bone disease.
- Control of BP.
- Small solute clearance (urea kinetic modelling (UKM), *Kt/V* and/or urea reduction ratio (URR)).
- UKM uses pre- and post-dialysis samples over two sessions to measure urea clearance and generation rates. It takes into account residual renal function, predicted dialyser clearance, blood and dialysate flow, time on dialysis and fluid removal. It can be used to assess protein intake as well, but is not commonly used because of its complexity.
- *Kt/V* (*K* = urea clearance of dialyser, *t* = treatment time, *V* = volume of distribution = 0.6 × body weight) can be predicted from the pre- and post-dialysis urea, weight loss, and duration of dialysis. There are several different formulae available for the calculation. Most would use the Daugirdas II formula (also discussed in this section).
- URR underestimates the dose of dialysis as it does not take into account convective losses or residual renal function. It is calculated as follows:

  [(Pre-dialysis urea – post-dialysis urea)/Pre-dialysis urea] × 100

- Errors can occur by incorrect blood sampling:
  - if the sample is contaminated by blood from the dialyser, or heparin, or if there is recirculation, the urea result will be underestimated, giving a falsely high *Kt/V*;
  - the earlier the blood is drawn after the completion of dialysis, the higher the apparent delivered dose, as urea rises rapidly post-dialysis;
  - methods of standardization of post-dialysis sampling are the slow-flow and stop-flow methods;
  - stop dialysate flow is the most commonly used, but gives higher results;
  - *stop-dialysate-flow method*—stop dialysate flow, but keep blood pump running for 5 min; take sample from anywhere in circuit.
- *Kt/V* (Daugirdas II) can be calculated as follows:

$$Kt/V = -\ln(C_1/C_0 - 0.008^{*}t) = (4 - 3.5^{*}C_1/C_0)^{*}UF/W$$

where C_0 and C_1 = pre- and post-dialysis blood urea (mg/dL), respectively, *t* = time (h), UF = ultrafiltration volume (kg), W = post-dialysis weight (see 📖 Appendix, p.599 for urea conversion figures).

- Urinary creatinine clearance can be calculated using the standard formula:

  (Urine creatinine × 24-h urine volume)/serum creatinine

  Problems include collecting a timed urine collection and that the true GFR is overestimated (due to ↑ tubular secretion of creatinine at low GFRs, resulting in a 25% day-to-day variation in the same patient.
- Measures of adequacy in children have not been defined, but consensus standards propose that they should be equal to or better than adult recommendations of >1.2 for *Kt/V* and >65% for URR.

Haemodialysis: vascular access

Acute HD will require either a temporary percutaneous dual lumen catheter (e.g. VasCath or Gamcath) or a tunnelled cuffed catheter (e.g. Permcath). Access for chronic HD is by tunnelled line, arteriovenous (AV) fistula, or rarely shunts or grafts.

Tunnelled lines

Used in children who are too young for an AV fistula or who are not expected to be on dialysis long; e.g. awaiting a living-related transplant. Such lines have a greater risk of poor function, infection, and hospitalization, and are associated with increased mortality in adults.

- Superior to non-tunnelled lines, but inferior to an AV fistula.
- The internal jugular vein is the preferred site. Lines should preferably not be sited in the subclavian veins as this may lead to vascular stenosis and, therefore, inability to create a fistula in the future.
- Stenoses typically occur at the catheter entry site into the vein and at the catheter tip site.
- Vascular access problems are indicated by arterial or venous pressure alarms:
  - low arterial pressure alarms indicate there is an insufficient blood flow reaching the blood pump;
  - commonly referred to as 'sucking' and is usually a result of poor access position in the vessel;
  - low venous pressure alarm also indicates poor blood flow;
  - high venous pressure alarm indicates that there is an occlusion to the flow of returning blood;
  - due either to poor access position, fistula stenosis or the presence of clot formation. Alteplase (tissue plasminogen activator, TPA) can be used to dissolve suspected clots in the central line. A solution of 1mg/mL is instilled in the dead space of the catheter and left for at least 1h, preferably overnight or between dialysis sessions, after which it is aspirated. It can also be used as a line lock post dialysis as prophylaxis against line clotting and infection.
- In order to achieve satisfactory blood speeds the larger the gauge of the access the better. Catheter sizes range from 6.5–14FG in differing lengths (12 or 18cm or 12–40cm for smaller or larger gauges, respectively) and are chosen according to the size of the child and their vessels (see Table 20.4).
- Most lines are dual lumen, but HD can also be achieved using single lumen access:
  - in infants, single lumen access may be more appropriate, as a larger catheter can be inserted, remembering that flow is proportional to the fourth power of the radius;
  - in order to obtain 2-directional blood flows with a single lumen line, the dialysis circuit has to be modified;
  - this can be achieved by the double-pump method, using 2 blood pumps which pump alternately, or by using a single pump that pumps intermittently, using gravity to let blood flow back in to the child;
  - both methods require an expansion chamber in the circuit to allow for the pressure changes;

  - this results in an increased volume of blood in the circuit and a larger degree of recirculation.
- Recirculation occurs when blood that has been dialysed returns to the dialyser inlet, i.e. the access flow rate is less than the blood pump and is a marker of venous stenosis. Recirculation >10% requires further access investigation.
- *Measurement of recirculation:*
  - take A and V samples from the access lines 30min after the start of dialysis (without UF);
  - halve the pump speed then switch it off;
  - clamp arterial line above the port and take a sample from it; restart dialysis;
  - measure urea in arterial (A), venous (V) and systemic (S) circulations

$$\text{recirculation (\%)} = [(S-A)/(S-V)] \times 100$$

Table 20.4 Catheter size and positioning according to the weight of the child

Size of child	Catheter size	Siting
Neonate	5Fr (single lumen)	Femoral vein
3–6kg	7Fr	Internal or external jugular or femoral vein (preferably not subclavian)
6–15kg	8Fr	
>15kg	9Fr	
>30kg	≥10Fr	

Vascular access infection

Catheter-related infections

Infections may be at the exit site, the SC tunnel, or in the catheter, with development of biofilm and difficultly eradicating the bacteria. Line sepsis may present as a rigor soon after starting dialysis, fever with raised CRP or septicaemic collapse.

Definitions

- *Exit site infection:* erythema, tenderness, and discharge within 2 cm of the exit site.
- *Tunnel infection:* tenderness, erythema and induration along the subcutaneous tract >2cm from the exit site.
- *Catheter colonization:* repeated growth of the same organism without signs of sepsis.
- *Catheter infection:* septicaemia, bacteraemia, or fungaemia with:
  - at least one positive culture of the same organism from the catheter and a peripheral vein;
  - clinical signs of infection (fever, hypotension);
  - no other cause of infection;
  - a raised CRP.

Prevention

- Strict attention to aseptic technique.
- Monthly culture of the exit site, and nose of child and carers, and treatment for 5 days every month with nasal or exit site mupirocin if *Staphylococcus aureus* grows.
- There is no evidence that the type of dressing or the use of lines impregnated with antimicrobials are superior in children.
- Post-dialysis heparin into the line decreases clot formation, which may lead to infection. Alteplase may be more effective, but is more expensive, although a recent study suggests that once a week administration may be enough to reduce line blockage and sepsis.

Factors increasing the risk of catheter infection

- Exit site and/or tunnel infection or contamination of the hub.
- Failure of aseptic technique, frequent catheter access, and long duration of use.
- Use of non-tunnelled, rather than tunnelled lines.
- Immunosuppression, hypoalbuminaemia, and diabetes.
- Nasal and cutaneous colonization with *Staphylococcus aureus*.

Treatment of exit site, tunnel and catheter infections

- Fig. 20.2 demonstrates the steps in the management of exit site, tunnel and catheter infections.
- Antibiotic locks, using an antibiotic to which the organism is sensitive and instilled into the line after dialysis, may be effective at treating line colonization. The antibiotic is then removed at the start of the next dialysis session.
- Antibiotic locks must be instilled into each lumen. Usual instilled volume would be 1.2mL. If the lumen is smaller, the calculated amount of antibiotic would be less, as the amount of heparin cannot be reduced. One schedule would be to start empirically with:
  - amikacin 55mg (i.e. 1.1mL amikacin) + 0.1mL preservative-free heparin 1000U/mL 12-hourly. If initial cultures grow gram positive cocci at 24–48h, change to
  - teicoplanin 146mg (i.e. dilute 200mg teicoplanin with 1.5mL water and take 1.1mL) + 0.1mL preservative free heparin 1000U/mL once daily;
  - the catheter can be recultured by omitting an antibiotic dose, and instilling heparinized saline (10U/mL) into the line instead, leave for 8h and then send the fluid for culture;
  - locks can be continued until a 48-h culture is clear.
- Empiric treatment of septicaemia is usually with vancomycin in units with a significant incidence of MRSA. If there is severe systemic illness, two antibiotics are used. For example, initially use both IV vancomycin and ciprofloxacin until Gram stain/culture available. Then modify treatment accordingly:

Gram positive organisms	=	vancomycin 10 mg/kg stat IV Repeat dose daily if 24-h post-dose level <10mg/L

Gram negative organisms = ciprofloxacin 5mg/kg dose 12-hourly IV (max dose 400mg 12-hourly)

- Antibiotics can be more specific when culture results are available.
- Prophylactic antifungal agents are recommended, e.g. oral nystatin, when on antibiotics.
- Antibiotic therapy (intravenous) would usually be continued for 2 weeks, but may need to be longer if there is endocarditis (all patients with proven line infection need an echocardiogram). Fungal infection also requires a prolonged treatment course.

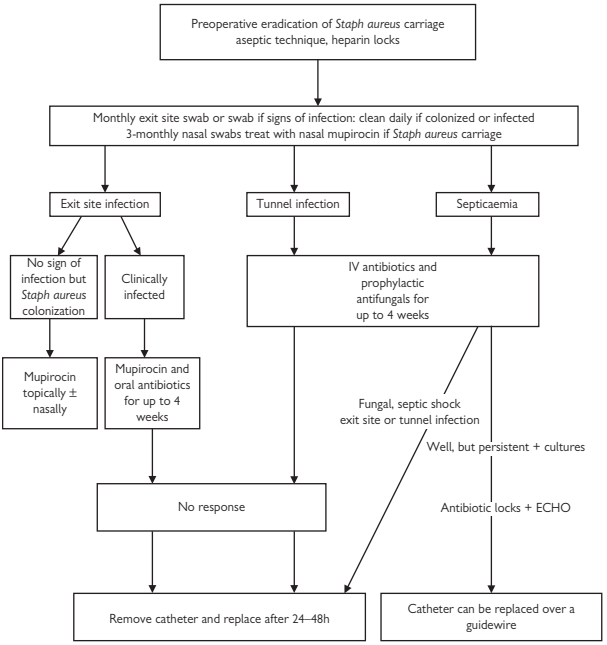

Fig. 20.2 Prevention and treatment of HD catheter related infection.

Removal of the catheter associated with septicaemia

Necessary if:

- It is not needed.
- It is not tunnelled.
- There is septic shock.
- Associated with an exit site or tunnel infection.
- Fungal infection.
- Persistence of fever after 48h of therapy.

Replacement of the line

- With ongoing positive growths from the line, but none of the conditions associated with septicaemia (see 🕮 'Removal of the catheter associated with septicaemia', p.501), it has been shown to be safe and effective (in adults) to replace the line over a guide wire, as long as antibiotics have been started.
- With ongoing positive blood cultures and any of the conditiions associated with septicaemia (see 🕮 'Removal of the catheter associated with septicaemia', p.501), the line should be removed and replaced, preferably after a minimum of 48h.

Fistulae

An AV fistula is the preferred method of vascular access in children on chronic HD because of the decreased infection risk (in comparison to a line) and preservation of vessels for future use. It can be used in children who are able to co-operate with needling; education and play therapy may enable this even in children with needle phobia. Children on short-term dialysis (e.g. awaiting a living-related transplant) may elect to be dialysed via a tunnelled line.

Pre-operative assessment

- A fistula should be created at least 6 weeks before it is needed as it takes some time to mature.
- The child who has had previous lines will need upper limb venography to establish patency of the vessels. A thrombosed subclavian vein will preclude a fistula being created in that arm as venous return may be obstructed. US is unreliable as collaterals may be mistaken for patent upper limb vessels and the veins cannot be seen under the clavicle.
- Children must be prepared for the use of the fistula using appropriate educational tools (play therapy, etc.).
- May be created at the wrist (radiocephalic or radiobasilic), the elbow (brachiocephalic) or by basilic vein transposition (brachiobasilic). It is preferable to start distally to preserve more proximal vessels for future use.
- *Allen test:* occlude the radial artery by pressure to ensure that the ulnar artery supply to the hand is adequate.

The surgery

- The child must be well hydrated or left at slightly above usual target weight if already on dialysis.
- Antihypertensives should be stopped if possible.
- Ensure IV fluids started when fasting begins preoperatively.
- Studies in children show a primary failure rate varying from 0 to 30% (highest risk in small vessels, particularly radial-cephalic), patency 61% at 1 year and 34% at 2 years.

Post-operative care of the fistula

- Elevate the arm to reduce swelling and keep it warm with a padded dressing.
- Assess the fistula thrill using finger tips or stethoscope, check for bleeding and the circulation of the hand every 30min for the first 24h.
- Loss of thrill requires an emergency Doppler US and urgent intervention if the fistula has clotted.
- Clots can be removed by catheter, surgery, or locally instilled TPA.

- Clot removal after 48h is rarely successful in restoring flow.
- Dialysis should be delayed by at least 24h if possible, and usual target weight increased for the next week.
- The arm should not be used for BP measurement or venepuncture thereafter.
- Dehydration should be avoided.
- Tight clothing and watches on the fistula arm should be avoided.
- After discharge, the fistula should be checked for a thrill every day; if the thrill is lost this is an emergency that should be managed as perioperatively.
- Prophylactic anti-platelet doses of aspirin (1–5mg/kg/day) may reduce the risk of clotting.

Cannulation of the arterialized veins when the fistula is mature

- Veins are rarely adequately arterialized ('mature') before 4 weeks.
- The skin should be cleaned before use and sterile topical analgesic creams can be applied.
- Single needling may be used at first.
- Needles should be placed proximal to the fistula, with the arterial needle distal to the venous one, which should be as far away as possible. The arterial needle can point in either direction, but the venous needle should be towards the heart.
- Fistula needles range from 15–17G.
- The needle sites should be changed as repeated needling in the same place will cause weakness of the vessel wall and aneurysm formation.
- It is also possible to use 'The buttonhole technique'. Two sites (one for each needle) are selected and needles are inserted in exactly the same spots at exactly the same angle. Over 8–10 cannulations, scar tissue will form creating a tunnel at each site. The scab is then removed prior to inserting special blunt needles. This is less painful and aneurysms are less likely to form. Cleaning of the area before needling must be scrupulous.

Fistula stenoses

- Stenoses can occur proximal to, distal to, or within the fistula, due to turbulent blood flow and intimal damage. The commonest site is a few centimetres distal to the anastomosis. They can also occur where the vein passes through the cribriform fascia.
- Venous stenosis will result in slow blood flow through the fistula and, therefore, a predisposition to thrombosis.
- The fistula should have an easily compressible pulse and a continuous thrill, which is palpable with blood flows >450mL/min.
- If there is a stenosis, the thrill is distal to the pressure drop. The risk of the fistula clotting increases when the flow is <650mL/min.
- *Elevation test evaluates outflow:* the fistula should collapse on elevation of the arm if there is no downstream stenosis.
- *Augmentation test evaluates inflow:* a finger is used to cause complete occlusion of the access several centimeters beyond the arterial anastomosis. If the fistula flow is normal, the portion of fistula upstream from the occluding finger demonstrates augmentation of the strength of the pulse.

- Fistulae should be screened 3–6-monthly using Doppler US to look for blood flow rates and the presence of stenoses. Blood flow is reduced if <200–300mL/min (400 for adults).
- Failed augmentation test, low blood flow or low arterial pressure suggests stenosis at the inflow to the fistula. Arteriography is necessary to examine the arterial flow into the fistula.
- Failed elevation test, increased venous pressure or thrombosis needs a fistulogram, when X-ray contrast is used to demonstrate the blood flow into and out of the fistula.
- In the presence of low flow or increased venous pressure, recirculation should be checked.
- Recirculation is when dialysed blood returning from the venous line to the circulation is taken back into the arterial line for redialysis. If >10–15%, this suggests venous stenosis.
- Stenosis >50% of vessel diameter needs angioplasty, stenting, or surgical repair.
- Central vein obstruction, with swelling of the arm and neck will occur if stenosed central veins (particularly subclavian).

Other complications

- Thrombosis.
- Infection.
- Ischaemia of the hand or 'steal syndrome'.
- Aneurysm.
- Pseudoaneurysm, due to communication of the fistula with an enclosed area of surrounding tissue. It may lead to prolonged bleeding and needs to be repaired.
- Extravasation injury.
- Central vein obstruction, with swelling of the arm and neck will occur if stenosed central veins (particularly subclavian).
- High cardiac output.
- Cosmetic.

Grafts and shunts

- An artificial conduit can be inserted between an artery and vein SC (graft), where it can be needled, or may be brought out externally (shunt) where the loop can be disconnected to attach to dialysis lines.
- They should only be used if AV fistulae or tunnelled lines are not possible.
- Pre- and post-operative care is as for AV fistulae. Risks are:
  - infection that can be difficult to eradicate;
  - stenosis at the anastomosis site;
  - thrombosis;
  - disconnection and blood loss (with shunts).
- US screening should be more frequent than for AV fistulae. Blood flows <600mL/min are considered significant, or a 20% reduction in flow in <3 months.

Haemodialysis: blood-borne viruses

- Haemodialysis unit patients and staff are at risk from blood-borne viruses, particularly hepatitis B, hepatitis C, and HIV.
- A number of outbreaks of hepatitis B were reported in HD units during the 1960s in the UK and elsewhere.
- Transmission may result from percutaneous exposure to blood or other fluids, via droplets or through contaminated equipment.
- Universal precautions should be followed as for all patients, and the entire dialysis circuit should be decontaminated after each use by heat or chemical disinfection. External surfaces should be wiped over between patients using a Cl-based disinfectant.
- All staff and patients should be immunized and/or show immunity to hepatitis B (see 📖 'Management: immunization schedule for infants and children', p.451).
- If a patient is exposed to hepatitis B or has been to an endemic area, such as the Middle and Far East, and has antibody titres <100IU/L in the last year, then hepatitis B immunoglobulin and vaccine should be given by IM injection, and the patient should be screened weekly for HbsAg for 3 months. Patients who are or who might become HbsAg positive should be dialysed in a separate room with their own machine.
- Although screening for hepatitis C or HIV is not universally recommended at present, many units do so. Hepatitis C can be spread nosocomially, so a separate room is recommended for the patient who is hepatitis C positive, but a dedicated machine is not necessary. HIV is less infectious, but the same criteria apply. Testing for hepatitis C antibody 3-monthly and for HIV annually is a reasonable compromise.

Further reading

Levy JE, Brown E, Daley C, and Lawrence A. (2009). *Oxford Handbook of Dialysis*, 3rd edn. Oxford University Press, Oxford.

Warady BA, Schaefer FS, Fine RN, and Alexander SR. (eds) (2004). *Pediatric dialysis*. Kluwer Academic Publishers, Dordrecht.

Continuous renal replacement therapy

Background

Continuous renal replacement therapy (CRRT) is a technique used in the intensive care unit (ICU) for the management of AKI. In the commonest type, blood is pumped from a vein, through the filter and back to a vein (continuous veno-venous haemofiltration (CVVH)), but an artery to a vein can also be used (CAVH). Solute movement is principally by convective flow so high UF rates are needed (see 📖 'Haemodialysis: principles', p.484). A countercurrent circuit can be used to haemodialyse too, thereby adding in diffusive solute clearance (CVVHD, CAVHD). CVVHDF employs both dialysis and UF. The UF contains electrolytes in a concentration similar to that of the plasma, so the larger the UF volume the greater the clearance. The UF is returned as 'replacement fluid', which is designed to correct abnormal biochemistry. The proportion of the UF that is replaced is adjusted in order to achieve or maintain euvolaemia. Slow, continuous UF (SCUF) can be used to remove fluid (UF) in smaller quantities, such that replacement is not required.

Advantages

- It is best for patients with cardiovascular instability as it allows slow fluid removal so that major fluid shifts do not occur.
- Episodes of hypotension are less likely to occur than with HD, decreasing the risk of further ischaemic insult if the kidneys are recovering.
- Therapeutic drug levels are more easily maintained than with HD.

Disadvantages

- Clearance is less than for HD, but can be increased by maximizing blood flow, UF, and/or dialysate flow rate, depending on the type of CRRT.
- Rough comparative clearance ratio for daily treatment is:

$$HD = CVVHD = 3 \times CVVH = 4 \times PD$$

- In patients with inborn errors of metabolism with very high ammonia levels (>400μmol/L), CRRT may not provide adequate clearance, and HD is preferable until the ammonia levels are <200μmol/L (see 📖 'The emergency renal management of inborn errors of metabolism', p.268).
- Potassium and phosphate losses may be excessive, but can be replaced in the replacement fluid or IV.

The prescription

- Standard blood flow is 3–5mL/kg/min, but can increase to 8–10mL/kg/min when high clearances are required.
- The extracorporeal circuit volume should not be >10% of the child's blood volume (as for HD).
- If the circuit is greater than 10% of blood volume the lines must be blood primed. If the haematocrit of the packed cells to be given is high, they must be reconstituted with saline to a haematocrit around 30% to prevent blood clotting in the filter.

- Filtrate is replaced with commercially available solutions containing Na, K, Ca, Mg, chloride and lactate (see Table 20.5), or bicarbonate via a separate infusion.
- Lactate is a better buffer than bicarbonate when the solution is stored in plastic bags, as plastic is soluble to CO_2. Lactate is stable, whereas bicarbonate will break down over time to H_2O and CO_2, and loose its buffering capacity. However, lactate will be delivered to the patient, making patient levels difficult to interpret. Bicarbonate is, therefore, preferable in children.
- Standard dialysate flow is 1–2L/h.
- UF rates of 35mL/kg/h may be used.
- Patient water loss = [UF + urine output + insensible losses + other losses (e.g. gut, drains)] – fluid replacement.
- Fluid removal of 0.5–2mL/kg/h can be tolerated, depending on need.
- The fluid is replaced before entry into the filter as it decreases blood viscosity and decreases the chance of clotting in the filter.

Table 20.5 Ranges of electrolyte concentrations in replacement fluid.

	Mmol/L
Na	132–140
K	0–2
Ca	1.6–1.8
Mg	0.5–1.5
Cl^-	100–115
Lactate	30–45

Anticoagulation

- Clotting of the filter is a common problem, often caused by mechanical problems and added to by slow blood flows and high UF rates.
- The use of anticoagulation must be carefully considered in the child with abnormal clotting, such as disseminated intravascular coagulation (DIC), as the potential for bleeding has to be balanced against clotting of the filter, which will be a particular risk in the child who is receiving fresh frozen plasma (FFP) and platelets.
- Heparin is given as a loading dose of 20U/kg and a prefilter infusion of 10–30U/kg/h to keep the partial thromboplastin time (PPT) at 60–90s or the activated coagulation time (ACT) at 130–170s.
- Epoprostenol may also be infused through the filter to prolong its life.
- Some centres prefer to use Na citrate prefilter, which binds Ca thereby stopping the coagulation cascade. Ca then must be infused post-filter to prevent hypocalcaemia.

Plasmapheresis and immunoadsorption

Plasma exchange

During plasma exchange the patient's plasma is exchanged for albumin or FFP. It may be undertaken by a centrifugal cell separator (when there is no limit to the molecular weight of the proteins that can be removed) or a membrane plasma filter (which may not remove large immune complexes).

The process

- Machines have large extracorporeal volumes (>200mL), so the lines need to be primed with blood in children <20kg in weight.
- The amount of plasma exchanged is related to the circulating plasma volume, such that 'one volume' is approximately two-thirds of the total blood volume, i.e. approximately 50mL/kg.
- A one volume exchange (50mL/kg) will remove 60% of plasma macromolecules, and 5 one volume exchanges will remove 90% of the total immunoglobulin.
- Usually the amount of plasma exchanged is 2 vols, i.e. 100mL/kg daily for 5 days, and may be followed by 5 further daily sessions.
- Fluid replacement is with warmed 4.5% albumin or FFP or Octoplas, which contain potentially missing complement and clotting factors. Dilution of albumin may be needed to prevent fluid shifts.
- Clotting must be checked before and after each session as clotting factors are depleted. Commonly by the third day fibrinogen levels have fallen to <2g/dL, so FFP can be added at the end of the exchange at a dose of 150–300mL, depending on the weight of the child.
- If the Ca is <2.0mmol/L, 1g of Ca can be added per L of albumin.
- Anti-coagulation is usually with heparin, but citrate can be used.
- Chlorphenamine can be given if allergic reactions are seen. Reactions are often related to the speed at which the FFP is delivered.
- Immunosuppression is used after the course to prevent the return of the immunological abnormalities if the exchange has been performed for immunological reasons.

Complications

- Coagulation disturbances.
- Infection.
- Allergic reactions to plasma, particularly FFP.
- Fluid imbalance.

Renal diseases for which it has been used

- Anti-glomerular basement membrane disease.
- Anti-neutrophil cytoplasmic antibody-associated vasculitis with crescentic nephritis and/or pulmonary haemorrhage or other life-threatening complications.
- Crescentic nephritis due to other causes.
- Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura with cerebral involvement.

- Recurrent focal segmental glomerulosclerosis post-transplant.
- Acute antibody mediated transplant rejection.
- Systemic lupus erythematosus: severe lupus nephritis resistant to conventional therapy, cerebral lupus, or other fulminant multi-systemic manifestation.

Immunoadsorption

Protein A columns selectively remove immunoglobulin (principally IgG) from plasma. They have been used to remove human immunoglobulins in diseases associated with pathogenic antibodies. Currently, they are being tried in the removal of human leucocyte antigen antibodies in highly sensitized transplant recipients and for removal of ABO antibodies to allow blood group incompatible transplantation, with encouraging results so far.

This page intentionally left blank

Chapter 21

Transplantation

Renal transplantation immunology

Background

The immune response in the context of transplantation consists of:

- Recognition of foreign antigens.
- Activation of antigen specific lymphocytes.
- The effector response.
- The major histocompatibility complex (MHC) located on chromosome 6 consists of a linked set of genetic loci containing many genes involved in the immune response.
- The human MHC includes the human leucocyte antigen (HLA) genes—the products of these genes are expressed on the cell surface as glycoproteins.
- There are 3 classes within the MHC region:
  - class I region—includes the HLA genes *HLA-A*, *HLA-B*, and *HLA-C*;
  - class II region—includes HLA genes *HLA-DR*, *HLA-DQ*, and *HLA-DP*;
  - class III region—includes the genes for components of the complement cascade and cytokines, e.g. tumour necrosis factor, LTA.
- Class I molecules are expressed on nearly all nucleated cells.
- Class II molecules are only expressed on B cells, antigen-presenting cells (APCs) and on activated endothelial cells (that can act as APCs).
- APCs are a group of cells (such as dendritic cells) that process antigens and present them, in association with HLA molecules, to T cells.
- Donor APCs may migrate out of the graft to a secondary organ and stimulate T cells directly (direct recognition) or host APCs may pick up donor antigens that have been shed from the graft and stimulate host T cells indirectly (indirect recognition).
- T cell receptors recognize peptides bound to HLA molecules.
- CD4 T cells (T helper cells) interact with class II molecules, which results in the production of cytokines that lead to a cascade of cellular and humoral reactions that are responsible for the effector responses important in transplant rejection.
- CD8 T cells (T killer cells) are cytolytic, directly interacting with cells expressing class I and maybe toxic to the cell to which they bind.

Blood group

- Although blood group O is the universal donor and AB the universal recipient, for reasons of equity, in the UK, and in most organ allocation systems, donor kidneys are first allocated on the basis of blood group, i.e. patients are only offered kidneys from donors of the same blood group as themselves.
- In certain cases, antibody removal techniques may be used to allow successful transplantation across the ABO barrier.
- The Rhesus antigen is not expressed on kidney cells and plays no role in organ matching.

Histocompatibility and immunogenetics laboratories

These laboratories support transplant programmes by providing three main services:

- HLA (tissue) typing.
- Detection and definition of HLA-specific antibodies.
- Pre-transplant cross-matching.

HLA typing

- HLA (tissue) typing refers to the identification of HLA antigens. HLA typing may be undertaken using microcytoxicity test (identification of HLA antigens using known HLA antibodies) or by DNA-based techniques.
- HLA antigens have been allocated numbers as they have been recognized. Subsequently, new antisera have demonstrated narrower specificities, which are conventionally shown in brackets, e.g. HLA-A9 has been split into HLA-A23 and HLA-A24 so is written as HLA-A23(9) and HLA-A24(9). These are called split antigens, and can usually be treated similarly in the matching process.
- DNA technology has led to identification of many more alleles so that at least two fields separated by a colon and a minimum of 4 digits are now used. The first field denotes the antigen family or allele group, e.g. HLA-A*01 where the * denotes that DNA technology has been used and the second field denotes the allele, e.g. HLA-A*01:01.
- The most common HLA antigen is HLA-A2, which is found in almost 50% of Caucasian people. 90% of Caucasians with HLA-A2 have HLA-A*02:01, although other ethnic groups may have different alleles. Frequencies of other HLA antigens vary with ethnicity, e.g. HLA-B8 is present in 30% of Irish; HLA-B54 is unique to Far Eastern populations, such as Japan; and HLA-A36 is found in the Black (Afro-Caribbean) population.
- Some antigens are inherited together more often than would be expected by chance, e.g. HLA-A1, HLA-B8 HLA-DR17 and HLA-A2, HLA-B44, HLA-DR7. This is known as linkage disequilibrium.
- Individuals may be homozygous for a HLA antigen, i.e. they will appear to only have one HLA antigen at any locus, rather than two as they have inherited the same antigen from each parent. For example, if they had only one HLA-A antigen, which was HLA-A2, and only one HLA-B, which was B44, together with DR1 and DR2 their HLA type would be recorded as follows: HLA-A2,-;B44,-;DR1,DR2.

Detection and definition of human leucocyte antigen-specific antibodies

- Sensitization is the development of antibodies to HLA antigens, which can result as a consequence of exposure to non-self HLA. This can occur three ways:
  - previous transplantation;
  - blood or platelet transfusion;
  - pregnancy, when the mother is exposed to paternal HLA antigens.

- HLA antibodies may be unique to a specific allele or limited group (private) or recognize an epitope that is shared by more than one HLA molecule (public) resulting in cross-reactivity. HLA antibodies do not develop to one's own HLA antigens, except in rare cases where a HLA allele is not expressed on the cell surface.
- The term reaction frequency (RtF) is an indicator of the level of sensitization for a patient. The result given for a particular patient is the percentage of blood group identical, HLA incompatible donors in the pool of 10,000 UK donors, i.e. if the RtF is 50%, then half of donors would be expected to give a positive cross-match and be unacceptable.
- Antibodies specific for HLA are now usually defined using microbead array or ELISA techniques that have proved more sensitive than cytotoxicity.
- IgM antibodies are usually auto-antibodies, of little relevance to tissue reactivity (in the context of transplantation biology), and can be ignored, unless directed at HLA.
- If a patient does not develop an antibody to a mismatched antigen on regular post-transplant checks it is likely that they have not responded to that antigen and may be given it again in a subsequent graft.
- If a patient has HLA specific antibodies to a potential living donor, antibody removal may be considered. This can be attempted in many ways, although none are guaranteed effective, and the procedure must be considered high risk (http://www.bts.org.uk).
- HLA specific antibodies can also develop during acute or chronic graft rejection before the graft is lost and are associated with adverse graft outcome.

Pre-transplant cross-matching

- The donor/recipient cross-match is an essential pre-transplant test performed to confirm the absence of donor directed HLA antibodies, which could initiate severe rejection in the recipient.
- The complement dependent cytotoxic cross-match is the most common test, where donor lymphocytes are incubated with recipient serum in the presence of complement. A positive cross-match is a contraindication for transplantation.
- Serum tested must have been collected within the previous 3 months and preferably within the last month. If the child has been transfused since the most recent sample, a fresh serum sample should be provided.
- Flow cytometry cross-match is a more sensitive cross-match test. It is particularly useful in patients who are sensitized.
- HLA specific antibodies should have been defined pre-transplant, decreasing the chances of a positive cross-match.
- The T cell cross-match identifies antibodies to HLA class I, whereas the B cell cross-match identifies antibodies to both HLA class I and class II.
- Historic positive, current negative cross-matches may be acceptable for transplantation if the sensitization event is blood transfusion or extra immunosuppression can be tolerated.
- Patients who can be identified as HLA antibody negative up to the time of the most recent sample tested (provided that an adequate range of samples over time have been received for testing) can proceed to

transplant on the basis of a 'Virtual cross-match' (VXm). A VXm can be performed pre-transplant, whereby the donor HLA type is reviewed against the patient's HLA antibody profile to determine whether the patient has donor-directed antibodies that would cause a positive cross-match test result. A VXm can be performed before cross-match material is available and allows the transplant team to proceed to theatre before the cross-match test. The purpose of this approach is to reduce the cold ischaemia time without compromising the safety of transplantation.

Human leucocyte antigen matching and organ allocation

- After blood group, kidneys are allocated according to the degree of HLA mismatching, those recipients with the lowest degree of mismatching to the donor being given priority. This is because:
  - HLA (particularly class II) mismatching is associated with worse graft outcome;
  - the development of antibodies to mismatched antigens will prejudice the chances of finding subsequent grafts.
- It is convention to count the number of donor HLA antigen mismatches, as this is a reflection of antigen dose. Three loci are considered—HLA-A, HLA-B, HLA-DR. Each individual has two antigens at each locus, and there can be 0, 1, or 2 mismatches at each locus. This mismatching is abbreviated to a 3-number code, whereby 000 is no mismatch at any locus, i.e. a perfect match and 222 is two mismatches at each locus, i.e. a complete mismatch.
- Deceased donor organs are allocated in the UK by NHS Blood and Transplant Organ Donation and Transplantation Directorate (NHSBT-ODT) using a complex algorithm. Paediatric patients are prioritized throughout. Where patients are equally matched, waiting time (i.e. the longer) will be used to determine the choice. In the event of a tie in waiting time, the recipient at the closest unit to the offering/retrieval centre, based on transport time, will receive the offer.
- The chance of a patient receiving a graft that is well matched for their HLA antigens will depend on the frequency of their antigens in the deceased donor population, which also reflects their ethnic background in comparison with the donor population. A 'matchability' score for a patient's antigens can be calculated from the deceased donor population and used to generate a score of 1–10, so that 1 is easiest to match and 10 is hardest to match.
- It may be considered unwise to mismatch at a common antigen, e.g. HLA-A2, particularly in children, to avoid sensitization to half the potential donors which would compromise retransplantation.
- As well as HLA, the major histocompatibility barrier, there are many minor histocompatibility loci. This means that only identical twins can be transplanted without immunosuppression, even if all HLA antigens are matched.

Parental donation

- Most children will share three antigens with each parent as they have inherited the genes found on one chromosome (e.g. 1A, 1B, 1DR antigen, often referred to as a haplotype). Even so graft survival has been found to be very good and equivalent to a 0 mismatched cadaveric graft. If parents have HLA antigens in common they could be better than 1 haplotype match.
- Parents must be made aware that tissue typing may identify potential non-paternity, but this is not a paternity test.
- All living donor transplants require approval from a representative of the Human Tissue Authority.
- If a relative is considering donation to a patient on the waiting list for a deceased donor kidney, it is a useful strategy to ensure the donor's antigens that are mismatched with the recipient are registered as unacceptable for any deceased donor kidney. If the deceased donor transplant then fails antibodies to the living donor should not develop.

Further reading

Dyer PA, Logan A, Poulton KV, Wood K, Worthington J. (2010). Testing for histocompatibility. In: Forsythe JLRF (ed.) *Transplantation – a companion to specialist surgical practice*, 4th edn. Elsevier Saunders, St Louis.

Vaccination after transplantation

Background

- Before transplantation children should be up to date with routine primary immunizations and additionally receive varicella, pneumococcal (if transplanted before this vaccine was routine), Bacille Calmette-Guérin (BCG), and hepatitis B vaccines (see 📖 'Management: immunization schedule for infants and children', p.451).
- After transplantation children should be given non-live vaccines normally according to the childhood immunization schedule, but should **not** receive live vaccines.

Vaccines that are not recommended post-transplant

- Oral polio vaccine (OPV/Sabin), including the vaccination of household contacts (this is now only rarely offered as the inactivated vaccine is given in a combined diphtheria, tetanus, pertussis, polio, and haemophilus type b conjugate vaccine as part of the routine immunization schedule).
- MMR or rubella vaccine.
- BCG, BCG SSI vaccine.
- Yellow fever vaccine (Arilvax®, Stamaril®).
- Oral typhoid vaccine (Vivotif®).
- Varicella vaccine (Varivax®, Varilrix®).
- All other live vaccines.

Vaccines that can be administered post-transplant

- Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed).
- *Haemophilus influenza type B*-HIB (Hiberix®) vaccine.
- Hepatitis A vaccine (Avaxim®, Havrix Monodose®).
- Hepatitis B vaccine (Engerix B®, HB-Vax Pro®).
- Inactivated polio vaccine (IPV/Salk).
- Meningococcal group C conjugate vaccine (Meningitec®, Menjugate®).
- Meningococcal polysaccharide A, C, W135 & Y vaccine (ACWY Vax®).
- Pneumococcal polysaccharide unconjugated vaccine (Pneumovax® II).
- Pneumococcal polysaccharide conjugated vaccine (Prevenar® 13).
- Rabies vaccine.
- Vi capsular polysaccharide typhoid vaccine (Typherix®, Typhim Vi®).
- Influenza vaccine is recommended annually.

Further reading

Cant A, Davies G, Finn A, et al. (2002). *Immunization of the immunocompromised child*, Best Practice Statement. Royal College of Paediatrics and Child Health, London.

Joint Formulary Committee (2011). *British National Formulary 2010–2011*. Pharmaceutical Press, London.

Kidney transplantation: the surgery

Living donation

Although many parents wish to donate a kidney to their child, up to 50% find they are unable because of either:

- Incompatible blood group.
- Preformed anti-HLA antibodies in their child.
- Diagnosis of ill health of which they were previously unaware.
- The detection of a single kidney.
- Social or financial reasons.

Most children are able to undergo successful transplantation using an adult kidney once they have reached 8–10kg in weight.

Advantages for the recipient

- The ability to plan the timing of transplantation, which can be before dialysis becomes necessary (pre-emptive or pre-dialysis transplantation).
- Outcomes (graft survival, acute rejection rate) for living donors is better than for deceased donation even if the degree of HLA matching match is inferior.

Disadvantages

- Mortality risk for the donor of 0.03%, donor readmission rate <1%, requirement for donor blood transfusion 1.5%, other donor surgical complications approximately 3%.
- Post-operative pain, which may be minimized by laparoscopic donor nephrectomy. May need up to 3 months to return to normal activity.

The lifetime risk for chronic kidney disease (CKD) in the general population is 2–7.5%, depending on ethnic background and is not increased in those who have donated a kidney. A number of studies have shown increased life expectancy in kidney donors compared with the general population, although it must be remembered that the former have undergone formal health screening.

Deceased donors

- Kidneys from deceased donors <5 years of age are not used for paediatric recipients as they are associated with an increased risk of technical problems and graft thrombosis. Some centres transplant both kidneys on a patch of aorta (*en bloc* transplantation), but most experience is in adult recipients.
- Deceased donors aged >55 years are not used in children (although a living donor over this age may be acceptable).
- Prolonged hypertension or hypotension may damage the donor kidney.
- Disseminated malignancy, renal malignancy and treated cancer within 3 years are contraindications to donation unless primary central nervous system, low grade non-melanoma skin cancer, or carcinoma *in situ* of the cervix.

- Hepatitis B (HBV) positive donors were previously thought to be unsuitable. However it is now clear that these organs can safely be used in HBV positive recipients. Furthermore, experience from adult transplantation suggests that transplantation can be safely performed where the donor has anti-HB core (anti-HBc) antibodies, which may reveal current HBV infection at a time when surface antigen is no longer detectable, but hepatitis B surface antibody has not yet reached titres sufficiently high to clear the virus. If the anti-HBc antibody is of IgM class this indicates recent HBV exposure and active infection, and the donor is therefore a high risk for transmission, whereas anti-HBc antibody of IgG class is most likely to represent remote exposure that has already resolved. However, in some cases, HBV might still be present despite the appearance of IgG anti-HBc antibody. Therefore, a donor positive for both hepatitis B surface and core antibody, but negative for antigen usually indicates recovery from HBV and naturally acquired immunity. The risk of transmission of HBV in a donor with anti-HBc antibodies can be assessed by measuring HBV DNA. Donors who are HBV DNA polymerase chain reaction (PCR) negative are unlikely to transmit HBV.
- Recipients should be immunized against hepatitis B.
- Hepatitis C (HCV) and HIV positive donors can be used for HCV and HIV positive recipients.
- Diabetes mellitus for >5 years or other donor diseases that might affect the kidney are contraindications to donation.
- Donors who have died from sepsis are accepted if the infection has been satisfactorily treated: some centres will not accept organs from donors with meningococcaemia who have had <48h of antibiotics, or active tuberculosis (TB) with <6 months of treatment.
- Kidneys can be used from non-heart-beating donors. Recent data suggest that short- to medium-term graft survival is no different from heart-beating deceased donors.
- Trauma may occur to the graft during its removal, e.g. a tear to the renal vessels, which need repair.
- Kidneys are harvested on a 'patch' of aorta. Those with multiple renal vessels may need 'bench' surgery to anastomose a small artery to a larger one if the patch is unsatisfactory.
- Kidneys with several adverse factors are called 'marginal' kidneys and are not often used in children. If they are, the family must be informed.

Warm and cold ischaemia times, and anastomosis time

- Warm ischaemia time is the time between circulatory arrest and cold storage. With *in situ* perfusion in the donor this can be close to zero, but will be significant in a non-heart-beating donor. A warm ischaemia time of over 20 min is associated with an increased risk of delayed graft function or primary non-function (when the graft never works).
- Cold ischaemia time is the period of cold storage. It results in endothelial activation and graft outcome worsens with longer cold ischaemia times. Every attempt should be made to transplant the organ within 24h of retrieval.
- Anastomosis time is the time between removal from cold storage and completion of the arterial anastomosis.

Ischaemic injury and acute tubular necrosis

Donor factors (see 📖 p.518), ischaemia and anastomosis times, and reperfusion injury may contribute to ischaemic injury and delayed graft function (acute tubular necrosis, ATN).

- It can only be diagnosed after exclusion of technical causes and rejection.
- There is good blood flow but no excretion on diethylene triamine pentaacetic acid (DTPA) or MAG3 scan.
- There may be no urine output and dialysis dependency or relative oliguria with a slowly falling plasma creatinine.
- Cytokine release in the kidney in ATN may make rejection more likely.

Delayed graft function masks diagnosis of other complications including acute rejection and recurrent disease, making weekly ultrasound (US), DTPA, or MAG3 and biopsy necessary.

The operation

- The external iliac artery and vein are used in older children, and the common iliac vessels or aorta and inferior vena cava in smaller ones. The right side is preferable as it is easier to expose the common iliac vein.
- If the aorta is used, the incision is midline or paraumbilical, and oblique if the iliac vessels are used.
- The transplant may be intraperitoneal in small children, although there is an increasing tendency to perform extraperitoneal surgery, even in the smallest recipients.
- If the kidney is large in comparison with the child, a right nephrectomy may be necessary.
- The ureter is anastomosed to the bladder, usually without a formal anti-reflux procedure. A stent may be temporarily left through the vesicoureteric junction (VUJ).
- Some children with abnormal bladders may require a ureterostomy or ureteric implantation into an augmented bladder or ileal conduit. This will be decided pre-transplant.

Surgical complications

- Wound infection.
- Lymphocoele, due to leakage from lymphatics that are cut during dissection around the blood vessels.
  - appears to be more common with the use of sirolimus and everolimus;
  - symptoms depend on size—may present with obstruction to transplant drainage, and swollen leg due to obstruction of venous return;
  - diagnosis by US and aspiration, when the biochemistry of the fluid is found to be similar to plasma, although the protein content may be higher;
  - treatment may be conservative, by external percutaneous drainage or by 'marsupialization', when the lymphocoele cavity is opened into the peritoneal cavity.

- Bleeding, particularly as most centres would use heparin or aspirin to prevent graft thrombosis.
- Steal syndrome, when blood is diverted away from the leg to the transplant or when narrowing of the iliac vessel occurs. This can result in claudication of the affected limb.
- Urinary leaks can be at the VUJ, from the ureter due to compromised ureteric blood flow or occasionally from a ruptured calyx. This may present with:
  - abdominal pain;
  - an abdominal collection on US;
  - a rising creatinine due to reabsorption;
  - a falling plasma creatinine with relative oliguria. diagnosis is by aspiration and biochemical analysis, when the aspirated fluid is similar to urine; or by imaging by cystogram (for a bladder leak), DTPA scan or intravenous pyelogram (IVP);
  - Treatment is by bladder catheterization to allow the leak to heal, although surgery may be necessary if there has been sloughing of tissue.
- Ureteric obstruction:
  - early may be acute post-surgery due to clots or a lymphocoele;
  - later may be due to VUJ obstruction or to ureteric stenosis, which is predisposed to by the tenuous blood supply to the ureter;
  - ureteric stenosis may also be due to BK virus infection;
  - rarely due to calculi;
  - diagnosis is by US, DTPA/MAG3 with furosemide or antegrade studies if necessary;
  - it may be possible to dilate a short (<2cm) narrowed segment endoscopically; otherwise surgical repair is necessary.
- Renal artery stenosis generally presents after the third month post-transplantation. It may result from:
  - clamp injury to the donor or recipient vessel;
  - vessel injury from the perfusion catheter;
  - kinking of the renal artery;
  - narrowing around the anastomosis site;
  - diagnosis is by Doppler US, DTPA scan and arteriography;
  - treatment is by balloon dilatation if feasible or surgery.

Graft thrombosis

This may start in the artery or vein, and usually occurs in the first 3 days post-transplant. Most centres use perioperative prophylaxis with low molecular weight (LMW) heparin (particularly if there is a positive procoagulant screen, see 📖 'Preparation for renal replacement therapy', p.458) or aspirin. This is started at surgery; thereafter protocols vary, but LMW heparin is usually continued until the child mobilizes. Aspirin 1mg/kg body weight/24h as a single daily dose (maximum 75mg) is more commonly used in the child with a normal procoagulant screen and is continued for 4–12 weeks post-transplant.

- Causes of graft thrombosis may be:
  - slow blood flow due to surgical technique or decreased circulating blood volume;

- procoagulant state (which should be excluded pre transplant);
- severe rejection.

- Presentation is with:
  - sudden reduction of urine output and rising creatinine;
  - macroscopic haematuria if venous;
  - graft swelling and pain or tenderness;
  - thrombocytopaenia.
- *Investigations:* no flow will be seen through the transplant on imaging by:
  - Doppler US;
  - DTPA or MAG3 scan.
- Treatment is graft nephrectomy as the transplanted kidney does not have collaterals to maintain its blood supply.

Immunosuppressive therapy in renal transplant patients

Immunosuppressive therapy is given following renal transplantation to prevent rejection of the graft and to treat episodes of acute rejection. The exception to this is where the donor is an identical twin of the recipient.

General principles

- Most paediatric kidney transplant recipients in Europe are commenced on a calcineurin inhibitor: tacrolimus or ciclosporin in conjunction with a corticosteroid and an antiproliferative immunosuppressant drug (azathioprine or mycophenolate mofetil).
- Following the results of the recent TWIST study, a number of centres now withdraw steroids after 5 days in low risk recipients.
- The anti-CD25 monoclonal antibody basiliximab may be added in patients deemed at risk of rejection, e.g. where steroid withdrawal is planned, with ciclosporin as the calcineurin inhibitor and where the risk of rejection is thought to be greater (e.g. second or subsequent transplants or poorly-matched kidney).
- Relatively intense immunosuppressive therapy is given in the early post-transplant period when the risk of acute rejection is greatest, with a subsequent tapering (reduction in steroid dose and target calcineurin inhibitor level) to reduce the risk of adverse-effects in the long-term.
- Because of concerns about the long-term nephrotoxicity of the calcineurin inhibitors, a number of regimens aim to reduce the dose of or remove these agents at various time intervals post-transplantation.
- Very few prospective randomized controlled trials (RCTs) have been performed in the field of paediatric renal transplantation and there is no good evidence to support the use of any particular regimen.
- Whilst all of the agents discussed in this chapter have specific individual adverse effects, immunosuppressive drugs are, in general, associated with an increased risk of infection (bacterial, viral, and fungal) and malignancy. The more potent immunosuppressive agents will reduce the risk of acute rejection at the price of an increased risk of adverse-effects. The goal of optimal immunosuppressive therapy is to balance these risks and benefits.
- Non-adherence with therapy is a major cause of morbidity and graft loss, particularly in the adolescent population. Therapeutic regimens should be kept as simple as possible, with the use of once daily medication where feasible. The importance of cosmetic side-effects of therapy should not be underestimated.

Calcineurin inhibitors: ciclosporin and tacrolimus

- These agents modify T-cell function, inhibiting interleukin-2 (IL-2). production by activated T-cells.
- Both drugs are licensed for use in children in the UK.

Tacrolimus

- Available as a twice daily preparation (Prograf® capsules or Modigraf® granules).
- A newer prolonged release preparation of tacrolimus (Advagraf®) may be given once daily.

- All of the RCTs investigating tacrolimus have been performed using Prograf®.
- Paediatric studies are currently ongoing to determine whether Prograf® and Advagraf® can be used interchangeably.
- There have been a number of instances where Prograf® and Advagraf® have been dispensed interchangeably with adverse patient outcomes. It is therefore recommended that the drug is prescribed using the appropriate brand name.
- Prograf® is started at 0.15mg/kg/dose 12-hourly (oral). Subsequent dosing is altered in response to trough tacrolimus levels, the dose being adjusted upwards or downwards to achieve desired target trough levels. Many centres will reduce the starting dose to 0.1mg/kg/dose (adult starting dose) in young adults.
- Advagraf® is given at same total daily dose, i.e. 0.3mg/kg daily or 0.2mg/kg daily. Advagraf® capsules are large and must be taken whole—as such they are generally only suitable for children of around 8 years and above.
- Monitoring of trough (concentration at 12h, C_{12}) levels is mandatory:
  - typical target ranges 10–12microgram/L for first 1–2 months and 5–10microgram/L thereafter;
  - many centres will progressively reduce target tacrolimus levels with increasing time post-transplantation, particularly in stable patients;
  - the Symphony study showed excellent outcomes in adults using a combination of low dose tacrolimus (target levels 3–7microgram/L), mycophenolate mofetil (MMF), and steroids;
  - levels below 2microgram/L cannot be reliably measured using conventional assays.
- Diarrhoeal illness will result in increased tacrolimus levels due to enhanced enterohepatic circulation and careful monitoring should take place when this develops.
- Food decreases the rate and extent of absorption of the drug with high fat meals producing the most pronounced effect—around a 35% reduction in AUC.
- Where IV tacrolimus needs to be given, one fifth of the oral dose should be administered over a 2-h period:
  - the drug interacts with polyvinyl chloride (PVC) and needs to be infused via non-PVC tubing;
  - experience with IV tacrolimus is limited and there is anecdotal evidence of the drug causing severe hypertension; oral tacrolimus is very well absorbed and there are very few instances in which IV therapy should prove necessary.

Ciclosporin

- Dose 3–5mg/kg/dose given 12-hourly (oral) with subsequent dose adjustment to achieve target levels.
- Monitoring of drug levels is mandatory. Typical target ranges at 12h after dose (C12) are 150–250microgram/L for the first 3–6 months and 75–150microgram/L thereafter.
- There has been much interest in monitoring drug levels at 2h post-dose (C2 levels), as this has been shown to be a better estimate of exposure to the drug in the first 4h following oral administration. No paediatric data has shown improved graft outcome using such an approach.

- Where IV ciclosporin needs to be given, one third of the oral dose should be administered over a 2-h period.

Adverse-effects of calcineurin inhibitors

- Many adverse effects are common to both agents including:
  - nephrotoxicity (reversible vasoconstriction in short-term, but also irreversible interstitial fibrosis in long-term);
  - hypertension;
  - headache;
  - tremor;
  - hepatic dysfunction;
  - diabetes mellitus (more common with tacrolimus);
  - hypomagnesaemia;
  - hyperkalaemia.
- Ciclosporin-specific cosmetic side-effects include:
  - hypertrichosis (worse in dark skinned, dark haired individuals);
  - gingival overgrowth (worse where dental hygiene is poor and improves with careful toothbrushing. May respond to azithromycin, occasionally requires gingivectomy).

Important drug interactions with calcineurin inhibitors

- Tacrolimus or ciclosporin levels should be very carefully monitored when a number of drugs are used in conjunction with them (Box 21.1). Interactions may result in either high levels risking drug toxicity or low levels risking under-immunosuppression that increases the risk of the development of rejection.
- Dose adjustments should be made in response to high or low levels.
- Oestrogens and progestagens: efficacy of oral contraception possibly decreased with tacrolimus.
- Increased risk of myopathy with statins and ciclosporin: avoid rosuvastatin.

Anti-proliferative agents: azathioprine, mycophenolate mofetil, and mycophenolic acid

- These agents inhibit purine synthesis.
- Azathioprine has been used since the earliest days of solid organ transplantation and remains in routine use as initial immunosuppressive therapy in a number of UK centres today.
- Its use has been superseded by MMF in the USA and many European countries, particularly when used in combination with ciclosporin. Meta-analysis of RCTs performed in adult patients have shown that compared with azathioprine, MMF results in a reduced risk of acute rejection (RR 0.62) and graft loss (HR 0.76); however, there was no improvement in patient survival or graft function. These studies were predominantly performed in ciclosporin-treated patients, and the benefits of MMF over azathioprine in tacrolimus-based triple therapy regimens are less clear.
- No paediatric RCTs have compared the two agents.
- Both drugs are licensed for use in childhood following renal transplantation in the UK.

Box 21.1 Drugs affecting calcineurin inhibitor levels and increasing risk of nephrotoxicity

The following increase calcineurin inhibitor levels

- Grapefruit juice (T+C)
- Allopurinol [C]
- Erythromycin [T+C]
- Chloramphenicol [T+C]
- Doxycycline [C]
- Clotrimazole [T]
- Fluconazole [T+C]
- Ketoconazole [T+C]
- Ritonavir [T+C]
- Nelfinavir [T+C]
- Nifedipine [T]
- Verapamil [C]
- Diltiazem [T+C]
- Omeprazole [T]
- Chloroquine [C]
- Methylprednisolone [C]
- Metoclopramide [C]
- Progestogens [C]
- Cimetidine [C]
- Tacrolimus [C]
- Clarithromycin [T+C]

The following reduce calcineurin inhibitor levels

- Rifampicin [T+C]
- Griseofulvin [C]
- Carbamazepine [C]
- Phenobarbitone [C]
- Phenytoin [C]
- St John's wort [C]

The following increase the risk of nephrotoxicity

- Ibuprofen and other NSAIDs [T+C]
- Amphotericin [T+C]
- Aminoglycosides[C]
- Co-trimoxazole and trimethoprim [C]
- Vancomycin [C]

The following increase the risk of hyperkalaemia

- ACE inhibitors and ACE II antagonists [C]
- K sparing diuretics [T+C]

T= tacrolimus C= ciclosporin

Azathioprine

- Dose 1–3mg/kg daily.
- Principal adverse-effect is myelosuppression:
  - most pronounced in those with genetically determined low levels of thiopurine methyltransferase (TPMT), an enzyme with a major role in azathioprine catabolism;
  - TPMT activity is controlled by a common genetic polymorphism and one in 300 patients has very low enzyme activity;
  - patients can be screened for TPMT levels or for the presence of genetic polymorphisms;
  - regular monitoring of full blood count is mandatory;
  - where neutropaenia occurs, the dose should be halved (absolute neutrophil count 0.5–1.5 × 10^9/L) or stopped (<0.5 × 10^9/L). Isolated lymphopaenia is not an indication for dose reduction.

Mycophenolate mofetil

- Dose 600mg/m^2 per dose given twice daily with ciclosporin. Maximum dose 2g daily.
- Dose reduced to 300mg/m^2 per dose when used in conjunction with tacrolimus.
- Metabolized to mycophenolic acid (MPA), which is the active drug.
- There is a 10-fold inter-individual variability in plasma MPA levels following a standard dose of MMF.
- There is uncertainty as to whether MPA levels should be measured to guide dosing. This is not, at present, standard practice in most UK centres. Recent studies in adult patients investigating whether monitoring levels improves outcomes have produced conflicting results.
- Risk of leukopaenia and invasive viral infection is greater than with azathioprine.
- Monitoring of full blood count is mandatory at every clinic visit.
- Principal adverse effects are upper and lower gastrointestinal (GI) symptoms: diarrhoea, vomiting, constipation, nausea, and dyspepsia, often necessitating a dose reduction to 50–75% of the previous dose, or the administration of the same daily dose given as four divided doses (beware adherence issues).
- There is increasing evidence that adverse effects may be linked to high MPA levels.

Mycophenolate sodium

- Metabolized to the active compound mycophenolic acid.
- Not licensed for use in children; there is little paediatric experience with this agent.

Corticosteroids

- The corticosteroids are potent immunosuppressants.
- Prednisolone is the most widely used agent in the UK, but the active drug prednisone is used in the USA and other parts of Europe.
- Prednisolone dosing schedules vary greatly, although most units will use relatively high doses in the early post-transplant period with a rapid taper. An example is as follows:
  - intraoperative: 600mg/m^2;
  - day 1: 60 mg/m^2 daily;
  - days 2–7: 40 mg/m^2 daily;
  - days 8–14: 30 mg/m^2 daily;
  - days 15–21: 20mg/m^2 daily;
  - days 22–28: 15mg/m^2 daily;
  - days 29–42: 10 mg/m^2 daily;
  - >day 42: <10 mg/m^2 daily.
- In the recent TWIST study, only 5 doses of corticosteroid were administered; this resulted in improved growth and metabolic profile with no increase in the rate of acute rejection.
- Methylprednisolone IV is often used in place of prednisolone in the first few post-operative days (1mg methylprednisolone = 1.25mg prednisolone).

- Where an early steroid withdrawal regimen is not used, daily therapy can be converted to alternate day therapy at around 2–3months post-transplant if rejection has not been a problem to improve growth velocity and reduce other adverse-effects.
- The adverse-effects of corticosteroids include obesity, growth disturbance, Cushingoid features, acne, reduced bone mineral density, striae, cataracts, diabetes, adrenal suppression, hypertension, gastrointestinal upset, myopathy, and hirsutism.

Anti-CD25 monoclonal antibodies

- These agents bind to the IL-2 receptor (CD25) on T cells and prevent the IL-2-mediated proliferation of activated T cells. They may also be cytotoxic to regulatory T cells, which also express CD25—the significance of this is not yet known.
- Their use has been shown to reduce the incidence of acute rejection, this effect being more pronounced with ciclosporin-based regimens.
- There are very few adverse-effects, although acute anaphylaxis has been reported to occur, albeit rarely.
- Daclizumab is no longer produced, though was used in a number of RCTs, including the TWIST study. Whilst there is no good evidence to show that basiliximab and daclizumab can be used interchangeably, for pragmatic reasons this has occurred.

Basiliximab

- Dose 10mg if patient <40kg and 20mg if patient 40kg or greater.
- Can be given via a central or peripheral vein.
- A total of two doses are given: one immediately prior to transplant surgery and the second on post-operative day 4.

Mammalian target of rapamycin (mTOR) inhibitors: sirolimus (rapamycin) and everolimus

- These agents inhibit T cell proliferation through binding to mTOR (the mammalian target of rapamycin (sirolimus), the prototypic drug in this group).
- They are not currently licensed for use in paediatric transplantation in the UK and global experience in paediatric transplantation is limited, though growing.
- Studies in adult patients show promising results and these agents are theoretically attractive as they are non-nephrotoxic and appear to have a beneficial effect on atherosclerosis (coronary artery stents are now coated with sirolimus and other similar agents).
- A recent uncontrolled paediatric study reported excellent results with the use of basiliximab, ciclosporin, and prednisolone with the introduction of everolimus and reduction of ciclosporin dose at 2 weeks followed by the withdrawal of prednisolone at 9 months.
- A recent CNI avoidance study incorporating sirolimus was halted early because of a high rate of post-transplant lymphoproliferative disease (PTLD).

- Adverse-effects include poor wound healing and lymphocoele, blood dyscrasias (anaemia, thrombocytopenia and leucopaenia), mouth ulcers, elevation of transaminases, proteinuria, and dyslipidaemia (hypercholesterolaemia and hyperlipidaemia).
- Sirolimus and everolimus have been used both as primary immunosuppressants, in cases of calcineurin inhibitor toxicity and also as rescue therapy in cases of acute rejection.

Sirolimus

- The drug half-life appears to be shorter in children than in adults and many have recommended a twice daily dosing regimen, particularly in children under 5 years of age.
- Increased clearance of sirolimus occurs in the presence of ciclosporin.
- Black patients may require higher doses; whether this also applies to children is not known.
- At present there are insufficient data to make clear dosing recommendations, though published regimens have used doses of 1–3mg/m^2 once daily to achieve levels of 5–15microgram/L when used in conjunction with calcineurin inhibitors and 15–25microgram/L in calcineurin inhibitor-free regimens.

Everolimus

- A dose of 0.8mg/m^2 twice daily has been recommended with trough levels of 3–6ng/mL.

Further reading

Ettenger R, Hoyer PF, Grimm P, et al. (2008). Multicenter trial of everolimus in pediatric renal transplant recipients: results at three years. *Pediatr Transplant* **12:** 456–63.

Grenda R, Watson A, Trompeter R, et al. (2010). A randomized trial to assess the impact of early steroid withdrawal on growth in pediatric renal transplantation: the TWIST study. *Am J Transpl* **10**(4)**:** 828–36.

Pape L, Offner G, Kreuzer M, et al (2010). *De novo* therapy with everolimus, low-dose ciclosporine A, basiliximab and steroid elimination in pediatric kidney transplantation. *Am J Transplant* **10:** 2349–54.

Venkataramanan R and Sindhi R. (2006). Sirolimus pharmacokinetic differences between children and adults. *Pediatr Transpl* **10:** 872–4.

Diagnosis and treatment of transplant rejection

The diagnosis of rejection in kidney transplant recipients is based on a combination of clinical, antibody, and histological features. Salient clinical and antibody features include:

- The timing of the episode post-transplantation.
- The degree of HLA sensitization pre-transplant.
- The presence or absence of blood group incompatibility.
- The presence or absence of proteinuria.
- The speed of deterioration of graft function.
- The panel reactive antibody and/or donor specific antibody status.
- The cross-match result.

Histopathological features on renal biopsy, using the Banff classification in combination with the clinical and antibody results allow a diagnosis of rejection to be made (Box 21.2):

- Hyperacute rejection.
- T cell-mediated rejection (TCMR).
- Antibody-mediated rejection (ABMR).
- Mixed rejection.
- Borderline changes.

Quantitative scoring categories for biopsies

Quantitative criteria for tubulitis ('t') score

- *t0:* no mononuclear cells in tubules.
- *t1:* foci with 1–4 cells/tubular cross-section (or 10 tubular cells).
- *t2:* foci with 5–10 cells/tubular cross-section.
- *t3:* foci with >10 cells/tubular cross-section, or the presence of at least two areas of tubular basement membrane destruction accompanied by *i2/i3* inflammation and *t2* tubulitis elsewhere in the biopsy.

Quantitative criteria for intimal arteritis ('v') score

- *v0:* no arteritis.
- *v1:* mild to moderate intimal arteritis in at least one arterial cross-section.
- *v2:* severe intimal arteritis with at least 25% luminal area lost in at least one arterial cross-section.
- *v3:* transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel.

Quantitative criteria for mononuclear cell interstitial inflammation ('i') score

- *i0:* no or trivial interstitial inflammation (<10% of unscarred parenchyma).
- *i1:* 10–25% of parenchyma inflamed.
- *i2:* 26–50% of parenchyma inflamed.
- *i3:* >50% of parenchyma inflamed.

Box. 21.2 Banff 1997 diagnostic categories for renal allograft biopsies with Banff 2007 update from Solez et al. (2008)

1. **Normal**

2. **Antibody-mediated changes** (may coincide with categories 3, 4 and 5 and 6) Due to documentation of circulating antidonor antibody, and C4d[3] or allograft pathology

C4d deposition without morphologic evidence of active rejection

C4d+, presence of circulating antidonor antibodies, no signs of acute or chronic TCMR or ABMR (i.e. g0, cg0, ptc0, no ptc lamination). Cases with simultaneous borderline changes or ATN are considered as indeterminate

Acute antibody-mediated rejection[4]

C4d+, presence of circulating antidonor antibodies, morphologic evidence of acute tissue injury, such as (Type/Grade):

I. ATN-like minimal inflammation
II. Capillary and or glomerular inflammation (ptc/g >0) and/or thromboses
III. Arterial—v3

Chronic active antibody-mediated rejection[4]

C4d+, presence of circulating antidonor antibodies, morphologic evidence of chronic tissue injury, such as glomerular double contours and/or peritubular capillary basement membrane multilayering and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries

3. **Borderline changes:** 'Suspicious' for acute T-cell-mediated rejection (may coincide with categories 2 and 5 and 6)

This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2 or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis

4. **T-cell-mediated rejection** (TCMR, may coincide with categories 2 and 5 and 6)

Acute T-cell-mediated rejection (Type/Grade:)

IA. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
IB. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
IIA. Cases with mild-to-moderate intimal arteritis (v1)
IIB. Cases with severe intimal arteritis comprising >25% of the luminal area (v2)
III. Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

Chronic active T-cell-mediated rejection

'chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

(Continued)

Box. 21.2 (*Contd.*)

5. **Interstitial fibrosis and tubular atrophy**, no evidence of any specific etiology (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features) Grade
I. Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)
II. Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
III. Severe interstitial fibrosis and tubular atrophy / loss (>50% of cortical area)

6. **Other:** Changes not considered to be due to rejection—acute and/or chronic (may include isolated g, cg or cv lesions and coincide with categories 2, 3, 4 and 5)

[1]The 2007 updates are underlined.
[2]All existing scoring categories (g, t, v, i, cg, ct, ci, cv, ah, mm) remain unchanged (42)
[3]Please refer to Table 2 and Figure 1.
[4]Suspicious for antibody-mediated rejection if C4d (in the presence of antibody) or alloantibody (C4d+) not demonstrated in the presence of morphologic evidence of tissue injury.
Solez K, Colvin RB, Racusen LC. (2008). Banff 07 classification of renal allograft pathology: updates and future directions. *Am J Transpl* **8:** 753–60.

Quantitative criteria for early allograft glomerulonephritis ('g') score
- *g0:* no glomerulonephritis.
- *g1:* glomerulonephritis in <25% of glomeruli.
- *g2:* segmental or global glomerulitis in 25–75% of glomeruli.
- *g3:* glomerulonephritis (mostly global) in more than 75% of glomeruli.

Quantitative criteria for interstitial fibrosis ('ci')
- *ci0:* interstitial fibrosis in up to 5% of cortical area.
- *ci1:* mild—interstitial fibrosis in 6–25% of cortical area.
- *ci2:* moderate—interstitial fibrosis in 26–50% of cortical area.
- *ci3:* severe—interstitial fibrosis in >50% of cortical area.

Quantitative criteria for tubular atrophy ('ct')
- *ct0:* no tubular atrophy.
- *ct1:* tubular atrophy in up to 25% of cortical tubules.
- *ct2:* tubular atrophy in 26–50% of the area of cortical tubules.
- *ct3:* tubular atrophy in >50% of the area of cortical tubules.

Quantitative criteria for allograft nephropathy ('cg')
- *cg0:* no glomerulopathy—double contours in <10% of peripheral capillary loops in most severely affected glomerulus.
- *cg1:* double contours affecting up to 25% of peripheral capillary loops in the most affected of non-sclerotic glomeruli.
- *cg2:* double contours affecting up to 26–50% of peripheral capillary loops in the most affected of non-sclerotic glomeruli.
- *cg3:* double contours affecting up >50% of peripheral capillary loops in the most affected of non-sclerotic glomeruli.

Quantitative criteria for mesangial matrix increase ('mm')

- *mm0:* no mesangial matrix increase.
- *mm1:* up to 25% of non-sclerotic glomeruli affected (at least moderate matrix increase).
- *mm2:* up to 26–50% of non-sclerotic glomeruli affected (at least moderate matrix increase).
- *mm3:* >50% of non-sclerotic glomeruli affected (at least moderate matrix increase).

Quantitative criteria for vascular fibrous intimal thickening ('cv')

- *cv0:* no chronic vascular changes.
- *cv1:* vascular narrowing of up to 25% of luminal area by fibrointimal thickening of arteries +/– breach of internal elastic lamina or presence of foam cells or occasional mononuclear cells.
- *cv2:* increased severity of changes described for cv1 with 26–50% narrowing of vascular luminal area.
- *cv3:* severe vascular changes with >50% narrowing of vascular luminal area.

Quantitative criteria for arteriolar hyaline thickening ('ah')

- *ah0:* no PAS-positive hyaline thickening.
- *ah1:* mild to moderate PAS-positive hyaline thickening in at least one arteriole.
- *ah2:* moderate to severe PAS-positive hyaline thickening in more than one arteriole.
- *ah3:* severe PAS positive hyaline thickening in many arterioles.

Quantitative criteria for peritubular capillaritis (ptc)

- *ptc0:* no significant cortical ptc or <10% of PTCs with inflammation.
- *ptc1:* ≥10% of cortical peritubular capillaries with capillaritis, with max 3–4 luminal inflammatory cells.
- *ptc2:* ≥10% of cortical peritubular capillaries with capillaritis, with max 5–10 luminal inflammatory cells.
- *ptc3:* ≥10% of cortical peritubular capillaries with capillaritis, with max >10 luminal inflammatory cells.

Hyperacute rejection

Occurring in the immediate post-operative period, hyperacute rejection is due to the presence of pre-existing donor specific HLA antibodies. Modern antibody screening and cross-matching techniques have virtually eliminated this form of rejection, although it remains high on the differential diagnosis list in patients undergoing desensitization protocols, those presenting with vascular thromboses, and those with C4d positive staining with acute tubular necrosis on biopsy or deteriorating graft function.

T cell-mediated rejection

- TCMR is defined histologically by the presence of interstitial inflammation comprising ≥25% of the unscarred compartment (classified as an i-score ≥ 2—see Box 21.2) and tubulitis with >4 mononuclear cells per tubular cross-section or group of 10 tubular cells (Fig. 21.1). Alternatively, a diagnosis of TCMR can be rendered in the presence of any degree of arteritis (so-called v-lesion—see Box 21.2) (Fig. 21.2).

- In the modern immunosuppression era, the incidence of TCMR has declined to as low as <10% in some programmes. Typically, the indication for biopsy is a rapid decline in graft function, tending to occur within the first year post-transplant. It can occur at any time, particularly with immunosuppression failure, as in non-adherent patients, or iatrogenically, through the weaning of immunosuppression regimens.
- TCMR, without concomitant ABMR, is very responsive to steroid or T cell-depleting therapy and does not lead to a progressive decline in function in the adherent patient, even in the presence of intimal arteritis. (In the modern immunosuppression era, there is no evidence for chronic active TCMR). TCMR in a non-adherent patient is the exception to this rule, with a high risk of developing donor specific antibodies and future graft loss.

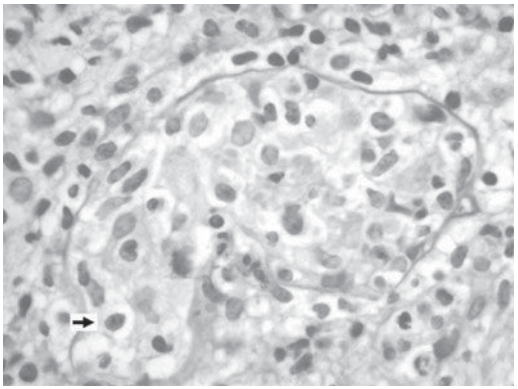

Fig. 21.1 Tubulitis. Lymphocyte nuclei seen within tubular epithelium inside tubular basement membrane. See also Plate 14.

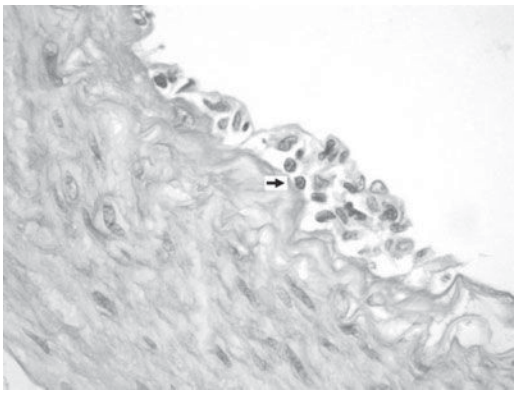

Fig. 21.2 Endothelialitis. Lymphocytes seen within intima of artery. See also Plate 15.

Antibody-mediated rejection

Antibody-mediated rejection (ABMR) is currently defined by Banff as the presence of all of the following:

- The presence of donor specific antibodies (DSA).
- Positive immunostaining for C4d.
- One or more of the following histological lesions:
  - glomerulitis (g-score > 0);
  - peritubular capillaritis (ptc-score > 0);
  - vascular thrombosis;
  - severe intimal arteritis (v3). See Fig. 21.2;
  - ATN-like minimal inflammation;
  - transplant glomerulopathy (cg-score > 0);
  - interstitial fibrosis and tubular atrophy (ci-score >0 and ct score >0);
  - peritubular capillary basement membrane multilayering (=ptcml >4 layers);
  - fibrous intimal thickening in arteries (cv-score >0).
- ABMR can be further defined as acute or chronic, based on the extent of chronic lesions (cg, ci and ct, cv, ptcml) and the presence of microvascular inflammation.
- C4d staining suffers not only from reproducibility issues, but also from false positives, as is the case in ABO incompatible transplantation. As a result, there is increasing evidence that active ABMR can occur in the absence of C4d staining—so-called C4d negative ABMR. Criteria for making this diagnosis are more stringent, not allowing the diagnosis to be made just on ci- and ct- score, cv-score, or ptcml number. Of particular importance is the presence of microcirculatory inflammation in making this diagnosis.
- The true incidence of ABMR in a low risk population is unknown, although it has been estimated to explain up to two thirds of graft failures. It typically occurs in the unsensitized patient any time after 6 months, particularly in the presence of *de novo* class II DSA.

Mixed rejection

TCMR and ABMR can occur concurrently in the form of mixed rejection, which shares the histological features of both diseases. Its TCMR component may respond to typical TCMR therapies initially, but it frequently progresses to failure.

Borderline changes

Sometimes known as borderline rejection, a label of borderline changes is applied when the Banff thresholds for TCMR are not met (v = 0 and I <2 and t >0 and C4d negative). The significance of this category is unknown with no good evidence on which to base treatment decisions. Empiric treatment before the biopsy may convert true TCMR into this category.

The terms chronic allograft nephropathy or chronic rejection are no longer used, following the recognition that up to 90% of cases can have a definitive diagnosis made of either ABMR or glomerulonephritis (recurrent or *de novo*).

Differential diagnosis of graft dysfunction

The differential diagnosis of graft dysfunction in the cross-match negative patient is heavily time-dependent with TCMR typically occurring in the first year, while ABMR tends to present later. Other potential causes of graft dysfunction include:

- *De novo* or recurrent glomerular disease.
- Polyoma virus nephropathy.
- Calcineurin inhibitor nephrotoxicity (a diagnosis of exclusion).
- Acute kidney injury ± acute tubular necrosis.
- Thrombotic microangiopathy.
- Pyelonephritis.
- Urinary leak or obstruction.

Treatment of T cell-mediated rejection

First line treatment is IV methylprednisolone:

- The dose given in most centres is 600mg/m^2 up to a maximum of 1g daily for 3–5 days, although there is no evidence for any particular regimen with some units giving the drug in lower doses or on alternative days (administered in 50mL 0.9% saline over 2–4h with ECG and BP monitoring).
- Response to treatment typically occurs within 3–5 days of commencing treatment, with a reduction in serum creatinine.
- Following successful treatment, some centres return patients to their original steroid dose (including no steroid therapy in those on steroid free protocols), while other centres increase maintenance steroid therapy for a period of time before tapering the dose. The level of background immunosuppression may be increased such as running higher target drug trough levels or switching from ciclosporin to tacrolimus or azathioprine to MMF.

Second line treatment is anti-thymocyte globulin (ATG), derived from rabbit (thymoglobulin) or equine (Atgam) serum, resulting in lymphocyte depletion.

- Indications for ACT include:
  - induction therapy;
  - TCMR refractory to steroid treatment;
  - recurrent TCMR;
  - TCMR with a v lesion (although there is growing evidence that this form of rejection responds well to methylprednisolone).
- ATG 2mg/kg is given daily for a total of 7–10 days. Patients should be administered IV hydrocortisone and anti-histamine 30min pre-dose:
  - must be diluted in a large volume (500mL in adults and older children) of either 0.9% saline or 5% glucose and given through a central venous catheter;
  - if leucopenia (<2.5 × 10^9/L) or thrombocytopenia (<80 × 10^9/L) occur, the dose should be halved;
  - if severe leucopenia (<1.5 × 10^9/L) or thrombocytopenia (<50 × 10^9/L) occur, treatment should be discontinued and recommenced at half the dose when the count has improved up to day 10, when treatment should be discontinued;

  - maintenance immunosuppression is usually discontinued for the duration of treatment.
- All patients should receive co-trimoxazole prophylaxis against *Pneumocystis jiroveci* for 3 months.
- Ganciclovir prophylaxis against cytomegalovirus (CMV) should be given for 3 months to all patients (AST 2009 guideline http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2009.02897.x/abstract) or D+R– and D+R+ (UK Renal Association guideline).
- *Complications:*
  - massive T cell depletion lasting months to years;
  - minor allergic reactions are very common;
  - minor and major infections during therapy or after;
  - PTLD and other malignancies, particularly viral related.
- Following successful treatment, most centres return patients to their original maintenance immunosuppresion or augment it.

Third line treatment is muromonab 3 or OKT3—a monoclonal antibody generated in mice that binds to the CD3 complex on T cells resulting in removal of these cells from the circulation in the reticuloendothelial system.

- Indication for use is refractory TCMR.
- Dose 2.5–5mg daily for 10 days. CD3 monitoring is performed daily to assess T cell depletion.
- Very rarely used due to serious side effect profile:
  - cytokine release syndrome typically occurs following the first or second dose with fever, rigors, myalgia, headaches, diarrhoea, flash pulmonary oedema, apnoea, and cardiac arrest;
  - contraindicated in heart failure and uncontrolled hypertension;
  - patients should be within 3% of their dry weight at the time of administration—may need diuresis or dialysis;
  - prior to the first two doses, patients should be premedicated with IV hydrocortisone, anti-histamine, and paracetamol; subsequent doses are preceded by paracetamol only;
  - vital signs should be monitored every 15min during the infusion;
  - apart from maintenance steroids, all other medication should be discontinued during treatment.
- Prophylaxis for CMV and *Pneumocystis jiroveci* infection for 3 months starting at the beginning of OKT3 treatment.
- High risk for future infections and PTLD.

Treatment of antibody-mediated rejection

Treatment strategies and potential benefits differ widely depending on whether acute ABMR occurs in the context of highly-sensitized patient early in the post-transplant period or after the development of *de novo* DSA later on. There is little evidence for any one agent or combination in the treatment of ABMR with more common current strategies as listed:

- Conventional agents: optimizing current immunosuppression such as increasing the tacrolimus or MMF dose or the addition of steroids.
- IVIG either as low dose (<0.5g) or high dose (1–2g).
- Plasmapheresis.
- Rituximab (anti-CD20).

- Other more experimental therapies include:
  - bortezomib (a proteasome inhibitor initially used for treatment of myeloma);
  - eculizumab (monoclonal antibody directed against the complement protein C5);
  - immunoabsorption;
  - splenectomy.

In cases of mixed rejection, concomitant TCMR should be treated as described (see 📖 'Treatment of T cell-mediated rejection', p.536).

- Patients with ABMR should be treated as per renal guidelines with renin-angiotensin system blockade for blood pressure (BP) control and reduction in proteinuria in addition to any of the treatments already mentioned.
- Chronic allograft nephropathy or 'creeping creatinines' were previously treated with reduction or elimination of calcineurin inhibitors with a view to reducing long-term calcineurin inhibitor toxicity:
  - evidence for this approach is seriously flawed in the modern era of good antibody detection techniques;
  - approximately 90% of graft failures can now be attributed to either glomerulonephritis or ABMR, with the ABMR accounting for almost two-thirds of cases;
  - reducing immunosuppression in the face of an undetected ABMR is likely to speed disease progression.

Suggested renal transplant recipient discharge follow-up (Table 21.1)

Table 21.1 Suggested renal transplant recipient discharge follow-up

Time	Until 2 weeks	2–4 weeks	4–8 weeks	8–12 weeks	3–5 months	5–12 months	Annual review
Visit*	Daily	×3/week	×2/week	Weekly	Fortnightly	Monthly	Yes
FBC	×3/week	×3/week	×2/week	Weekly	Fortnightly	Monthly	Yes
Biochemistry	Daily	×3/week	×2/week	Weekly	Fortnightly	Monthly	Yes
Tac/Ciclo levels	×3/week	×3/week	×2/week	Weekly	Fortnightly	Monthly	Yes
Additional tests	Once	Once	Once	Once	Once	6, 9, 12 months	Yes
Urine ACR or PCR	A (below)	A (below)	A (below)	Once	Once	6, 9, 12 months	Yes
EBV/CMV PCR DNA	Twice	Twice	Twice	Twice			
HLA antibodies#		Once	Once			6 + 12 months	Yes
Transplant renal US	Week 1					6 + 12 months	Yes
DTPA	B	B	B	B	B	B	B
DMSA		3 weeks				C	C
GFR						6 + 12 months	Yes

(Continued)

Table 21.1 *(Contd.)*

Time	Until 2 weeks	2–4 weeks	4–8 weeks	8–12 weeks	3–5 months	5–12 months	Annual review
DXA scan						12 months	Yes
Protocol biopsies					3 months	6 + 12 months	
24-h ABPM	D	D	D	D	D	D	Yes

Key: Visit* = minimum visits or more frequently if any clinical concerns.

HLA antibodies also measured if develop acute rejection.

Additional tests = ferritin, iCa, PTH, urate, fasting glucose and lipids:

A = once or if proteinuria on dipstick or daily if primary disease is FSGS or CNS.

B = perform DTPA to exclude obstruction (e.g. primary non-function/renal allograft dysfunction if increased creatinine +/– transplant hydronephrosis).

C = at 3 weeks post-transplantation if abnormal bladder, recurrent UTI's, blood vessel sacrificed at transplantation plus 3 months after transplant pyelonephritis/UTI.

D = only when severe hypertension to improve BP control and help in investigation.

Recurrent and *de novo* renal disease following renal transplantation

Introduction

- Proven disease recurrence is the cause of up to 20% of graft losses.
- This may be an underestimate as there may be further additional undiagnosed cases.
- Table 21.2 summarizes the recurrence risk and incidence of graft loss.

Table 21.2 Recurrent disease post-transplant

	Recurrence risk (%)	Graft loss (%)
CNS	25	50
FSGS	20–40	50
MCGN type 1	30	33
MCGN type 2	30	8
HUS	50	33
Membranous	30	8
Alports (anti-GBM)	10	10
IgA/HSP	60	5
SLE	30	Rare
ANCA + vasculitis	17	?

Finnish-type congenital nephrotic syndrome (CNS)

Nephrotic syndrome may occur in up to 25% of children with Finnish type CNS following transplantation:

- Related to the production of anti-nephrin antibodies following exposure to 'normal' nephrin in the transplanted kidney.
- Most common in those with the Finn-major *NPHS1* mutation.
- May respond to treatment with cyclophosphamide +/– plasma exchange.
- Up to 50% graft loss may occur due to recurrence.

Focal segmental glomerulosclerosis (FSGS)

- Variable incidence according to population studied, but most studies quote a recurrence rate of 20–40%.
- There is a 50% rate of graft loss associated with recurrent FSGS.
- There may be a link with the presence of an unidentified circulating factor which increases capillary permeability.
- Typically occurs early in the post-transplant period with heavy proteinuria, and progressive renal insufficiency and graft failure.

- Risk factors for recurrence:
  - short time from initial disease presentation to development of CKD 5 (consistent finding across most studies);
  - recurrent FSGS in a previous transplant (subsequent risk 75–100%);
  - presence of mesangial proliferation on initial native biopsy;
  - children experience recurrent disease more frequently than adults;
  - risk appears to be greater in older children;
  - risk lower in US African Americans (who have a higher incidence of primary disease).
- Children with FSGS associated with mutations in the NPHS2 (podocin) gene appear to be at very low risk of developing recurrent disease. This observation is consistent with the theory that the defect is intrinsic and specific to the kidney.
- Risk is not increased with the use of living donors. However, US data report that the graft survival benefit of living donor transplantation is lost in the adolescent population, living donor transplant survival in FSGS patients equating to deceased donor graft survival in non-FSGS patients.
- Recurrent FSGS is associated with an increased risk of acute tubular necrosis and acute rejection.
- Diagnosis is clinical:
  - urine should be tested daily for proteinuria;
  - recurrent disease will be indicated by the development of heavy (nephrotic proportion) proteinuria within days to weeks following engraftment, which may be associated with a progressive fall in plasma albumin;
  - occasionally, immediate recurrence can manifest as primary non-function;
  - early renal biopsy will not show any significant change on light microscopy, but podocyte foot process fusion may be seen on electron microscopy (EM); it may take weeks to months for the characteristic FSGS lesions to develop.

Treatment

No single therapy or regimen has been shown to be superior and a variety of different regimens have been reported. None have been subjected to RCTs.

- Plasma exchange and cyclophosphamide—Cochat protocol:
  - 2 vol plasma exchange for 10 days (2 day break after 5th exchange), then once weekly for 8 weeks;
  - IV methylprednisolone 250mg/m^2 for 3 days then return to existing post-transplant steroids;
  - oral cyclophosphamide 2mg/kg daily in place of azathioprine/MMF for 8 weeks.
- High dose IV ciclosporin may be effective in preventing and treating recurrent FSGS. This may be due to direct action on the podocyte.
- Rituximab and immunoadsorption have also both also been used, with mixed results.

Membranoproliferative glomerulonephritis (MPGN)

- MPGN type 1 recurs in up to 30% of adults and children. Recurrence is manifested by proteinuria, which may initially be low level. Progressive deterioration of renal function leading to graft loss is common, occurring in around one-third.
- MPGN type II recurs in close to 100% of patients, though only 12–25% will develop heavy proteinuria and renal impairment and ultimately lose their grafts to recurrent disease.
- There is no good evidence for any effective treatment of recurrent type I or II MPGN.

IgA nephropathy/Henoch–Schönlein purpura

- Recurrence at a histopathological level occurs in up to 60% of adult patients. Such recurrence was initially thought to be benign, although more recent studies have shown that around 13% will lose some function and around 5% lose their grafts secondary to this. Good paediatric data are not available.
- Risk of graft loss is increased where a previous graft has been lost to recurrent disease.
- Recurrence is thought to be less common where MMF is used for immunosuppression as opposed to azathioprine.
- Henoch–Schönlein purpura (HSP) nephritis recurrence rate is around 20%.
- There is no good evidence for any form of treatment for recurrent IgA nephropathy or HSP nephritis.

Membranous nephropathy

- Around 30% recurrence rate in adults at 3 years with graft loss of 8%.
- Presents with proteinuria of varying degrees.
- Renal function is generally preserved in the early stages, although patients with heavy proteinuria and early recurrence progress rapidly towards graft failure.
- In contrast to idiopathic membranous nephropathy in the native kidney, the rate of spontaneous remission is very low.
- The use of IV methylprednisolone has been shown to be effective in one series of adult transplant recipients.
- General measures should be instituted, similar to those for any patient with proteinuria, including the use of angiotensin converting enzyme inhibitors and angiotensin II receptor blocker, control of BP, and use of lipid lowering therapy where indicated.

Crescentic glomerulonephritis of multiple aetiologies

- Risk is 3–10%.
- Treatment should comprise plasma exchange in combination with cyclophosphamide.

Primary hyperoxaluria

The risk of graft loss is very high where isolated kidney transplantation is performed because of rapid deposition of oxalate in the transplanted kidney. This results in graft loss in around 90% of cases and there is no effective therapy. Liver transplant followed by kidney transplant or

combined kidney-liver transplantation will restore both renal function and the missing enzyme, allowing normal oxalate production and clearance (see 'Specific causes of calculi: investigation and management', p.178).

Haemolytic uraemic syndrome

- The cause of CKD 5 in 2–4% of children.
- Most recurrences occur early, usually within a month of transplantation.
- Presentation of recurrence is with thrombocytopaenia, microangiopathic haemolytic anaemia and graft dysfunction.
- Renal biopsy demonstrates typical HUS glomerular changes including endothelial cell swelling, widened subendothelial spaces, and glomerular capillary fibrin deposits.
- In contrast to diarrhoea and pneumococcal-associated HUS, where the risk of recurrence is probably non-existent (unless there is a coexisting genetic mutation), children with atypical HUS (aHUS) have a high rate of recurrence post-transplantation and this is frequently associated with graft loss.
- Mutations in genes encoding complement regulatory proteins and secondary disorders of complement regulation play a central role in most cases of aHUS. Endothelial damage occurs through an unregulated complement cascade.
- Gene mutations are identified in at least 50% of cases.
  - complement factor H (50–60% of mutations), membrane co-factor protein (MCP, 20%) and complement factor I (CFI, 10–15%);
  - gain of function mutations in genes encoding CFB and C3 have also recently been reported (see Chapter 17, 'Haemolytic uraemic syndrome: definitions', p397).
- The risk of recurrence differs according to the genetic abnormality which has caused the primary aHUS. Overall, the risk is 50%:
  - around 80% with complement factor H (CFH) and CFI mutations—usually associated with graft loss;
  - there appears to be a lower risk for recurrence where mutations occur in the first 15 short consensus repeats of CFH;
  - lower, but still significant rate with CFB and C3 mutations;
  - in contrast MCP mutations are associated with a very low rate of recurrence;
  - CFH, CFI, CFB and C3 mutations all produce abnormalities in circulating complement components that are mainly produced by the liver; these persist following kidney transplantation, but MCP is expressed in all cells, including renal cells; the transplantation of a kidney which expresses normal MCP does not result in recurrence;
  - a number of cases with combined mutations have been reported with variable outcomes.

Guidelines have been produced regarding transplantation in aHUS (Saland et al. 2009[1]).

- Children with CKD 5 and a CFH or CHI mutation should be considered for combined liver-kidney transplantation because of the high risk of recurrence:
  - intensive preoperative plasma exchange and intraoperative plasma infusion should be performed;
  - low molecular weight heparin should be administered;
  - calcineurin inhibitors are not contraindicated;
  - previous concerns about ciclosporin causing recurrent disease are almost certainly unfounded.
- Isolated kidney transplantation may be performed where there is no evidence of CFH, CFI, CFB or C3 mutations. It can be safely performed with MCP mutations, or where any mutation is present and another family member has previously successfully undergone isolated renal transplantation. Plasma exchange is recommended pre- and post-operatively.
- The use of living related donors should be avoided if the presence of mutations in the child and donor have not been identified. This is because of the increased, but incomplete understanding of the genetics of this condition, and awareness that some individuals carrying mutations do not express the disease until middle age or later. However, if the genetic abnormalities have been identified in the child and one parent, it is possible to consider the other parent as a donor.
- Biological agents blocking complement activity e.g. eculizumab are showing promise in a number of clinical trials and it may be that this agent will be used as prophylaxis or treatment for even CFH or CFI abnormalities in the future.

Treatment of established recurrent HUS

- Plasma exchange therapy.
- Biological agents blocking complement activity, e.g. eculizumab.
- Purified factor H may prove to be effective in the future.

Systemic lupus erythematosus (SLE)

- Reports of recurrence rates of 2–30% in adult patients, though graft loss secondary to recurrent disease appears to be relatively rare.
- A NAPRTCS series reported one case of disease recurrence resulting in graft loss in 94 children with SLE undergoing 100 transplants.
- The common misconception that 'SLE burns itself out' after the kidneys fail should be dispelled.

Vasculitis

- The number of transplanted patients is small, although recurrences of the large majority of the vasculitides are reported, and has been reported as high as 17% for ANCA-associated vasculitides in adults. In this analysis, ANCA positivity at the time of transplantation was not a risk factor for recurrence.
- Treatment is with corticosteroids and cyclophosphamide or mycophenolate mofetil as in *de novo* disease.

1 Saland JM, Ruggenenti P, Remuzzi GN and the Consensus Study Group (2009). Liver–kidney transplantation to cure atypical hemolytic uremic syndrome. *J Am Soc Nephrol* **20:** 940–9.

Cystinosis

Although the donor kidney's lysosomes are normal, there are recipient cells within the donor kidney. Cystine may, therefore, be deposited in the transplanted kidney, although graft survival does not appear to be compromised. Treatment with mercaptamine (Cystagon®; see 🕮 'Cystinosis', p.271) should be continued to prevent deposition of cystine in other organs.

Alport syndrome

- The number of children undergoing renal transplantation with a diagnosis of Alport syndrome is relatively small.
- An anti-GBM nephritis may develop following *de novo* exposure to normal type IV collagen, resulting in rapidly progressive glomerulonephritis.
- Risk is 3–10%.
- Risk is increased with large truncating mutations in the *COL4A5* gene.
- Treatment is as for RPGN, with cyclophosphamide +/– plasma exchange.
- Graft prognosis is poor with graft loss over weeks to months.

De novo disease

De novo membranous nephropathy

- More common than recurrent membranous nephropathy (MN).
- Probably due to antibodies directed against glomerular antigens in the graft.
- Occurs late post-transplant with worsening of renal function and heavy proteinuria.
- Treatment with diuretics will improve oedema. There are reports of disease remission being induced with the use of steroids.

Further reading

Golgert WA, Appel GB, Hariharan S. (2008). Recurrent glomerulonephritis after renal transplantation: an unsolved problem. *Clin J Am Soc Nephrol* **3:** 800–7.

Urinary tract infection post-transplantation

Introduction

- Bacteriuria is a common complication of renal transplantation, occurring in 20–88% of childhood transplant recipients.
- The wide-ranging reported incidence may reflect differences in the rate of reporting of both symptomatic infections and apparently asymptomatic bacteriuria.
- It is, however, well recognized that a number of episodes of seemingly asymptomatic bacteriuria are associated with a transient deterioration of graft function, implying the presence of asymptomatic parenchymal involvement warranting antibiotic therapy:
  - in such cases it must be assumed any symptoms have been masked by the immunosuppressive therapy;
  - for this reason, all transplant recipients should undergo regular routine urine microscopy and culture as part of their follow-up.
- Urinary tract infection (UTI) within the first 6 months post-transplantation is associated with a higher rate of graft loss.
- UTI may precipitate an episode of acute rejection.

Specifics

- UTI is most common in the first month after transplantation when immunosuppression is heaviest and urinary stents and catheters may be *in situ*.
- The most common infecting organisms are:
  - *Escherichia coli*;
  - *Pseudomonas aeruginosa*;
  - Enterococci (*Enterobacter cloacae*, *Streptococcus faecalis* and Proteus spp.).
- Risk factors for post-transplant UTI include:
  - abnormal bladders (posterior urethral valve bladders with and without augmentation, neuropathic bladders);
  - vesicoureteric reflux (VUR) into the native kidneys;
  - VUR into the graft;
  - pre-transplant history of UTI;
  - the presence of a ureteric stent;
  - diabetes mellitus.

Diagnosis

Made by urine microscopy and culture.

Treatment

- Antibiotics should be given IV in the early period post-transplantation where immunosuppression is heaviest or where there is significant fever or systemic upset.
- There may be an additional case for the administration of IV therapy where there is a significant rise in the plasma creatinine, even if the infection is seemingly asymptomatic.

- If there is a ureteric stent, early removal must be considered if the infection is difficult to eradicate or if *Candida* is present.
- *Candida* UTIs should be treated with oral fluconazole in the first instance, although IV therapy (fluconazole, amphotericin, or flucytosine) may be required if this is not effective or if the child is significantly unwell (see 📖 'Infection post-transplantation', p.552). **Caution**: fluconazole will increase the levels of calcineurin inhibitors.
- There is no broad agreement about the use of prophylactic antibiotics in at-risk patients. Most units will use co-trimoxazole for the first 6 months post-transplantation as prophylaxis against:
- *Pneumocystis jiroveci*: this will additionally provide some prophylaxis against UTI. Where this is not used most would use a prophylactic antibiotic such as trimethoprim for 3–6 months, particularly where there is underlying urological abnormality as the cause of CKD 5 or where there is known to be VUR into the graft.

Subsequent investigation and management

Children should undergo imaging of their graft following a UTI:

- Many centres perform a DMSA scan to determine whether renal parenchymal scarring has developed.
- Where parenchymal scarring is detected, controversy exists as to whether a micturating cystourethrogram should be performed. This is an invasive unpleasant procedure with a significant radiation burden.
- VUR occurs in over 50% of transplanted kidneys: most transplant surgeons do not perform a formal anti-reflux procedure when anastomosing the allograft ureter to the native bladder.
- The importance of VUR is controversial. There is some evidence that it increases the risk of acute pyelonephritis and subsequent scarring of the graft and it has been suggested that these children should receive antibiotic prophylaxis.
- Some have advocated the use of anti-reflux procedures, e.g. STING when VUR is clinically significant, although this is not without risk as the distal ureteric blood supply is precarious.

New onset diabetes after transplantation

Introduction

- New onset diabetes after transplantation (NODAT) has been reported as a complication in between 2 and 53% of transplants in adult and paediatric patients.
- There is much variation in the definition of NODAT (ranging from transient hyperglycaemia to long-term requirement for insulin), hence, the wide variation in reported incidence.
- In many instances there is unidentified abnormal glucose tolerance pre-transplant, which worsens following transplantation.
- Around 2–7% of children develop significant NODAT requiring insulin or oral hypoglycaemic therapy. The incidence appears to be increasing.
- The significance of NODAT has previously been underestimated.

Aetiology

The aetiology of NODAT is multifactorial:

- Steroids are known to increase peripheral insulin receptor resistance and may inhibit beta cell insulin secretion.
- The calcineurin inhibitors are known to be toxic to beta cells; the risk appears to be somewhat greater with tacrolimus than ciclosporin.

Risk factors

Reported risk factors include:

- Ethnicity (African American and Hispanic race).
- Family history of diabetes mellitis (DM).
- Abnormal glucose metabolism pre-transplant or other components of the metabolic syndrome (e.g. dyslipidaemia, hypertension, and hyperuricaemia).
- Use of corticosteroids.
- Use of calcineurin inhibitors, particularly tacrolimus.
- Higher degree of HLA mismatch (related to a need for more intensive immunosuppression).
- High body mass index (BMI).
- Treatment for acute rejection.
- Cystinosis or the HNF1β mutation as a cause of CKD 5.

NODAT is associated with a significantly poorer long-term outcome for both the patient and the graft.

- NODAT is a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients.
- Associated with reduced patient survival, increased risk of graft loss and increased risk of infection.
- Costs of NODAT $12,000–$13,000 at end of first year post-transplantation.
- Adult series have shown survival with NODAT to be comparable with that observed in patients with pre-transplant DM, emphasizing the importance of strategies to avoid the development of NODAT where possible.

Investigation

Avoidance

- Centres that have used steroid-free immunosuppressive regimens have reported very low rates of NODAT (see Stanford data and TWIST study).
- There may be a case for avoiding the use of tacrolimus in those patients with a strong family history of DM and other significant risk factors.
- A number of fasting blood glucose measurements should be made as part of the transplant work-up.
- Screening for known risk factors for NODAT.
- Some have proposed performing formal glucose tolerance tests on all children awaiting renal transplantation to identify those at risk of NODAT and to alter the immunosuppressive regimen accordingly.

Identification and investigation of NODAT

- Early detection and appropriate treatment of transplant recipients who have developed NODAT can ameliorate the long-term consequences of the condition.
- Guidelines for adult patients recommend monitoring of fasting blood glucose levels in patients post-transplant at least weekly in the first 4 weeks, then at 3, 6, and 12 months, then annually.
- This may be difficult to achieve in smaller children, in whom random blood sugars should be measured.
- Random blood sugar levels of >5.5mmol/L should prompt measurement of a fasting blood sugar (FBS):
  - FBS <6.1mmol/L is normal;
  - FBS 6.1–6.9mmol/L represent impaired glucose tolerance: an oral glucose tolerance test should be performed; fasting insulin, anti-glutamic acid decarboxylase (GAD) antibodies and anti-islet cell antibodies should be measured;
  - FBS >7mmol/L is diagnostic of NODAT: fasting insulin, anti-GAD antibodies, and anti-islet cell antibodies should be measured.

Treatment

- Expert endocrinological advice should be sought.
- Every attempt should be made to reduce immunosuppressive therapy in an attempt to reverse the NODAT. This should be achievable in the long-term in 50–75% of patients:
  - steroid dose should be lowered to the minimum acceptable and discontinuation of steroid therapy considered;
  - where tacrolimus is used, the target trough level should be reduced to around 3–5microgram/L;
  - a switch from tacrolimus to ciclosporin might be considered;
  - there is a clear risk of inducing an episode of rejection with these strategies and there is a strong case for increasing other immunosuppressive therapy to try and prevent this, e.g. replacing azathioprine with MMF.
- Adult guidelines recommend a stepwise approach to treatment, beginning with non-pharmacological therapy (weight loss, exercise, stopping smoking), progressing to oral agent monotherapy, oral combination therapy then insulin therapy, with or without oral agents.

- Many children (particularly those with low serum insulin levels) will require insulin therapy, although some (particularly those with significant obesity, evidence of peripheral insulin resistance and negative antibody status) may be treated with oral hypoglycaemic agents, such as metformin.
- Careful attention should be paid to weight loss, exercise, and smoking avoidance.
- Patients should be carefully monitored:
  - lipid levels measured regularly;
  - annual screening for retinopathy;
  - aggressive treatment of hypertension.

Further reading

Davidson J, Wilkinson A, Dantal J, et al. (2003). New-onset diabetes after transplantation: 2003 International consensus guidelines, Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* **75:** SS3–24.

Infection post-transplantation

The risk of infection post-transplantation is increased by:

- Malnutrition.
- Immunosuppression, particularly if this has been increased because of rejection or recurrent disease.
- Infection transmitted by the graft.
- Lack of host immunity.
- The presence of catheters and lines.

Bacterial infections

It is common practice to culture a sample of the preservation fluid used for the transport of deceased donor kidneys and to use antibiotic prophylaxis (e.g. with ciprofloxacin) until the culture result is known. Infection may be related to the wound, to intravascular or bladder catheters, or to the Tenckhoff catheter. Consideration should be given to removal of the Tenckhoff catheter at the time of transplant, particularly if there is infection of the exit site. Infected intravascular catheters should be removed as soon as possible. Infection of a peritoneal catheter is difficult to diagnose as flushing it may introduce infection so it should be removed if infection is suspected.

Urinary tract infection

UTI is the commonest infection post-transplant: (see 🕮 Chapter 4, p.75).

Diarrhoea

- May be infectious or related to medications, particularly MMF.
- *Clostridium difficile* is the commonest infective cause, and may be mild (or asymptomatic) or lead to pseudomembranous colitis. Treatment is initially with metronidazole.

Fungal infections

Colonization of the skin and gut with fungi can occur post-transplantation. Growth from urine, particularly if recurrent, or blood may signify invasive disease, and will be unlikely to clear if associated with an in-dwelling catheter, which should be removed.

- Patients being treated with broad spectrum antibiotics or high doses of immunosuppression (particularly steroids) are at greatest risk, so some centres use antifungal prophylaxis, such as oral nystatin 100,000 units qds or fluconazole (see Table 21.3) in these situations.
- Commonest are *Candida* species. Infection can be anywhere, but oesophagitis and cystitis are the commonest sites. *Candida* in the urine should be treated to prevent ascending infection, which can result in fungal balls and obstruction to urinary drainage.
- *Aspergillus* is the second commonest fungal infection. It may be isolated from sputum, and on chest X-ray appears as opacities or empyema.
- Fluconazole should be given as first-line therapy for invasive candidiasis. This can be given orally (the drug is well absorbed) or by IV infusion over 10–30min. The dose is the same orally and IV.
- Fluconazole increases calcineurin inhibitor levels, so if their levels are already high, it is advisable to make a small (e.g. 10%) reduction in the dose of the calcineurin inhibitor and check drug levels within 48–72h.

- Fluconazole dose should be halved if the GFR is <50mL/min/1.73m^2.
- Duration of treatment will vary with severity of infection, varying between 7 days and 8 weeks.
- Liposomal amphotericin B (a potentially less nephrotoxic preparation of amphotericin) is indicated in severe candidal infection. This is also first line treatment for *Aspergillus* infection.
- Other agents, including flucytosine, itraconazole, and voriconazole can be used in refractory cases or for resistant organisms.

Table 21.3 Dose of fluconazole according to age and infection type

	<2 weeks	2–4 weeks	4 weeks to 12 years	12–18 years
Mucosal *Candida* and for prophylaxis in the immuno-compromised patient	3–6mg/kg on day 1 then 3mg/kg every 3 days	3–6mg/kg on day 1 then 3mg/kg every 2 days	3–6mg/kg on day 1 then 3mg/kg every daily. Maximum 100mg daily	50mg daily (up to 100mg daily with difficult infections)
Invasive disease	6–12mg/kg every 3 days	6–12mg/kg every 2 days	6–12mg/kg daily. Maximum 400mg daily	

Pneumocystis jiroveci pneumonia

- Usually presents during the first 6 months of intensive post-transplant immunosuppression with fever, cough, oxygen desaturation with exercise, and a diffuse interstitial infiltrate on chest X-ray. Diagnosis is by broncho-alveolar lavage.
- *Pneumocystis* may co-exist with CMV.
- Co-trimoxazole should be used as prophylaxis and is particularly useful in the first 6 months post-transplant. It is usually given at night. Patients with G6PD deficiency (or other situations where co-trimoxazole is contraindicated) can receive nebulized pentamidine as prophylaxis, although this drug requires specialized facilities for administration because it is teratogenic and potentially toxic to those administering it.
- 480mg of co-trimoxazole contains sulfamethoxazole 400mg and trimethoprim 80mg (Table 21.4).

Table 21.4 Dosage for co-trimoxazole for the first 6 months post-transplant

Weight	Dose of co-trimoxazole, mg, once daily
10–15 kg	240mg (1/2 tablet or 5mL of paediatric suspension
15–30 kg	360mg (3/4 tablet or 7.5mL of paediatric suspension
30–60 kg	480mg (1 tablet or 10mL of paediatric suspension)
60kg+	960mg (2 tablets)

Co-trimoxazole will additionally provide prophylaxis against post-transplantation UTI. Patients requiring long-term UTI prophylaxis should be restarted on their routine prophylaxis when the co-trimoxazole is stopped.

Viruses

Viral infection can be a particular problem in children post-transplant because:

- Vaccines are not currently available for all viruses.
- Natural immunity is acquired with increasing age.
- Children are more likely to be immunologically naïve to viruses transmitted in the donor kidney.
- Once infected, certain viruses may lie dormant (latent) and can be reactivated.
- Immunosuppressive medications profoundly affect cell mediated immunity, increasing the risk of severe viral infection (primary or reactivation).
- Antiviral therapy is effective for CMV and BKV, but not Epstein–Barr virus (EBV).

Cytomegalovirus

Major cause of morbidity in children undergoing renal transplantation. Primarily occurs in the first 3 months following transplantation where no preventative steps are taken—onset may be delayed in those receiving prophylaxis. Infection may be primary or secondary (due to reactivation or reinfection with a new strain), asymptomatic (CMV infection), or symptomatic (CMV disease).

Risk factors

- Those most at risk are the antibody negative recipient (R–) of a positive donor (D+), although disease can also occur with R+ D– and R+ D+ combinations, but not with R– D– unless infection is acquired from a source other than the transplant. CMV may also be transmitted by blood products containing leucocytes.
- Use of ATG/OKT3 for induction or treatment of rejection.
- Intensive immunosuppressive protocols.
- Co-infection with related viruses (HHV-6 and 7).

Classification

(American Society of Transplantation, 2009 http://onlinelibrary.wiley.com/doi/10.111/j.1600-6143.2009.02897.x/abstract)

CMV infection

- Growth of CMV *in vivo*.
- Evidence of viral replication by PCR.

CMV disease is divided into CMV viral syndrome and tissue invasive disease.

CMV viral syndrome

- Evidence of CMV infection plus one or more of the following:
  - fever >38°C for at least 2 days;
  - new or increased malaise;
  - leucopenia;

- >5% atypical lymphocytes;
- thrombocytopenia;
- transaminases >2× upper limit of normal.

CMV tissue invasive disease

- Pneumonia.
- GI disease.
- Hepatitis.
- Central nervous system (CNS) disease.
- Retinitis.
- Others (nephritis, cystitis, myocarditis, pancreatitis).

Indirect effects of CMV infection

- Acute and chronic allograft injury (with increased risk of rejection). Important role in chronic graft vasculopathy.
- Depressed immune response (with increased risk of opportunistic infection).
- Increased risk of EBV-related PTLD.

Diagnosis

- CMV DNA PCR quantitative viral load assay.
- The pp65 antigenaemia assay is an alternative, although less frequently used.

Management

Substantial efforts should be made to prevent infection occurring and to treat early where invasive disease occurs.

- Pre-transplant antibody status of donor and recipient must be established.
- All sero-negative recipients should receive CMV negative or leukodepleted blood products.
- Management options include:
  - the use of anti-CMV prophylaxis in all at-risk individuals; *or*
  - regular surveillance post-transplantation with prompt pre-emptive treatment where evidence of infection develops.
- Both strategies have advantages and disadvantages, which need to be considered in the context of the patient and the allograft.
- Many US authorities prefer prophylaxis for the higher risk D+ R– group, while recognizing the utility of preemptive therapy in the R+ group.
- There is real lack of large multicentre RCTs comparing the two strategies.

Prophylaxis

- Proven efficacy in a large number of clinical trials.
- Easy to co-ordinate.
- Higher drug costs.
- Potential for greater drug toxicity.
- Theoretical advantage of preventing replication of other viruses, including HHV-6.
- Theoretically more likely to prevent indirect effects of CMV.
- Late onset CMV (disease occurring after discontinuation of prophylaxis) may be a significant problem.

Surveillance and pre-emptive treatment

- Fewer trials, particularly in children.
- May reduce drug costs and toxicity.
- Higher laboratory costs.
- Requires excellent logistic co-ordination.
- Can be difficult if families live a distance from the transplant centre.

Antiviral prophylaxis against CMV

- British Transplantation Society (BTS) Guidelines (2004) state that prophylaxis should be given to CMV negative patients (R–) receiving CMV positive organs (D+) and also where donor and recipient are CMV positive and treatment with ATG/ALG/OKT3 is being given.
- American Society of Transplantation (AST) Guidelines (2009) recommend prophylaxis for D+/R– and also all R+ kidney transplants. Prophylaxis should also be given to those receiving ATG/ALG/OKT3.

Treatment is generally administered for the first 3 months post-transplantation.

- CMVIg has been investigated in a small number of trials with contradictory findings. It has a potential role as additive therapy, though further studies are required.
- Aciclovir has poor *in vitro* activity.
- Ganciclovir has been investigated and shown to be effective in many clinical trials and the Cochrane meta-analysis found it to be superior to aciclovir in preventing CMV disease (RR 0.37). It is generally administered IV because oral administration results in lower serum levels (low bioavailability and increased weight adjusted clearance). This requires continuous IV access and is expensive.
- Valaciclovir, the valyl ester of aciclovir has improved bioavailability, and has been shown to be effective against CMV disease and to reduce the incidence of acute rejection.
- Valganciclovir, the valine ester prodrug of ganciclovir has improved bioavailability (10 times that of oral ganciclovir), allowing once daily dosing. It has proven efficacy in preventing CMV disease in adults and is most units agent of first choice for chemoprophylaxis against CMV:
  - available as 450mg tablets and 50mg/mL oral solution;
  - not licensed in UK, but FDA approved from 4 months to 16 years for prophylaxis against CMV in solid organ recipients;
  - dose (mg) = 900 × BSA(m^2)/1.73 × eGFR(mL/min/1.73m^2)/125 once daily for 3 months (RMCH protocol);
  - an alternative dosing schedule has been recommended by Vaudry et al.[2] Dose (mg) = 7 x BSA x eGFR (pharmacokinetics (PK) studies performed using this dose showed very similar exposure to that reported in adult patients receiving 900mg daily).

2 Vaudry W, Ettenger R, Jara P, et al. (2009). Valganciclovir dosing according to body surface area and renal function in pediatric solid organ transplant recipients. *Am J Transpl* **9:** 636–43.

Surveillance for CMV

- On day 1 post-transplant and weekly thereafter for 3 months screen for CMV DNA by PCR.
- If CMV DNA is detected in the blood by PCR, treat with ganciclovir as 60% will go on to develop disease within 10 days.
- Treat for 14 days with IV ganciclovir (see 📖 'Treatment of CMV disease', p.557).
- Repeat the blood PCR twice weekly and if this remains positive after the third test the child will need a further course of IV ganciclovir for 14 days.
- If the child is clinically well, it is possible to use oral valganciclovir after 14 days of IV ganciclovir.

Treatment of CMV disease

CMV viral syndrome and invasive disease.

IV ganciclovir is the mainstay of treatment in children.

- Has been shown to be efficacious in many uncontrolled studies in adult patients.
- Dose is 5mg/kg bd. though dose needs reducing if GFR reduced (see Table 21.5). Ganciclovir is removed by haemodialysis, therefore doses must be given post-dialysis.
- Duration of therapy 2–4 weeks, although uncertainly exists regarding optimum duration:
  - BTS guidelines recommend at least 2 weeks of therapy;
  - AST guidelines recommend 2–4 weeks of therapy;
  - PCR results can tailor duration of therapy;
  - risk of relapse is lower in those where PCR is negative at the end of therapy;
  - treatment should continue until there is clinical resolution of symptoms, negative PCR, and at least 2 weeks of therapy have been administered (AST guideline);
  - the child treated for rejection is more likely to remain PCR positive and may need a longer course of IV ganciclovir;
  - where the child improves clinically, it is possible to change to oral valganciclovir;
  - AST guidelines warn against this practice in children because of lack of (PK) and efficacy data;
  - may be associated with leucopenia and thrombocytopenia, although it must be remembered that this may be a manifestation of the CMV disease;
  - the blood count should be regularly monitored and consideration given to dose reduction if cause of leucopenia and/or thrombocytopenia felt to be ganciclovir.

Immunosuppression should be reduced in the presence of CMV disease.

- The removal of MMF/azathioprine alone may be sufficient where there is only minor organ, e.g. marrow involvement:
  - If more major organ involvement, halving of calcineurin inhibitor dose is conventional.
- CMV Ig may be used in serious infection in conjunction with IV ganciclovir (Table 21.5).

- Care should be taken to exclude other opportunistic infections.
- Ganciclovir resistance may develop after the first course of treatment, so persistence of a positive PCR needs to be investigated for drug resistance.
- If there is resistance to ganciclovir, cidofovir or foscarnet can be used:
  - cidofovir is nephrotoxic—this is heightened in the presence of calcineurin inhibitors;
  - foscarnet is nephrotoxic, neurotoxic (seizures), and may cause electrolyte disturbance, including hypocalcaemia.

Table 21.5 Intravenous ganciclovir dosing

Creatinine clearance (mL/min/1.73m^2)	Dose of IV ganciclovir (mg/kg)	Dosing interval
>80	5mg/kg	Twice daily
50–80	2.5mg/kg	Twice daily
10–50	1.25–2.5mg/kg	Once daily
<10 and haemodialysis	1.25mg/kg	Once daily post-dialysis

Varicella

Varicella is associated with a high morbidity and mortality in immunosuppressed children.

- All children should have anti-varicella IgG antibody titres measured on entry to a CKD 5 programme.
- If blood products have been given in the previous 3 months antibody titres may be falsely positive so need to be rechecked.
- Children without antibodies are assumed to be at risk from chickenpox, even when there is a history of the disease.
- Varicella vaccine is now available and should be given to all varicella naïve children pre-transplant (see 📖 'Immunosuppressive therapy in renal transplant patients', p.523).
- If the child has been antibody positive there is no need to re-check antibodies if the child is in contact with chickenpox.
- If the child is varicella naïve because transplantation has taken place before chickenpox exposure or vaccination and is a chickenpox contact:
  - check anti-varicella IgG antibody status;
  - human varicella zoster immunoglobulin (VZIG) should be given if antibody negative;
  - VZIG should be given as soon as possible after exposure; it must be given within 10 days of contact. Protection from VZIG may only last for three weeks and, therefore, if a second exposure occurs a further dose is required.
- VZIG dosage:
  - *<5 years:* 250mg IM;
  - *5–10 years:* 500mg IM;
  - *>10 years:* 750mg IM.

- The incubation period is 8–21 days post-contact, but add 7 days to incubation period if VZIG is given = 8–28 days post-contact. Patients are contagious for 1–2 days prior to the rash appearing and until the spots have scabbed over, and must be nursed in isolation. Varicella spots can crop several times, so careful examination is necessary.
- If chickenpox or shingles develops, treatment is with high dose oral aciclovir for 7 days as follows and adjust dosage for reduced GFR.
- Children who develop severe chickenpox should be given IV aciclovir for 7 days. The dose for immunocompromised patients is IV aciclovir (Tables 21.6 and 21.7).
- The course of IV aciclovir can be reduced or changed to oral treatment dependent on the severity of the illness.
- It is not usually necessary to stop or reduce azathioprine/MMF, but this can be done if presentation is severe.
- Once the course of aciclovir has finished return to normal maintenance immunosuppression if the azathioprine/MMF has been changed.
- Serum antibody titres should be checked after 3 months to ensure future immunity.

Table 21.6 Oral aciclovir

Age	Dose mg	Dose interval
<2 years	200mg	× 4 daily for 5 days
2–6 years	400mg	× 4 daily for 5 days
6–12 years	800mg	× 4 daily for 5 days
>12 years	800mg	× 5 daily for 7 days
If the eGFR is <10mL/min/1.73m^2		
<2 years	100mg	Twice daily for 5 days
>2 years	200mg	Twice daily for 5 days

Table 21.7 Intravenous aciclovir

Age	Dose	Dose interval
<3months	10–20mg/kg	× 3 daily for 7 days
3 months–12 years	500mg/m^2	× 3 daily for 5 days
>12 years	10mg/kg	× 3 daily for 5 days
Reduced creatinine clearance, mL/min/1.73m^2		
25–50 years	As above	Twice daily
10–25 years	As above	Once daily
<10 years	125mg/m^2	Once daily or after dialysis

BK virus

BK is a polyoma virus. It is so called because BK were the initials of the first patient it was described in. BKV infection, as with CMV, may be primary or secondary (due to reactivation or infection with a new strain) and asymptomatic or symptomatic. Primary infection may be asymptomatic or present with mild pyrexia, malaise, vomiting, respiratory illness, pericarditis, and transient hepatic dysfunction. BKV is important in immunosuppressed patients because after primary infection BKV remains latent in the kidney and urinary tract where it may be reactivated. BKV infection in transplant recipients is associated with:

- Polyomavirus-associated nephropathy (incidence 1–10% of kidney recipients).
- Polyomavirus-associated haemorrhagic cystitis (though this is mainly a problem in bone marrow transplantation).
- Rarer manifestations include ureteric stenosis, pneumonitis, encephalitis, retinitis, multi-organ failure, and leukoencephalopathy.

Diagnosis

- Presentation may be inconspicuous, with no clinical or laboratory signs other than high level viruria as defined by decoy cell (urinary epithelial cells infected with BKV) shedding, and the detection of BKV by PCR in the urine and blood.
- Diagnosis of BKV nephropathy is by transplant biopsy. Specific cytopathic changes are seen—these may mimic rejection or drug toxicity, and should be confirmed by an ancillary technique such as immunohistochemistry for BKV protein or by *in situ* hybridization for BKV nucleic acids.
- All children with acute rejection refractory to conventional treatment should have their biopsies re-evaluated to ensure that evidence of BKV associated nephropathy has not been overlooked.
- Acute rejection and BKV associated nephropathy may occur concurrently. This requires expert diagnosis.
- Diagnosis of BKV-induced ureteric stenosis and cystitis is by tissue biopsy.

Screening

- AST guidelines recommend that screening for BKV should occur to identify patients at increased risk of BKV-associated nephropathy.
  - 3-monthly for the first 2 years post-transplantation and then annually to 5 years;
  - urine should be screened by PCR or cytology for decoy cells—those with evidence of high level urinary replication should undergo blood BKV PCR assessment;
  - where viral loads are consistently high consideration should be given to renal biopsy.

Treatment

Treatment is by reduction of immunosuppression. The following strategies have been reported (AST guidelines 2009 http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2009.02897.x/abstract):

- Reduce calcineurin inhibitor (CNI) by 25–50%, then reduce antiproliferative agent (MMF or azathioprine) by 50% then discontinue latter if necessary.

- Reduce antiproliferative drug by 50% then reduce CNI by 25–50% followed by discontinuation of the antiproliferative drug if necessary.
- In those with sustained high level BKV PCR values despite these measures, antiviral agents should be considered:
  - cidofovir has been shown to be effective in a number of adult series;
  - adverse effects include nephrotoxicity and anterior uveitis;
  - leflunomide has immunosuppressive as well as antiviral properties, and is therefore a potentially attractive option;
  - data regarding use in children are very sparse.
- Where acute rejection occurs following reduction of immunosuppression, this should be treated according to standard protocols.

Epstein–Barr virus and post-transplant lymphoproliferative disease (PTLD)

Over-immunosuppression leading to breakdown of cytotoxic T-cell (CD8+) surveillance for EBV allows latently infected cells to undergo lytic replication and ultimately B-cell transformation. PTLD is one of the most serious complications of kidney transplantation. The incidence in children is 1–2%. EBV is associated with the majority of cases. The highest rate of PTLD is seen in the first year post-transplant; non-EBV PTLD may be responsible for up to one-third of late cases.

Risk factors for the development of PTLD

- Seronegative recipient status.
- The use of potent immunosuppressive agents (particularly antibodies against T cells such as ATG).
- The development of primary EBV infection and infectious mononucleosis.
- Co-existent CMV disease.
- Young recipient age.

PTLD should be considered with the following symptoms:

- Sore throat and tonsillar enlargement, particularly if associated with a tonsillar membrane.
- Lymphadenopathy, hepatosplenomegaly.
- Fever, weight loss, night sweats.
- Malaise and lethargy.
- Chronic sinus congestion.
- Abdominal symptoms, e.g. pain, change in bowel habit, bowel obstruction.
- GI bleeding.
- Respiratory symptoms, dyspnea, or stridor.
- Headache.
- Focal neurological symptoms.
- A fulminant illness, often accompanied by high LDH and uric acid, which may lead to urate nephropathy.

Although the most concerning EBV-related disease after transplantation is PTLD, children may experience non-PTLD-related EBV disease. Features include infectious mononucleosis manifestations (fever, malaise, pharyngitis, lymphadenopathy, etc.). Many of these features are similar to those seen in PTLD.

Histology

- EBV positive neoplastic PTLD is a B-cell lymphoproliferative process. Mono- or oligoclonal cell populations replace the underlying tissue structure. With benign hyperplasia (infectious mononucleosis) nodular architecture is preserved; with polymorphic PTLD there is polyclonal proliferation and local invasion with destruction of the nodal architecture; with monomorphic PTLD, neoplastic transformation of the tissue occurs. Although the first 2 are more likely to respond to reduction of immunosuppression, monomorphic PTLD may also, so treatment must be guided by specific histopathology (see Box 21.3).
- The presence of EBV in the cells can be demonstrated by in-situ hybridization for Epstein–Barr Early RNA (EBER) on fixed tissues and EBNA-CFT on fresh tissue. EBV latent membrane proteins (LMPs) may be found on immunostaining (but not always) and may be useful in diagnosing Hodgkin's type PTLD.
- PTLD can be confused with transplant rejection unless the cells are identified by B-cell markers such as CD19, CD20, CD21 or CD22 (although B cells can be present with rejection in the absence of PTLD).

Box 21.3 Categories of PTLD

- Early lesion:
  - plasmacytic hyperplasia;
  - infectious mononucleosis-like lesion.
- Polymorphic PTLD.
- Monomorphic PTLD (classified according to lymphoma they resemble).
- B-cell neoplasms:
  - diffuse large B-cell lymphoma;
  - Burkitt lymphoma;
  - plasma cell myeloma;
  - plasmacytoma-like lesion;
  - other.
- T-cell neoplasms:
  - peripheral T-cell lymphoma;
  - hepatosplenic T-cell lymphoma;
  - other.
- Classical Hodgkin lymphoma-type PTLD.

Taken from Allen et al. (2009). 'Epstein–Barr virus and post transplant lymphoproliferative disorder in solid organ transplant recipients', *Am J Transpl* 9(S4)**:** S87–96.

Prevention of PTLD

- Recipient EBV antibody status must be established pre-transplant. Donor status can be obtained with living donors and can be requested for deceased donor kidneys.
- Patients at risk of primary CMV infection should also be recognized as being at significantly increased risk of PTLD.
- A vaccine against the gp350 envelope protein has been tested in phase 1 trials and awaits further development.

- At risk patients should be monitored carefully for symptoms/signs suggestive of PTLD and where these are detected, appropriate investigations should be urgently pursued. Where biopsies are performed because of dysfunction, PTLD should always be considered in the differential diagnosis.
- Anti-viral therapy (aciclovir and ganciclovir) inhibits the lytic-replicative cycle of EBV, but has no effect on the latent or oncogenic virus. There is no good evidence to support the use of these agents as a preventative strategy.

Epstein–Barr virus surveillance: the use of viral load and assessment of the immune response

Regular surveillance post-transplant for the development of EBV viraemia and an immune response to it can be useful in the prevention of PTLD. Reduction of immunosuppression (see 📖 'Treatment of established PTLD', p.565) should be considered in those without pre-existing immunity, rising EBV loads, symptoms and lack of an immune response on T cell phenotyping that suggests over-immunosuppression.

Viral load (EBV DNA by PCR)

- Viral load should be measured every 1–2 weeks in the first 6 months and monthly thereafter to one year. However, in the post-transplant immunosuppressed state intermittent low grade viraemia with circulating EBV-DNA may be detected in whole blood at all times. The presence of EBV-DNA in plasma implies a higher viral load and is more suggestive of ongoing viral replication.
- The viral load that represents potential progression to PTLD is not known, but a rising titre at any level is likely to represent over immunosuppression, particularly if accompanied by CMV and/or BKV. Even viral loads as low as 200 copies/mL whole blood may be significant. In the normal individual with mononucleosis the EBV viral load is around 2,000 copies/mL. Current views are that an EBV load >20,000 copies/mL whole blood by real-time PCR on 2 occasions, even if stable, is cause for concern, and that if >100,000 reduction of immunosuppression is indicated. These figures must be viewed in the context of pretransplant immune status, the clinical presentation and the level of immunosuppression.
- In the patient who was EBV naïve at transplantation, monthly measurement of IgM VCA and EBNA IgG antibody will assist in following the immune response. A chronic infection is denoted by a combination of an increased titre of anti-VCA IgG and the lack of EBNA antibodies; these patients are at a particularly high risk of developing PTLD.

Measurement of the immune response (T cell phenotyping) to EBV

Whenever reduction of immunosuppression is contemplated, measurement of the lymphocyte activation phenotype characteristic of an anti-EBV response may be helpful in determining whether it is possible to hold off with further reduction of immunosuppression or whether reduction should continue:

- CD8+ DR+ T cells are best recognized as being helpful in monitoring the immune response. They are directed against EBV transformed B-cells. They are low during active PTLD and rise with recovery of

the immune response and a 'switching off' of the lymphoproliferative process. They may appear before regression of PTLD occurs. A sustained expansion of CD8+ T cells is necessary for PTLD clearance.
- Other T and NK cell phenotypes may assist in monitoring. Whilst individual groups have some experience with this, their clinical usefulness is not yet known.
- As reduction or withdrawal of immunosuppression carries with it a very real risk of allograft rejection, serial monitoring of graft function, often with biopsies, is necessary to differentiate PTLD from acute rejection.
- A suggested schema for surveillance and response to EBV PCR positivity is shown in Fig. 21.3.

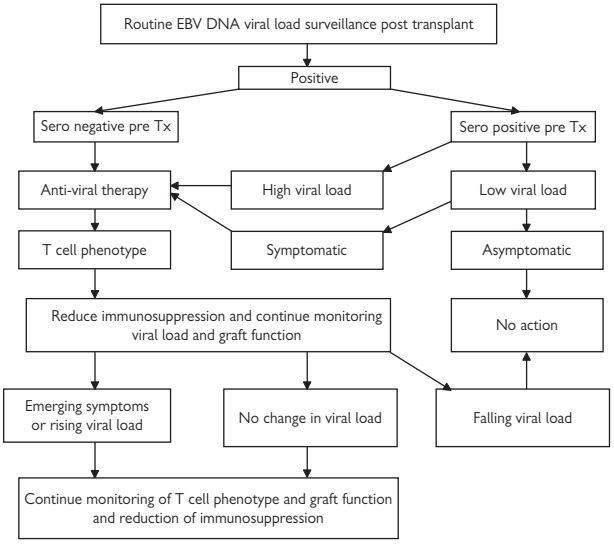

Fig. 21.3 EBV surveillance and T cell monitoring post-transplant.

Investigation of suspected PTLD

If symptoms persist or develop, full investigation is necessary and a histological diagnosis is essential in order to guide future management:
- EBV DNA quantitative assay and EBV serology (VCA IgM, EBNA IgG).
- Immunoglobulins and T and B cell subsets.
- US looking for lymphadenopathy and US of the renal transplant as the transplanted organ is commonly involved in PTLD.
- Biopsy of the most accessible site likely to yield a diagnosis,

Investigations at diagnosis of PTLD
- Uric acid, LDH.
- Chest X-ray.
- Whole body CT with contrast.

- MRI of the head if there are any neurological signs and symptoms.
- Bone marrow aspirate and trephine for morphology, immunophenotyping, and cytogenetics.
- Lumbar puncture if Burkitt's or T cell lymphoma.

Treatment of established PTLD

Progressive reduction of immunosuppression is continued until there is:

- An effective anti-viral cytotoxic T cell response.
- Marked reduction of the EBV genome copy number.
- Resolution of any masses.
- Acute rejection, in which case, if there are still significant masses, cytotoxic therapy is necessary.
- EBV load should not be ignored because the child is otherwise well.

Slow and gradual reduction of immunosuppression is effective and safe if

- The patient is not acutely sick. Life-threatening illness (often accompanied by elevated LDH, increased age, fever, night sweats and weight loss), organ dysfunction, extra-lymphoid and multi-organ involvement by PTLD are independent prognostic factors for lack of response to reduction in immunosuppression and poor survival. Faster reduction of immunosuppression, rituximab, cytotoxic T cells and/or early chemotherapy are usually necessary.
- The patient does not deteriorate clinically.
- The tumour bulk does not increase during the process.
- The histology is not Hodgkins or Burkitt's lymphoma, when specific chemotherapy is necessary.

A suggested schema for reduction of immunosuppression for established PTLD

- Stop azathioprine, mycophenolate mofetil and sirolimus as these have a negative effect on the bone marrow, which needs to be in the best possible condition in case chemotherapy is needed.
- Leave steroids unchanged.
- Reduce the calcineurin inhibitor depending on clinical symptoms as per Table 21.8.
- If the patient is not deteriorating clinically and the disease bulk is not increasing, slow reduction of immunosuppression can continue.
- Complete response is likely by 6 months, but may take longer.
- Immunosuppression should be restarted if rejection occurs, unless PTLD becomes life-threatening.
- If the PTLD is within the first 2 years, immunosuppression will need to be restarted after remission, but at a lower dose. If after 2 years, the patient may not need reintroduction of immunosuppression.
- If the patient has progression of disease, the immunosuppression can be withdrawn faster. If this is not effective, rituximab (anti-CD20 antibody) may be necessary, followed by cytotoxic T cells and/or chemotherapy if this fails.
- Complete or partial surgical resection, as well as radiotherapy, have been used as adjunctive therapy along with reduced immunosuppression.

A suggested schema for the response to persistence of EBV positivity or the development of symptoms in Fig. 21.4.

Table 21.8 Reducing the calcineurin inhibitor

Weeks post-diagnosis	0	1	2	3	4	5	6	7	8	9	10	11	12
% Dose remaining													
Clinically stable	90		75		60		45		30		15		0
Progressive rise in tumour size	90	75	60	45	30	15	0						
Life threatening disease	40	30	20	15	0								

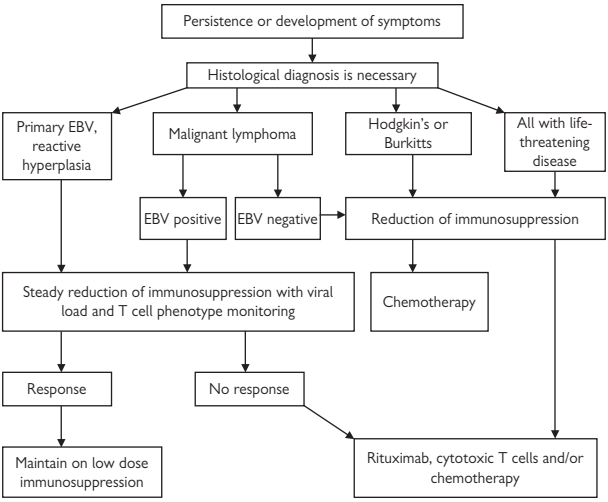

Fig. 21.4 Response to persistence of EBV positivity or development of symptoms

Clinical assessment of remission

The aim is complete remission:

- The clinical response must be assessed every week by checking for fever, lymphadenopathy, tonsillar enlargement, respiratory symptoms, organomegaly, and size of any masses, which can often be measured by US or chest X-ray.
- Monitoring of the T lymphocyte phenotype may guide treatment by identifying recovery of the immune system.
- A follow-up CT with contrast should be done 4 weeks after the initial assessment.
- If clinical and radiological response occurs, continue monitoring fortnightly until complete remission is achieved. After this patients should be evaluated monthly for 1 year and 2 monthly for a further year.

Rituximab

The anti-CD20 monoclonal antibody, rituximab, is safe and relatively effective in studies so far, but there are no controlled trials. It is therefore currently the best second line therapy (unless there is fulminant disease).

- The CD20 antigen is expressed on more than 90% of PTLD cells, but also on B lymphocytes. Rituximab will not work if CD20 is not present on the PTLD cells.
- Rituximab causes lysis of the B-cells expressing CD20 and thus aborts the lytic-replicative phase of EBV-driven lymphoproliferation. As serum immunoglobulin levels are maintained by persisting plasma cells, infection risk is low, although a cytokine release syndrome and/or tumour lysis syndrome can occur for bulky PTLD.
- Rituximab is given in a dose of 375mg/m^2/dose/week IV × 4:

Guidelines for the administration of rituximab in PTLD

Note: differs from its use in SLE.

- Dosage: 375mg/m^2 as an IV infusion, weekly for 4 weeks.
- For patients <10kg a dose of 12.5mg/kg is recommended.
- Premedicate with chlorphenamine and paracetamol 1h prior to the infusion.

Comments

- Vials are available as 500- and 100-mg units.
- Dilute the required dose with NaCl 0.9% or glucose 5% to a final concentration of 1–4mg/mL.
- Initial infusion rate is 25mg/h then increase rate by increments of 25mg/h every 30min up to a maximum of 200mg/h, according to tolerance. Consider halving the rate for patients <10kg.
- Infusions have been associated with a cytokine release syndrome of fever and rigors which usually present within the first 2h. Other reported symptoms include pruritus and rashes, dyspnoea, bronchospasm, angioedema, and transient hypotension.
- Consider stopping antihypertensives 12h prior to administration due to risk of hypotension.
- In the event of an infusion-related adverse event, stop infusion and recommence at half the previous rate once the symptoms have resolved.
- Incidence of infusion-related side effects decreases substantially with subsequent infusions.
- In view of the potential for infusion related adverse events, rituximab must be given between 09.00 and 17.00 on Monday to Friday. It is recommended that a doctor is present on the ward during the administration of rituximab.

Hepatitis B reactivation and fulminant hepatitis have been reported following rituximab therapy. All patients should therefore have their hepatitis B surface antigen and serology checked prior to rituximab therapy. This should not delay therapy as hepatitis B carriers are still eligible, but should be monitored closely for hepatitis B reactivation and abnormalities of liver function.

- Responses of PTLD to rituximab therapy occur at a median of 25 days and up to 2 months after treatment, which is why it may not be adequate in fulminant disease.
- Some patients fail to respond to antibody treatment. This may be due to loss of CD20 antigen from the tumour cells or rapid elimination in certain individuals.
- Response may be lost after relapse.
- Rituximab is generally well-tolerated, the most common toxicity being infusion-related reactions, neutropaenia, and thrombocytopaenia.
- Check clinical response, viral DNA load, and graft function weekly.
- IV immunoglobulin replacement is not routinely recommended in patients who receive rituximab after solid organ transplant. However, immunoglobulin levels should be checked after completion of therapy. Consider immunoglobulin replacement in patients with a history of recurrent chest infections or significant hypogammaglobulinemia.

Follow-up

- Restaging with clinical examination, EBV viral load, LDH, and repeat CT scans with contrast should be performed 2–3 weeks after the last dose of rituximab.
- If the patient goes into complete remission after rituximab then no further treatment need be given.
- The child should be followed up monthly for the first year after diagnosis and 2-monthly for a further year with radiological imaging as appropriate. EBV DNA viral loads should be performed monthly for the first year.
- Immunosuppression should be kept at the minimum that maintains satisfactory graft function.

Cytotoxic T cells

Passive immunization using in vitro expanded EBV-specific cytotoxic T lymphocytes (CTL) has been used to successfully treat EBV-driven lymphoproliferation. However, this approach currently remains experimental, and takes some time to be prepared, which affects its usefulness.

Chemotherapy

The following patient groups need treatment with chemotherapy. The type of chemotherapy should be that which is appropriate for the underlying histology.

- Patients with aggressive disease or worsening despite reduction of immunosuppression may need chemotherapy together with the first 2 doses of rituximab, to gain more rapid disease control.
- Patients with bone marrow involvement and cytogenetic rearrangements.
- Patients who relapse after or fail to respond to Rituximab.
- Patients with Hodgkin's or Burkitt's lymphoma.

Prognostic indicators

The following have been shown to be associated with poorer outcomes in PTLD:

- Severe clinical symptoms.
- Multisite disease.
- CNS disease.
- T or NK-cell PTLD.
- EBV negative PTLD.
- Co-infection with hepatitis B or C.
- Monoclonal disease.
- Presence of mutation of proto-oncogenes or tumour suppressor genes.

Malignancy following renal transplantation

- There is evidence that dialysis patients who have yet to undergo transplantation are at increased risk of malignancy:
  - 1.2–1.9 times that of expected rates in general population;
  - relative risk appears higher in younger patients;
  - risk appears highest for renal cell carcinoma, bladder cancer, and thyroid and other endocrine cancers.
- The incidence of malignancies in adult renal transplant recipients is 6–7 times higher than in the general population:
  - non-melanoma skin cancer is most common;
  - other common cancers include renal cell carcinoma, melanoma, leukaemia, hepatocellular, cervical and vulvovaginal carcinoma, PTLD, and Kaposi sarcoma.
- The overall risk of malignancy post-transplant in children is 2–3% and is 10 times higher than expected for age.
- Increasing immunosuppression increases the risk of malignancy.
- The pattern of malignancy in children as reported to the Israel Penn Transplant Tumor Registry Study (IPTTRS) differs significantly from that observed in adults:
  - PTLD accounts for 52% of malignancy;
  - skin cancers account for 20% (compared with 38% of adult malignancies);
  - others (28%) including carcinoma of vulva/perineum, Kaposi sarcoma, thyroid carcinoma, liver and bile duct carcinoma, sarcomas.
- 60% of malignancies reported to the IPTTRS developed during childhood.
- A Dutch study found 22 cancers in 21 out of 231 children who had undergone renal transplantation:
  - 13 skin cancers (59%);
  - 5 PTLD (23%);
  - 1 each of leukaemia, fibrosarcoma, renal cell carcinoma, and leiomyosarcoma.
- There is a low rate of malignancy until >15 years post-transplant.
- Probability of a cancer by 25 years is 17% (peak 15 years).
- Risk factors for malignancy include:
  - use of cyclophosphamide pretransplant (dose related increased risk);
  - intensive immunosuppressive regimens, particularly those using ATG and OKT3;
  - virus infection: EBV, HPV, HTLV-1, Herpes virus 8;
  - presence of genetic mutations associated with increased tumour risk: WT-1;
  - pre-transplant rGH use has been associated with PTLD, although others have shown that there is no increased risk of this and other malignancies, e.g. renal cell carcinoma;
  - patients who have undergone ileocystoplasty and those with ileal loops are at increased risk of adenocarcinoma and transitional cell/squamous cell carcinoma.

Graft survival in transplant recipients

Graft survival

- The outcomes of kidney transplantation continue to improve.
- Results for living donor recipients are superior to those receiving deceased donor grafts (see Tables 21.9 and 21.10).
- Longer-term follow-up data report graft survival of 23–95% at 10 years, 35% at 15 years, and 21–36% at 20 years.

Table 21.9 US data by year of transplant (NAPRTCS report 2010)

	1 year	3 year	5 year	7 year
Living donor 1987–1995	91.2%	84.6%	78.9%	72.3%
Living donor 1996–2010	95.5%	91.3%	85.7%	80.5%
Deceased donor 1987–1995	80.7%	70.5%	62.4%	56.3%
Deceased donor 1996–2010	93.9%	84.3%	78.4%	67.9%

Table 21.10 UK data 2003–2007 (http://www.uktransplant.org.uk)

	1 year	95% CI	5 year	95% CI
Living donor	97%	93–98%	89%	83–93%
Deceased donor	93%	89–95%	78%	73–82%

Prognostic variables affecting graft survival

- NAPRTCS 2010 registry data report the following as being the most influential adverse prognostic variables of graft survival for recipients of living donor grafts (see Box 21.4):
  - race;
  - previous transplantation;
  - no induction antibody therapy;
  - HLA-B mismatches;
  - history of previous transfusion.
- Adolescence is associated with an increase in graft loss secondary to non-adherence.
- Results are superior with pre-emptive transplantation, although any analysis is complicated because many such transplants will be from living related donors.
- Survival and cold ischaemia time have a reciprocal relationship.

Box 21.4 Causes of graft failure (2309 graft losses following 11603 transplants in 10632 paediatric recipients: NAPRTCS 2010 report)

• Chronic rejection	35.6%
• Acute rejection	13.2%
• Other/unknown	11.6%
• Vascular thrombosis	9.8%
• Death with functioning graft	9.0%
• Recurrent disease	6.9%
• Patient discontinued medication	4.5%
• Primary non-function	2.6%
• Bacterial/viral infection	1.8%
• Accelerated acute rejection	1.4%
• Malignancy	1.2%
• Other technical	1.1%
• Hyperacute rejection	0.7%
• Renal artery stenosis	0.5%
• Ciclosporin toxicity	0.5%
• *De novo* kidney disease	0.3%

Further reading

NAPRTCS (2010). Report. Available at: https://web.emmes.com/study/ped/annlrept/2010_Report.pdf.

Rees L. (2009). Long-term outcome after renal transplantation in childhood. *Pediatr Nephrol* **24:** 475–84.

Chapter 22

Drug prescribing

Basic principles

Varying degrees of renal failure will result in reduced clearance of drugs and their metabolites which are excreted primarily by the kidney:

- Great care needs to be taken when prescribing in renal failure.
- Details of necessary dose adjustments are available in the British National Formulary for Children and other texts (see 📖 'Further reading', p.575).
- Where uncertainty exists, consultation with an expert paediatric renal pharmacist should take place.
- Dose modification is generally only necessary where drugs or their metabolites are >90% renally excreted.
- Drugs that are nephrotoxic and renally excreted, e.g. the aminoglycosides are most likely to cause problems.
- Wherever possible, drug levels should be measured in renal failure.

Drug handling is altered in renal failure

- Bioavailability may be altered by reduced gastrointestinal motility, nausea, vomiting, and anorexia. Phosphate binders may form insoluble products with some drugs, e.g. sodium bicarbonate.
- Volume of distribution may be altered by the presence of volume overload (oedema and ascites), and reduced in volume depletion or muscle wasting.
- Protein binding is altered by acidosis, malnutrition, and inflammation. This can result in high levels of the free drug despite normal blood levels (e.g. phenytoin).
- Renal clearance of drugs and metabolites is reduced in the presence of impaired renal function, the reduction in clearance being linked to the reduction in glomerular filtration rate (GFR). It may be the metabolites that produce the adverse reaction because of their accumulation, e.g. morphine glucuronides, which accumulate to prolong analgesia and respiratory depression.
- Patients with renal failure are often taking multiple medications, thus increasing the risk of drug interactions.
- Many drugs will be cleared by haemodialysis. This depends on the molecular weight and the degree of protein binding of the drug:
  - drugs with a large volume of distribution are generally lipid soluble and not confined to the circulation;
  - they are not well cleared by haemodialysis;
  - peritoneal dialysis is less efficient at clearing drugs unless they have a low volume of distribution and low protein binding.

Important calculations

- Body surface area (m^2) = $\sqrt{}$(height in cm × weight in kg/3600).
- Calculated GFR (mL/min/1.73m^2) = height in cm × 40/plasma creatinine in μmoL/L.
- Normal GFR values are low in infancy and increase to adult values by 1–2 years of age.

Drug dosing in patients on haemodialysis

- Compared with adult patients, there are few published studies on drug dosing in children on haemodialysis.
- Much of the existing adult data on drug clearance on haemodialysis is based on older dialysis technologies and clearance by modern filters may be significantly greater.
- It is logical to administer drugs known to be cleared by haemodialysis immediately at the end of the dialysis sessions.

Drug dose adjustment

- Where renal failure necessitates a reduction in drug dosage, this can be achieved by either reducing the dose and keeping the dosing interval the same, or maintaining the same dose and increasing the dosing interval.
- Increasing the dosing interval is advantageous with drugs with long plasma half-lives and may help with compliance.
- However, increasing the dosing interval may result in wide variation in the plasma concentration and for drugs with a narrow therapeutic window, dose reduction may be a preferable strategy.
- Where dose reduction is performed, there is a smaller difference between Cmax (peak) and Cmin (trough) levels.
- Where there is an increase in the half-life of a drug because of reduced renal clearance, this results in an increased time until steady state blood levels are reached (i.e. more than five doses are required to achieve this, in contrast to patients with normal renal function).

Further reading

Aronoff GR, Bennett WM, and Berns JS. (2007). *Drug prescribing in renal failure. Dosing guidelines for adults and children*, 5th edn. American College of Physicians, Philadelphia.

Daschner M. (2005). Drug dosage in children with reduced renal function. *Pediatr Nephrol* **20:** 1675–86.

Paediatric Formulary Committee (2010). *British National Formulary for Children* Pharmaceutical Press, London.

Specific drug issues of importance

Opiate analgesics

- Certain active opiate metabolites, e.g. morphine-3-glucoronide and morphine-6-glucoronide are renally excreted and can therefore accumulate in renal failure, resulting in depressed conscious level and respiratory depression.
- IV infusions of morphine should be run at up to a maximum of 50% of the standard dose where the GFR is <10mL/min/1.73m^2 and at 75% of the standard dose when 10–50mL/min/1.73m^2. Great care needs to be taken with long-term oral dosing, where the dose should be similarly reduced.
- Pethidine has a potent active metabolite (norpethidine), which accumulates in moderate to severe renal failure and may cause seizures.

Antibiotics and other anti-infective agents

- Gentamicin and other aminoglycosides (e.g. tobramycin and amikacin) need to be used with great care in renal failure as they are significantly nephro- and ototoxic. The risk of nephrotoxicity is increased by the presence of volume depletion, pre-existing renal impairment, hypokalaemia, hypomagnesaemia, and the concomitant administration of other nephrotoxic drugs e.g. calcineurin inhibitors, diuretics, etc.
  - gentamicin should be dosed at 60% of the daily dose divided into 2 doses where the GFR is <40mL/min/1.73m^2 and at 10% of the total daily dose given once daily where the GFR is <10mL/min/1.73m^2;
  - levels should be accurately measured—target trough levels should be <2mg/L (<1mg/L for endocarditis) and peak levels 5–10mg/L (3–5mg/L in endocarditis, and 8–12mg/L in cystic fibrosis);
  - aminoglycosides are extensively cleared by haemodialysis and dosing should take place post-dialysis.
- Vancomycin is used quite frequently in haemodialysis patients for the treatment of dialysis catheter infections. The drug is not extensively cleared by haemodialysis and dosing may only be required once every 5–7 days. Random levels should be checked and a repeat dose administered once the trough falls below 10mg/L.
- The penicillins and third generation cephalosporins require dose reduction in severe renal failure.
- Amphotericin B requires dose adjustment in the presence of renal failure, and may need further reduction if nephrotoxicity occurs. The liposomal preparation does not need dose adjustment and is associated with a lower risk of nephrotoxicity.
- Aciclovir, valaciclovir, valganciclovir, and ganciclovir: see 🕮 'Infection post-transplantation', p.552.

Drugs that require/do not dose alteration, or need to commence at low levels in all levels of renal failure including patients receiving renal replacement therapy and those to be avoided are listed in Tables 22.1 to 22.4.

Table 22.1 Drugs that do not require dose alteration in all levels of renal failure including patients receiving renal replacement therapy

Alfacalcidol	Levothyroxine
Amiodarone	Mesna
Amitriptyline	Metolazone
Amlodipine	Micafungin
Atorvastatin	Minocycline
Azithromycin	Mycophenolate mofetil (accumulation of metabolites possible)
Caspofungin	
Calcium channel blockers	
Clonidine	Omeprazole
Chloramphenicol	Ondansetron
Clindamycin	Pantoprazole
Clonazepam	Paracetamol
Diltiazem (may exacerbate hypokalaemia)	Phenoxymethylpenicillin
	Phenytoin
Dipyridamole	Pravastatin
Disodium pamidronate (though rate of infusion should be reduced)	Rifampicin
	Simvastatin
Domperidone	Sirolimus
Doxazosin	Sodium valproate
Furosemide (not HD)	Steroids
Fusidic acid	Tacrolimus
Imipramine	Terfenadine
Itraconazole	Verapamil
Labetalol	Voriconazole
Lansoprazole	Warfarin

Table 22.2 Drugs to be avoided in severe renal failure including patients receiving renal replacement therapy

- Amphotericin B (excluding liposomal preparation)
- Cidofovir
- Chlorothiazide/hydrochlorothiazide (not effective)
- Disodium etidronate
- Foscarnet
- Gaviscon (high Na content)
- Glibenclamide
- Lithium
- Nitrofurantoin
- NSAIDs (see also Table 22.3)
- Pethidine
- Spironolactone
- Sucralfate
- Tenofovir
- Tetracycline

Table 22.3 Drugs that if necessary should start on low doses, and monitor response and/or levels

ACE inhibitors	Ibuprofen
Beta blockers	Indometacin
Chlorphenamine	Mesalazine and Sulfasalazine
Diazepam	Nitrazepam
Enoxaparin/Dalteparin	Temazepam

Table 22.4 Drugs where dose alteration is necessary; see 📖 'Further reading', p.579

Anti-infective agents	**Other drugs**
Aciclovir	*Anticonvulsants (monitor levels)*
Amikacin	Carbamazepine
Amoxicillin	Clonazepam
Amoxicillin/clavulinic acid	Ethosuximide
Ampicillin	Gabapentin
Benzylpenicillin	Lamotrigine
Carbamazepine	Levetiracetam
Cefotaxime	Midazolam
Cefradine	Phenobarbital
Ceftazidime	Topiramate
Ceftriaxone	*Antihistamines*
Cefuroxime	Cetirizine
Cefalexin	*Gout therapies*
Chlorambucil	Allopurinol
Chloroquine	Colchicine
Ciprofloxacin	*Antineoplastic agents*
Clarithomycin	Cisplatin
Co-trimoxazole	Cyclophosphamide
Doxycycline	Ifosfamide
Erythromycin	Methotrexate
Ethambutol	*Antiviral agents*
Flucloxacillin	Didanosine
Fluconazole	Lamivudine
Flucytosine	Stavudine
Ganciclovir	Zidovudine

Table 22.4 (*Contd.*)

Anti-infective agents	Other drugs
Gentamicin	*GI drugs*
Imipenem/Cilastatin	Cimetidine
Isoniazid	Metoclopramide
Mefloquine (use with caution)	Ranitidine
Meropenem	*Opiates*
Metronidazole	Codeine phosphate
Pentamidine	Diamorphine
Piperacillin/Tazobactam	Digoxin
Pyrazinamide	Bisphosphonates
Rifampicin	Disodium pamidronate sodium clodronate
Teicoplanin	
Tobramycin	
Valaciclovir	
Valganciclovir	
Vancomycin	

Further reading

Aronoff GR, Bennett WM, and Berns JS. (2007). *Drug prescribing in renal failure. Dosing guidelines for adults and children*, 5th edn. American College of Physicians, Philadelphia.

Daschner M. (2005). Drug dosage in children with reduced renal function. *Pediatr Nephrol* **20:** 1675–86.

Paediatric Formulary Committee (2010). *British National Formulary for Children* Pharmaceutical Press, London.

Intraperitoneal drug doses

See 🕮 Chapter 19, p.465.

A number of antibiotics can be administered intraperitoneally for the treatment of peritonitis. Here, drugs are dosed per litre of dialysis fluid, and will reach equilibrium with the blood so that the level in the dialysate will be the same as the blood. Some centres use an intraperitoneal loading dose. Where there is severe systemic illness or the child is immunocompromised, an IV loading dose is recommended (Table 22.5).

Table 22.5 Drug loading doses

Drug	Intraperitoneal loading dose	Intraperitoneal maintenance dose
Amikacin	25mg/L	12mg/L
Cefotaxime	500mg/L	250mg/L
Ceftazidime	250mg/L	125mg/L
Cefuroxime	500mg/L	15mg/L
Ciprofloxacin	50mg/L	25mg/L
Clindamycin	300mg/L	150mg/L
Gentamicin	8mg/L	4mg/L
Teicoplanin	400mg/L	125mg/L
Tobramycin	8mg/L	4mg/L
Vancomycin		12.5–25mg/L

Further reading

Aronoff GR, Bennett WM, and Berns JS. (2007). *Drug prescribing in renal failure. Dosing guidelines for adults and children*, 5th edn. American College of Physicians, Philadelphia.

Daschner M. (2005). Drug dosage in children with reduced renal function. *Pediatr Nephrol* **20:** 1675–86.

Paediatric Formulary Committee (2010). *British National Formulary for Children* Pharmaceutical Press, London.

Chapter 23

Psychosocial issues

Ethical issues

Ethics provides a means of evaluating and choosing between different, often competing options and is about analysing values, rather than facts. Contemporary bioethics utilizes four principal axioms upon which arguments may be developed:

- Respect for autonomy.
- Beneficence.
- Non-maleficence.
- Justice.

The aim is to determine whether, for any particular decision, harm is outweighed by benefit and that any decision is made in the best interests of the child. Advances in the field of renal replacement therapy (RRT) allow the provision of life sustaining therapy for virtually any child, including the newborn and children with other severe co-morbidities, who previously would have succumbed to their renal disease. This raises a number of key ethical issues, the following of which are frequently recurring themes in all paediatric nephrology units:

- The commencement of RRT in infants, children, and adolescents with significant co-morbidity.
- The commencement of RRT in the newborn.
- The withdrawal of RRT in infants, children, and adolescents.
- The management of non-adherence with prescribed therapy and the impact of non-adherence on subsequent decisions regarding listing for renal transplantation.
- Identification of non-paternity following tissue typing.
- Families who wish to travel abroad to purchase a kidney.
- Live related transplantation when there is a significant risk of disease recurrence in the graft.
- The use of siblings who offer themselves as donors, but may be considered too young.
- Parental discord over management, e.g. live donor transplant from a 'separated' partner.

These scenarios all create ethical dilemmas because:

- Clinical facts alone do not determine what course of action should follow.
- There may be disagreements between parties (team members, parents, parents and children, parents and professionals) as to what is the right course of action.
- Applying ethical principles may produce conflicting outcomes.
- The law is ambiguous or silent in directing what must be done.

In trying to resolve dilemmas it is important to analyse the moral basis of the dispute and determine how the application of ethical theories (e.g. utility, duty) or principles (e.g. beneficence, non-maleficence, respect for autonomy, justice) may help.

The moral basis of medicine requires that professionals offer treatments that are in the best interests of their patients. In practice, this means that professionals should offer treatment that is intended to produce more benefit than harm, and respect as much capacity for self-determined choice (autonomy) as their patients are capable. The latter is more problematic in children because they may lack the capacity to make an informed choice about their treatment. Their parents have the ethical and legal right to make such choices on their behalf provided they act in their child's best interests. Disputes about best interests and who should decide them are at the heart of many of the themes identified in the provision of RRT. What follows is a practical approach to decision making in RRT cases. It is important to recognize and separate facts from values.

- Establish and agree which consultant is leading the care for the family.
- Check that the family have read and understood available information, or had access to explanations (on more than one occasion).
- The lead consultant should discuss the child with other members of the nephrology subspecialty team, including clinical nurse specialists, dieticians, play therapists, psychologists, social worker to obtain relevant information, and ascertain their views.
- The lead consultant or appropriate member of the renal team should inform and discuss with local team (paediatrician) and GP; this will provide more information about family background, co-morbidities, etc.
- It may be necessary to convene a multidisciplinary team meeting, to be chaired by the lead Consultant to share information and to clarify issues.
- It is important to ensure good note keeping.
- Consideration should be given as to whether a second independent opinion would be useful:
  - offer to facilitate, but allow family to also select independently should they wish;
  - it is important to be clear as to the purpose of the second opinion, i.e. whether to clarify clinical facts or to provide an opinion of what should be done (the latter involves value judgements, rather than pure clinical fact).
- Once appropriate background clinical, psychological and social facts have been obtained and controversy about further proceedings remain, either within the team or between the team and the family, a formal full clinical ethical committee review should be considered to facilitate the decision-making process.
- The time frame over which the decision needs to be made (and by whom) should be defined. Where possible, take time to come to decision. In an emergency and in the presence of a critical ethical problem, consider a consultant second opinion.
- Consider whether legal services should be involved.

- The family should be provided with advance notice of important meetings. There should be due consideration of timing and place (e.g. out of clinic/ward, 'neutral' area), so as to maximize freely-informed decision making. Attendance is best limited to preserve the privacy/intimacy of the occasion.
- Consideration should be given as to how the views of the child (in accordance with their age, experience, and capacity) are obtained and what weight is placed upon those views.
- Ensure all relevant professionals (inside and outside the hospital) are aware of decisions, and that the latter are recorded properly:
  - staff may need support (often led by the psychosocial team);
  - consider meeting to reflect or debrief (usually after an appropriate interval);
  - the decision making process should be transparent inclusive, accountable, responsive, and reasonable.

Further reading

Kurz R, Gill D, Mjones S, and Ethics Working Group of Confederation of European Specialists in Paediatrics. (2006). Ethical issues in the daily medical care of children. *Eur J Pediatr* **165:** 83–6.

Non-adherence in paediatric renal disease

Non-adherence

- Defined by the World Health Organization (WHO) as 'the degree to which the person's behaviour corresponds with the agreed recommendations from a health care provider'.
- Is a common problem with particularly severe consequences after renal transplantation:
  - systematic review in adult subjects has shown that 22% of organ recipients are non-adherent with treatment and that a median of 36% of graft losses are associated with prior non-adherence;
  - the odds of graft failure increase seven fold where non-adherence occurs;
  - a review of paediatric studies investigating non-adherence following solid organ transplantation revealed a prevalence of medication non-adherence of 32% for kidney recipients (31% for liver recipients and 16% for heart recipients).

Consequences of non-adherence

Post-transplant

- Aetiological factor in graft loss in 14% of paediatric kidney recipients.
- Increased risk of late acute rejection resulting in additional hospital admissions, clinic visits, time absent from school/parental employment, etc.

In chronic kidney disease

- Phosphate binders are commonly omitted, resulting in an increased risk of hyperphosphataemia and therefore chronic kidney disease-mineral bone disorder (CKD-MBD).

Risk factors for non-adherence

- Adolescence is a major risk factor for non-adherence and rates are much higher in this population than in adults. This is reflected in:
  - the poorest long-term graft survival compared with all other age groups;
  - higher rates of late acute rejection in this age group.
- Demographic and socio-economic factors:
  - low socioeconomic status;
  - ethnicity (increased non-adherence reported in US African Americans);
  - single parent families;
  - family instability;
  - poor communication within family;
  - insufficient family social or emotional support.

- Patient-related factors:
  - poor knowledge of medications/disease;
  - low self-esteem;
  - forgetfulness;
  - learning difficulties;
  - history of non-adherence;
  - prior history of child abuse.
- Condition-related factors:
  - longer post-transplant;
  - longer on dialysis.
- Treatment-related factors:
  - cosmetic adverse effects of drugs;
  - number of drugs and number of doses per day;
  - taste/palatability;
  - cost of drugs.
- Health care setting and health care provider related factors:
  - poor communication between multi-professional team and patient;
  - authoritarian consultation style;
  - lack of understanding of non-adherence;
  - family lack of trust in health care providers.

Methods of documenting non-adherence

- Self-reporting.
- Observation by parents or other family members.
- Physical or biochemical markers:
  - absence of adverse cosmetic or other effects (e.g. non-Cushingoid when on high doses of corticosteroids);
  - unrecordable or low blood drug levels;
  - persistent biochemical abnormalities, particularly phosphate.
- Adverse events related to non-adherence, e.g. acute rejection, graft loss.
- Electronic monitoring: microchip inserted into medicine container/bottle tops records each time the container/bottle is opened. This can be downloaded onto a PC by the doctor or the patient.
- Monitoring of pill usage or dispensing records.

Strategies to improve adherence

- *Simplification/modification of drug regimen:*
  - reducing number of drugs and doses;
  - use of once daily medications;
  - use of drugs with longer half-lives requiring less strict adherence with timing;
  - more palatable drugs;
  - drugs with fewer cosmetic adverse effects.
- *Patient education:*
  - understanding of medication purpose;
  - understanding of medication dose;
  - understanding of importance of adherence, medication adverse effects, etc.

- *Behavioural strategies:*
  - use of medication intake records with reward system;
  - use of cues (meals, teeth cleaning etc.);
  - dosette boxes into which all drugs are inserted for the coming week;
  - alarms (watch, mobile phone prompts, etc.).
- *Strategies to improve social support:*
  - involvement of family;
  - peer support groups.
- *Other:*
  - practical help with cosmetic issues (make-up and hair removal strategies);
  - regular discussion about/monitoring of non-adherence;
  - early intervention by psychologist/psychiatrist where problems detected with patient and/or family.

Further reading

Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. (2005). Growing pains: non-adherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant* **9:** 381–90.

Long-term growth

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry has identified:

- At entry into the CKD registry, 36.6% of patients have a height SDS below –1.88.
- The mean height SDS at the start of dialysis in 3910 children was –1.66.
- The youngest children enter RRT programmes with the greatest height deficits.
- Height SDS on dialysis decreased from –1.64 to –1.71 after 1 year and –1.84 after 2 years.
- Post-transplant, the youngest children (Table 23.1) and those with the greatest pre-transplant height deficit show the best growth.
- Post-transplant growth is adversely affected by steroids (there is emerging evidence that steroid avoidance regimens enhance post-transplant growth) and progressive graft failure.
- Height SDS at time of transplant has improved: in 1987 the mean was –2.4, and was –1.4 in 2007.

The International Pediatric Peritoneal Dialysis Network (IPPN) collects data from >1400 children on peritoneal dialysis around the world, and is, therefore, able to provide comparisons of growth according to region.

- The mean height SDS is below normal throughout the world, but there is a large variation, from –1.5 in the UK (where paradoxically rhGH use is the lowest), to –3.5 in Brazil.
- The mean body mass index SDS does not parallel the height SDS, however, with less variation from normal, but a high incidence of obesity in the US, and of low body weight in India.
- Longitudinal growth varies around the world. Overall there is a decline in height SDS with time, but children in some countries (e.g. UK) show an improvement in height SDS over time on PD.

The UK registry shows that:

- Between 1999 and 2008, height SDS for both dialysis and transplant patients has remained remarkably stable, at a median of –1.4 to –1.9 for dialysis and –1.2 to –1.4 for transplanted patients.
- Weight too has remained stable, at a mean SDS of around 0 for transplant and –0.9 to –1.6 for dialysis patients.

Some centres (UK and Finland) using intensive nutritional support have reported catch-up growth at all ages, particularly in the under 2s.

Final height

- Many databases do not select out children with comorbidities that may cause short stature in their own right.
- In an analysis over 20 years, those without comorbidity achieved a mean adult height within the normal range.
- Mean final heights vary from 148 to 158cm for females and 162 to 168cm for males (2nd centiles 151and 163cm, respectively), with little difference to be seen whether treated with rhGH or not.

Table 23.1 Mean Height SDS at transplant and after 6 years (NAPRTCS)

Age (years)	Mean Height SDS at transplant	Mean Height SDS after 6 years
0–1	–2.2	–1.4
2–5	–2.3	–1.7
6–12	–1.9	–1.9
>12	–1.4	–1.6

Further reading

Mak R and Rees L. (2011). Nutrition and growth in chronic kidney disease. *Nature Rev Nephrol*, in press.

Long-term survival of children on renal replacement therapy

Survival on dialysis

- After 5 years is:
  - 60% for 0–1 year of age;
  - 80% for 2 –5 years of age;
  - 85% for > 6 years of age.
- Comorbidity increases the mortality risk 7-fold, and is commonest in the youngest children.
- There is no difference in outcome in infants who are otherwise normal in comparison to older children.
- Mortality increases with increasing duration of dialysis.
- The presence of residual renal function improves outcome.
- There is no difference between PD and HD.
- There has been no significant improvement since the 1990s.
- Causes of death on dialysis:
  - co-morbidity;
  - treatment withdrawal (+/– co morbidity);
  - failure to obtain or maintain dialysis access;
  - infection, cardio-pulmonary or cerebrovascular events;
  - cardiovascular disease in up to 38%—arrhythmias, valve disease, cardiomyopathy, and arteriosclerosis;
  - CVD is commoner after 10 years of RRT, with a risk for a young adult in their 20s 800-fold greater than for the normal population.

Survival post-transplant

- Longer term follow-up data report patient survival of 75–95% at 10 years, 83–94% at 15 years, 54–86% at 20 years, and there is one report of 81% 25-year patient survival (see Table 23.2).
- Age does not affect mortality in most recent studies.
- There is a small benefit from pre-emptive transplantation.
- There is a small benefit from living donation, particularly in the very young.
- The risk of death from CVD is increased by 1.6 in Afro-Americans.

See Table 23.3 for causes of death following transplant.

The average life expectancy at age 20–25 years is:

- 55–60 years in the normal population.
- 35–40 years with a renal transplant.
- 10–15 years on dialysis.
- Compared with normal children the lifespan of a child on dialysis is reduced by 40–60 years and a child with a transplant reduced by 20–25 years.

Table 23.2 UK renal transplant patient survival data 1999–2007

	1 year	95% CI	5 year	95% CI
Living donor	99%	96–100%	95%	90–97%
Deceased donor	100%	98–100%	98%	96–99%

Available at: www.uktransplant.org.uk

Table 23.3 Causes of death following renal transplantation (NAPRTCS) 2010 report

	%
Cardiopulmonary	14.7
Bacterial infection	12.7
Malignancy	11.3
Unspecified infection	8.0
Viral infection	7.7
Haemorrhage	5.8
Dialysis-related complications	3.1
Recurrence	1.7
Other	25.3
Unknown	9.6

Palliative care

Background

The decision to focus on palliative care and not treatment aimed to cure or prolong life often evolves gradually. Different members of staff and members of the family may be working towards the decision at different rates and time, and discussion is essential for the transition. This time can also be helpful in providing an opportunity for planning.

Palliative care for the sick child and their family needs to be comprehensive and consider medical and nursing needs, psychosocial and spiritual care, and the practical needs of the family wherever care will be taking place. If available, the local palliative care team should be consulted early on and, if the families agree, involved in discussions with the family. As they have experience with symptom care, staff to follow the patient outside the hospital and a network of contacts in the local community (hospices, community nurses, etc.), their help is invaluable.

Symptom management

The following points are important:

- Assessment of the child's symptoms and their likely cause.
- Development of a management plan for each symptom, including both pharmacological and non-pharmacological approaches.
- How are these symptoms likely to progress and what are the plans for management when this occurs.
- What new symptoms may arise; consider probable ones, possible ones, and even those which are unlikely.
- Develop a clear management plan for each of these.
- Consider prescription and availability of drugs, appropriate routes of administration now, and later in the illness.
- Consider any equipment that will be needed such as syringe pumps, catheters, special mattresses, oxygen, etc.

Liaison and planning care

- If the families are keen to care for their child at home, the earlier links can be developed with the community and the closer these are, the easier the discharge will be.
- Since community services vary, arrangements need to be made individually for each family, according to their circumstances.
- Family doctors, community nursing teams, local shared-care hospitals and hospices are likely to be involved.
- The role of each care group needs to be decided before the child's discharge. In particular, who will be available at nights and over weekends, and how the family has access to them needs to be planned. A key worker, usually one of the nursing staff either from the hospital or community, should take on the role of co-ordination of care.
- Often a system develops whereby local carers, such as the GP and community nurses take on routine 24-h care, but they need back up and access to experience and advice in paediatrics and paediatric palliative care, also on a 24-h basis.

- Information about symptom management and the network of carers should be clearly communicated both to the family and all those involved in their management.

Support for the Child and Family

- This needs to be ongoing as the illness progresses.
- If the family are taking the responsibility of care on in the home they need as much information and confidence as possible in managing the child's symptoms and the likely progress of the disease. As the illness progresses they will also need information about how the child may die and what to do after the child has died in relation to death certificates, registration, funerals etc.
- They may need information and support in talking about illness and the child's death with siblings, grandparents and with the sick child themselves.
- Families need the opportunity to talk about their own feelings and the wide range of emotions they are likely to be experiencing at this time.
- The sick child needs the opportunity to talk about their understanding of what is happening to them, their fears and their feelings.
- All the family may need to think about their immediate aims and also plan short term goals both in relation to care and also socially.

Palliative care checklist

The following should be involved in discussions regarding discharge and subsequent care:

Within the hospital

- Consultant in charge.
- Counsellor.
- Ward sister.
- Ward registrar.
- Consultant in palliative care.
- Psychologist.
- Social worker.
- Religious representative.
- Pharmacist.
- Dietician.

Outside the hospital

- Paediatric community nurse.
- Local paediatrician.
- General practitioner.
- Health visitor.

Discharge plans

These must begin as soon as possible, preferably before the final decision to discharge has been made. The child may be discharged either to his/her home or to the local hospital or to a children's hospice.

Potential problems

Checklist to be reviewed at least weekly:

- Mobility.
- Weakness.
- Anorexia, nausea and vomiting and weight loss.
- Sore mouth.
- Diarrhoea or constipation.
- Cough or dyspnoea.
- Headache.
- Fits.
- Abnormalities of micturition.
- Bone pain.
- Abdominal pain.
- Skin (itching, sweating).
- Oedema.
- Anaemia.
- Bleeding.
- Infection, fever.
- Behaviour/sleep disturbance/anxiety/depression.

Symptom management

- A number of drugs used in symptomatic care are excreted renally and therefore the drug levels may be affected. As the illness progresses the use of individual drugs needs to be considered in relation to the goals of the treatment and the priority of the child's comfort and dignity.
- It is essential to aim for high quality symptom management throughout the child's illness. The suffering they experience from treatment and its side effects will be what the child remembers.
- For those children who unfortunately cannot be cured, palliative care, including rigorous attention to symptom management, will help to provide as good a quality of life as possible for the time that remains.
- Although pain may not be a prominent problem for children dying from renal disease, it will be a fear for parents and its management should be anticipated and planned for. Pain is a complex sensation related not only to physiological insult to the tissues, but is also influenced by psychological, social, and cultural factors.
- Pain assessment tools, according to the child's age and ability, are available. Body charts are helpful for all ages to locate and identify sites of pain, whilst colour scales, faces, numeric, and visual analogue scales can be used to measure severity. Parents usually interpret their child's feelings reliably, but may sometimes under or over-estimate the pain because of their own attitudes.
- Physical and psychological management includes education, explanation, distraction, relaxation and hypnosis, physical care (including attention to warmth and cold), massage, and physiotherapy.

Drug management

- Pharmacological management of pain includes non-opioids, mild opioids, strong opioids, NSAIDs, amitriptyline, and anticonvulsants.
- In most situations analgesics of gradually increasing strength can be used, according to the World Health Organization's concept of an analgesic ladder (Fig. 23.1).
- Paracetamol is helpful in mild to moderate pain and has few side effects. When pain is no longer relieved by regular paracetamol a mild opioid can be introduced. Side effects are similar to the strong opioids (see 📖 'Opioid side effects', p.596). The analgesic effect of codeine has a ceiling and when pain is no longer relieved a strong opioid is needed.
- Morphine sulphate is the strong opioid of choice and four-hourly or twelve-hourly (slow release) preparations are available. When using slow-release preparations always provide a short-acting preparation also, to use for breakthrough pain.

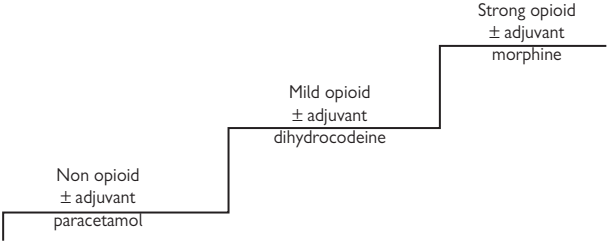

Fig. 23.1 The WHO analgesic ladder.

Doses and frequency

- The initial dose should be calculated according to the child's weight and then increased, in increments, to provide adequate analgesia. In most situations pain is constant and analgesics should be given regularly, not as required (prn).
- Strong opioids are metabolized in the liver and eliminated via the kidneys:
  - accumulation may occur with renal disease, and lower doses given less frequently may be appropriate; this must be determined for each patient individually depending on their need for pain relief, the progress of the disease and where palliative care is occurring (i.e. home, hospital);
  - good analgesia should remain the primary aim, but may be achieved more gradually by starting with half the recommended dose/kg and giving subsequent doses only when pain recurs, observing carefully, and working out a personal dose and dosing schedule for each individual.

Routes of administration

- The route of choice is oral, with increasing doses as necessary.
- If the oral route is not possible, for example because of nausea and vomiting, difficulty swallowing or gradual loss of consciousness another route is needed.
- During palliative care some children tolerate rectal medication well, and prefer it to the thought of any needles.
- When the child is no longer conscious or for the last few hours of life morphine suppositories and slow release morphine tablets can be used rectally.
- Analgesics can easily be given by continuous infusion.
- Diamorphine is usually substituted for morphine because of its greater solubility. If a central in-dwelling intravenous catheter is *in situ* this can be used, otherwise the needle is placed SC and a simple infusion pump can be used.

Opioid side effects

- Constipation is invariable. Laxatives should always be prescribed prophylactically.
- Drowsiness is also common at first, but this almost always wears off within 2–3 days. It is useful to warn parents about this or they may worry that the disease has suddenly progressed.
- Nausea and vomiting may be managed with intermittent or prophylactic anti-emetics.
- Some children experience itching; this usually also wears off, but if not antihistamines are helpful.
- Respiratory depression does not appear to cause problems in children being treated with opioid drugs for pain, as there is a wide margin between the dose causing respiratory failure and that required for analgesia. Pain has been described as a physiological antagonist to the respiratory depressant effects of morphine.
- Sometimes parents are reluctant to consider the use of morphine for their child's pain. In order to overcome this reasons for their concern need to be explored:
  - often it is not the use of morphine itself, but that it represents an acknowledgement that the child is actually dying;
  - parents may also be confused about addiction and need reassurance that psychological addiction does not seem to occur in children requiring opioids for severe pain;
  - although tolerance will develop, should the pain be relieved then the morphine dose can easily be tapered and then stopped.

Bone pain

- Bone pain may be related to renal osteodystrophy. Adjustment of phosphate binders and activated vitamin D may help.
- Although non-steroidal anti-inflammatory drugs can be helpful for bone pain careful consideration is necessary in children with renal failure because of potential problems from gastrointestinal bleeding and further renal impairment.

Nausea and vomiting

There are many causes of nausea and vomiting. Identifying the cause can help in making a logical choice of anti-emetics. If initial choices are unsuccessful then combining a number of drugs, which work through different mechanisms may improve the situation.

Constipation

Constipation may be due to inactivity, poor nutrition, poor fluid intake, hypercalcaemia, and hypokalaemia, as well as a side effect of opioid therapy. A suggested treatment schedule is in Fig. 23.2.

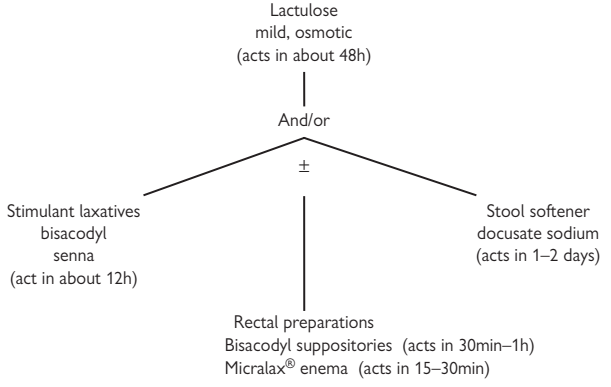

Fig. 23.2 Treatment of constipation.

Convulsions

Convulsions are a risk for a child dying from renal disease, and parents should be warned and prepared. Occasional, short fits may not require medication, although rectal diazepam should be available, either in hospital or at home, in case they are more prolonged. Regular oral anticonvulsants may be appropriate for some children having frequent convulsions over a prolonged period. SC midazolam (which is compatible with diamorphine and can be mixed in the same syringe) is helpful for children being cared for at home and requiring regular parenteral medication for convulsions.

Anxiety and agitation

Anxiety as the disease progresses may reflect a patient's need to talk about their fears and be helped by discussion and reassurance. Low dose oral diazepam may also be helpful. Restlessness and agitation are common in the final stages of life and can be treated with haloperidol, levomepromazine, or midazolam, all of which are compatible with diamorphine in subcutaneous infusions.

Itching

Itching may be a problem from increasing uraemia and as a side effect of opioids. Oral antihistamines may help relieve opioid-related itching. Topical preparations, such as calamine, can also be used. In some uraemic patients itching is the major problem and the following practical advice can be useful in this specific context:

- Avoid excessively warm baths.
- When drying the skin dab with a towel, rather than rub.
- Dietary measures that help to control uraemia may help with itching.

Hiccups

These may be helped by chlorpromazine.

Excess secretions

In the terminal phase a child may develop noisy breathing from an inability to swallow secretions. This is rarely distressing to the child, but difficult for parents and can be effectively helped with hyoscine, conveniently given via a transdermal patch or subcutaneously.

Further reading

Children's Palliative Care Services. Association for Children with Life-threatening or Terminal Conditions and their Families and Royal College of Paediatrics and Child Health, 1997.

Supplementary information

Assessment of glomerular filtration rate

Plasma creatinine

- Creatinine is produced at a constant rate from the breakdown of creatine and creatine phosphate (almost exclusively found in muscle) at a rate of around 10–25mg/kg/day (90–210μmol/kg/day).
- Normal plasma creatinine levels, therefore, increase progressively with growth and, in particular, muscle mass.
- Creatinine is renally excreted by filtration without reabsorption, except in the premature infant, when 'back-diffusion' can occur.
- Tubular secretion of creatinine increases early in chronic kidney disease (CKD) so that the plasma level may not rise until saturation of tubular secretion occurs. Thus, plasma creatinine may overestimate glomerular filtration rate (GFR).
- As renal function declines, decreasing muscle mass due to malnutrition may lead to a fall in the plasma creatinine, which may underestimate the severity of CKD.
- Conversely, the child starting recombinant growth hormone therapy (rhGH) may show a rise in plasma creatinine due to the effects of rhGH on muscle bulk.
- Plasma creatinine levels may also be affected by dietary meat intake and drugs that interfere with its tubular secretion, e.g. trimethoprim.
- Plotting of the reciprocal of creatinine against time may be useful to illustrate the rate of decline in renal function. However, the constraints already mentioned apply to this method too.
- Clearance is the volume of blood cleared of a substance in unit time (mL/min). It is corrected for size by conversion to a surface area of $1.73m^2$.
- Measurement of creatinine clearance is rarely undertaken in children because of the difficulties of a timed urine collection.
- Cystatin C is a proteinase inhibitor produced by all nucleated cells at a constant rate. Measurement of plasma cystatin C levels is a more accurate means of assessing renal function than measurement of plasma creatinine levels but is not used routinely at present.

Glomerular and tubular functions are interdependent. Assessment of GFR provides an indication of overall level of renal function. Although GFR cannot be measured directly in clinical practice, an estimation of GFR may be made by a number of methods.

An estimate of GFR can be obtained by measuring the clearance of a solute, which is:

$$Cx = (U_x \times V)/P_x$$

where: Cx = clearance of solute x; U_x = urine concentration of solute x; V = volume of urine over a given time period; P_x = plasma concentration of solute x.

Methods employed

- Inulin clearance.
- Creatinine clearance.
- Plasma disappearance method.
- Haycock–Schwartz formula.

Inulin clearance

Currently the gold standard, although expensive, the method involves the administration of an IV bolus of inulin, followed by a continuous infusion of the solution to maintain the plasma inulin concentration at a constant level. After a period of equilibration, a diuresis is induced by oral or IV fluid administration, and serial timed urine collections are commenced. Inulin concentration is measured in plasma samples obtained at approximately the midpoint of each urine collection period. The inulin excretion rate ($U_{inulin} \times V$) and plasma inulin concentration for each time period are then used to calculate GFR from the equation for C_X given in 📖 'Plasma creatinine', p.600. A mean value is calculated from the serial GFR results. Disadvantages include the need to administer an exogenous marker substance and the requirement for accurately measured, timed urine collections, which are frequently difficult to obtain in paediatric practice.

Creatinine clearance

A timed urine collection and plasma creatinine concentration may be used to derive an estimate of GFR from the equation for C_X given in 📖 'Plasma creatinine', p.600. Although simple, the major disadvantage relates to accuracy limited by the fact that a timed urine sample is required. Also, since creatinine is excreted by tubular secretion, as well as glomerular filtration, GFR may be overestimated. Cimetidine has been found to inhibit tubular secretion of creatinine and estimates of GFR obtained from cimetidine-primed creatinine clearance have been shown to equate better with inulin clearance.

Plasma disappearance method

This method uses an alternative approach. For a marker substance that fulfils the general criteria required for GFR estimation, the rate of decline of plasma concentration after bolus intravenous administration will reflect the rate at which the substance is cleared from the plasma by glomerular filtration. The obvious advantage is that this technique avoids the need for timed urine collections. [^{51}Cr]EDTA can be used as a marker in this type of study. The radiation dose is low and, as the compound is excreted in urine, exposure may be minimized by diuresis and frequent micturition. However, iohexol is now used more commonly. Mathematical modelling allows estimation of the GFR. The accuracy of this technique is dependent upon knowledge of the exact dose administered. It should be noted that this method tends to overestimate the GFR at high-normal levels of renal function. Accuracy is also unreliable in patients who are oedematous or dehydrated ('volume of distribution error'). Moreover, the time between plasma samples may need to be extended at low GFR in order to have a substantial decline in the plasma concentration. Despite these limitations, GFR estimation by the plasma disappearance method is a clinically useful tool.

Haycock–Schwartz formula

The Haycock–Schwartz formula may be used to estimate GFR from the plasma creatinine concentration, without the need for a timed urine collection.

$$eGFR = (k \times ht)/P_{Cr}$$

where eGFR = estimated glomerular filtration rate (in mL/min/1.73m^2); k = an empirically derived value relating height to muscle mass; ht = height (in cm); P_{Cr} = plasma concentration of creatinine (in μmol/L or mg/dL).

Most centres would use a k value of 40 (for creatinine in μmol/L) or 0.45 (for creatinine in mg/dL) for all ages. However, k may vary for different age groups, reflecting increasing relative muscle mass during childhood and adolescence. Also, k values represent the body mass of individuals with normal nutritional status: in malnourished chronically ill children, lower muscle mass may lead to lower levels of P_{Cr} causing a misleading overestimate of GFR. A trend in eGFR may be a clinically useful tool, but absolute values should not be relied upon in isolation. Values of k may also vary depending on how plasma creatinine is measured and hence are different between laboratories. Clinicians should thus be aware of the limitations of this approach to estimating GFR.

Furosemide test of urinary acidification

Indication

Assessment of urinary acidification (e.g. in a child with suspected renal tubular acidosis). The furosemide test can be used as an alternative to ammonia loading, which is often poorly tolerated in children as it is highly emetic. Usually, a child with RTA will present with metabolic acidosis and the urine can be analysed directly. In that case, there is no need for a further test of urinary acidification. The test can be considered if a 'sub-clinical RTA' is suspected, that is a mild RTA that is apparent only when the system is stressed.

A major problem in assessing urinary acidification in children is the method of obtaining the sample: if exposed to air, CO_2 will diffuse out of the sample, resulting in an artificial increase in pH (see 📖 'Disorders of acid-base balance: basic principles', p.130). Thus, urine obtained by bag or from cotton balls in the nappy is useless for acid-base assessment. Ideally, the urine is collected under oil to avoid any diffusion of CO_2 and assessed immediately (i.e. not sent in an air-filled container to the laboratory).

Contraindications

If the child has marked electrolyte imbalance, in particular, hypokalaemia (K <3.5mmol/L), furosemide may potentiate the abnormality. Obstruction of the urinary tract may be accentuated by furosemide.

Basis

Furosemide causes volume depletion, which in turn up-regulates distal sodium reabsorption, which is in exchange for K and H ions, thus increasing urinary hydrogen concentration and lowering urinary pH (see 📖 'Disorders of renal salt handling: basic principles', p.140). Furosemide inhibits the Na/K/Cl pump in the thick ascending limb of the loop of Henle, thereby increasing Na delivery to the distal tubule.

Protocol

- Ensure the child is not on bicarbonate (or citrate) supplements.
- Fast from midnight (not essential, e.g. in infants).
- *Baseline biochemistry:* urine Na, K, pH (by glass electrode), creatinine, plasma Na, K, TCO_2, urea, creatinine.
- Give an oral (or IV) dose of furosemide, 1mg/kg.
- Collect urine every 30min for 3h (or each specimen) and measure the urine pH straight away.
- After 3h, recheck plasma Na, K, TCO_2, urea, creatinine.
- Prior to discharge, ensure the child is not clinically dehydrated.

Results

Normal children and adults will lower urine pH to <5.5, usually by 2h, always by 3h. Any urine pH <5.5 indicates normal urine acidification and the test can be stopped. Failure to achieve a urine pH <5.5 suggests a distal tubular acidification defect.

Further reading

Rodriguez Soriano J and Vallo A. (1988). Renal tubular hyperkalaemia in childhood. *Pediatr Nephrol* **2:** 498–509.

DDAVP® test

Aim

To assess the capacity of the kidneys to maximally concentrate urine.

Background

Final concentration of urine is achieved by the action of antidiuretic hormone (ADH, also known as vasopressin) acting on the collecting duct cells within the kidney tubule. Vasopressin, secreted by the posterior pituitary gland, binds to a receptor (V2R) and through a number of steps causes aquaporin 2 (AQ2) water channels to be localized on the luminal surface of the tubular cells. This allows water to pass from the urinary lumen into the cells, thereby concentrating urine.

Inability to concentrate urine may be congenital (usually due to mutations in the genes encoding V2R or AQ2). In these situations, babies have adequate vasopressin, but no renal response (congenital nephrogenic diabetes insipidus, usually X-linked).

Acquired defects may affect the secretion of vasopressin, in which case there is insufficient hormone to act on the kidney (central diabetes insipidus) or due to a variety of kidney diseases or drugs damaging or affecting the V2R pathway (secondary nephrogenic diabetes insipidus).

Assessment of urinary concentration includes

- History.
- Examination.
- Routine investigations (include early morning urine (EMU) osmolality).
- *Water deprivation test:* see 🕮 'Water deprivation test and DDAVP® test', p.156, not safe in babies in whom congenital nephrogenic diabetes insipidus considered.
- 1-desamino-8-D-arginine vasopressin (DDAVP®) test.

Basis of DDAVP® test

A pharmacological dose of synthetic vasopressin (desmopressin) will maximally stimulate the V2R, thereby driving the kidney to maximally reabsorb water.

Potential hazards

The major risk of this test is water overload, which can occur if a child is given fluid in excess of the volume of fluid passed in urine. This occurs when desmopressin 'works', i.e. a positive test, see 🕮 'Interpretation of test', p.605. The risk can be avoided, by strict control of fluid input by carers and health professionals.

Procedure

- Ensure child has been assessed (as described, and check this test is appropriate).
- Inform biochemistry laboratory of the test.
- Take baseline plasma biochemistry (Na, K, TCO_2, urea, creatinine, osmolality) and collect baseline urine (this can be done up to 4h before test).
- Withhold feeds and water/juice for 2h before test commences.

- Thereafter, the child should only receive a fluid input (milk/juice/water) equivalent to the volume of urine passed for the next 4h (if test negative, i.e. no significant urinary concentration) or 6h (if test positive, i.e. significant urinary concentration).
- A notice 'Do not feed this child water/feed/juice without nurse approval' should be placed over cot and explained to carers.
- At start of test, give intramuscular injection desmopressin. The dose is 0.4microgram (400ng) in infants and children under 2 years of age and 2microgram in children over 2 years of age.
- Collect and send every urine sample to laboratory for urgent urine osmolality. Note times urine collected carefully (see Table 24.1 for sample information sheet).
- After 4–6h repeat the plasma biochemistry and osmolality. Urine collection can stop at 6h.
- Return to normal feeds by 6h unless plasma biochemistry is abnormal.

Table 24.1 Information required for sampling

Sample	Time	Urine osmolality	Plasma osmolality	Plasma sodium
Baseline				
Last sample				

Interpretation of test

Babies with a genetic defect in urinary concentration typically have a urine osmolality between 30–100mOsm/kg. Most will show no significant increase after the desmopressin, but a few (with milder mutations) may increase the urine osmolality to perhaps 200mOsm/kg.

A normal response would be a value >1000mOsm/kg (older children/adults) or >600mOsm/kg (infants, under 1 year). Typically, a normal individual will stop passing urine after the injection for a few hours, but the effect should wear off after 4–6h.

The 'Bichet'-protocol

Background

In selected children, intravenous application of desmopressin at a higher dose will need to be considered. Typically, this will be in children who had an intermediate response to the standard DDAVP® test. Reasons for an intermediate response include incomplete absorption or so called partial nephrogenic diabetes insipidus (NDI). In partial NDI, patients have mutations in the gene encoding the vasopressin receptor (V2R) that lower its sensitivity, thus requiring higher doses to initiate urinary concentration ('shift in the dose–response curve'). To assess these patients,

desmopressin is administered intravenously at a dose of 0.3microgram/kg (the same dose used in von Willebrandt disease), according to a protocol developed by D. Bichet[1]. This protocol has been used for over 20 years in several hundred children without serious complications. However, as with the standard protocol, patients are at risk of hyponatraemia if they respond to the desmopressin *and* they keep on drinking fluids.

Patients with a normal thirst mechanism will stop drinking, when their kidney conserves water, but at risk are patients with psychogenic polydipsia and infants who keep on being fed by their cares. It is therefore of paramount importance to closely monitor the fluid intake of the patient during the observation period, so that it not exceeds the amount excreted during this time. Desmopressin at this dose will also lead to a slight drop in blood pressure (~10mmHg) 30–60min after the infusion with a concomitant increase in heart rate (~25bpm).

The effect of desmopressin wears off after approximately 60–90min. Thus, the observation period needs to be only 2h after finishing the infusion.

Preparation and procedure

- Continue hydrochlorothiazide or amiloride, but discontinue indometacin at least 3 days in advance (if the patient receives any of these medications).
- Admit the patient to ward.
- Do not dehydrate, but stop fluids 2h prior to infusion to avoid absorption of fluid from the gut during the test. Start IV (with a large bore catheter) with a 3-way stop-cock to be able to repeat blood samples.
- Note all observations (blood pressure (BP), pulse, urine volume, fluid given) on the flow sheet (see Table 24.2 for a sample).
- *Before the infusion:* 3 periods of observation of 15min each (–30, –15, 0min) for BP, pulse, urine volume. On each urine sample obtain volume and osmolality.
- It is important that the child voids before desmopressin is given. This will prevent mixing of urine produced after desmopressin with that already present in the bladder. It will also provide a baseline urine osmolality.
- Infuse desmopressin 0.3microgram/kg of body weight in 1mL/kg of saline over 20min.
- Observe for 2h after finishing the infusion.

1 Bichet D, Razi M, Lonergan M, et al. (1988). Hemodynamic and coagulation responses to 1-desamino[8-D-arginine] vasopressin in patients with congenital nephrogenic diabetes insipidus. *N Engl J Med* **318:** 881–7.

Table 24.2 Observation flow sheet

Time (mins)	**-30**	**-15**	**0**	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**80**	**90**	**100**	**120**	**140**
actual time (eg: 09:00)	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__	__:__
dDAVP infusion															
Blood pressure (mmHg)															
Pulse (b/min)															
Fluid intake (ml)															
Urine: volume (ml)															
osmolality															
Na															
Plasma: U&E															
osmolality															

The open cells indicate times of observations. The suggested times for urine measurements are for patients with a urinary catheter only. In patients without a catheter, a urine sample should be obtained before the desmopressin infusion and then every void during the observation period. If no urine is produced during this time, the first void after the test should be used. It is important to measure the volume of urine as accurately as possible and to limit fluid intake of the proband during the observation period to the volume of urine produced during that time.

Disodium pamidronate infusion

May be used for the treatment of hypercalcaemia (when the PTH is normal) resistant to conventional therapy (see 📖 'Disorders of calcium: hypercalcaemia', p.116). Other indications include osteoporosis and for the calcinosis of juvenile dermatomyositis (anecdotal).

During the infusion

- Check temperature, pulse, and respiratory rate prior to, and at end of infusion.

The infusion

- The dose is 1mg/kg/day to a maximum of 60mg on three successive days.
- Dilute pamidronate initially in water, but infuse in saline or 5% dextrose.
- Final concentration should not exceed 12mg/100mL of diluent.
- Give infusion over 4h on first occasion. Thereafter, pamidronate can be given over 2–4h.
- Give a 30mL flush over 20min.
- Time interval between doses is 12–36h.

Expected side effects

Side effects are more prominent during the first infusion. Approximately half of the children undergoing their first infusion may experience temporary 'flu-like' symptoms' including fever, musculoskeletal aches, and pains and vomiting, but side effects become less marked over time. Treat with paracetamol.

Pamidronate is reported to cause asymptomatic hypocalcaemia, hence, its use for hypercalcaemia. Although calcium supplementation is recommended for those receiving pamidronate for osteoporosis, this is not recommended when it is being used to treat hypercalcaemia. The manufacturer advises avoiding use if GFR <30mL/min/1.73m^2.

Intravenous cyclophosphamide

Cytotoxic drugs such as cyclophosphamide act predominantly on rapidly dividing cells, such as T lymphocytes, and are therefore immunosuppressive and anti-inflammatory, as well as having anti-cancer properties. Pulse IV cyclophosphamide may be used for the treatment of some vasculitic disorders: polyarteritis, systemic lupus erythematous (SLE), dermatomyositis.

Potential adverse effects

- Includes bone marrow suppression, gastrointestinal (GI) symptoms, haemorrhagic cystitis, and hair loss. Males may be rendered azoospermic. Amenorrhoea and female infertility can occur with an increase in risk with increasing age over 25 years.
- Cyclophosphamide is contraindicated in pregnancy.
- Contact with infectious diseases should be avoided as far as possible during the period of cyclophosphamide therapy and infections should be treated vigorously.

Dose

Cyclophosphamide IV 500–1000mg/m^2 per dose (based on National Institutes of Health (NIH) protocol, usual starting dose 500mg/m^2; maximum dose 1.2g).

Investigations

Each dose is preceded by a full blood count, urea & electrolytes (U&Es), liver function tests (LFTs), and creatinine. Dosage should be reduced or delayed if there is evidence of bone marrow suppression, particularly if neutrophils are less than 1.5×10^9L. Bone marrow suppression is most likely to occur 7–10 days following administration of the dose so the full blood count should be checked at this time. Urine should be monitored for haematuria and proteinuria throughout the treatment period.

Administration

- The dose is given with sodium 2-mercapto-ethanesulphonate (mesna) cover (120% of cyclophosphamide dose) with IV hydration, to reduce the incidence of haemorrhagic cystitis, and with ondansetron to reduce nausea.
- Mesna is a sulphydryl-containing compound that is excreted in the urine. Co-administration with alkylating agents, such as cyclophosphamide significantly reduces their urotoxic effects by reacting with the metabolites in the urinary system.
- For patients with a history of haemorrhagic cystitis the total mesna dose may be increased in 20% increments up to 180%. Administration time for the cyclophosphamide is increased, and the hydration time may also be increased to 16–20h.
- For those patients who have an allergic reaction to mesna a revised protocol is used: give IV cyclophosphamide over 1h. Omit mesna, but ensure patient is adequately hydrated and increase hydration fluids to 125mL/m^2/h for 12h.

Sequence of administration

See cyclophosphamide infusion chart, Fig. 24.1.

- 15min before cyclophosphamide slow IV bolus of ondansetron 5mg/m^2 (max 8mg), *and*
- Mesna (20% cyclophosphamide dose) IV bolus over 15min.
- Cyclophosphamide (20mg/mL concentration) given over at least 10min via 3-way tap into hydration fluids, with the patient supine.
- *Hydration with:* mesna (100% cyclophosphamide dose) in 2.5% glucose/0.45% NaCl run over 12h at 85mL/m^2/h.
- Ondansetron 4mg (4–12 years) or 8mg (over 12 years) orally twice a day for 2 days if required.
- If emesis is a problem an IV dose of dexamethasone 100microgram/kg (maximum 4mg) may also be given.

Take care to ensure that the IV cannula is correctly sited and that saline flushes in easily before administering cyclophosphamide. If extravasation occurs the duty plastic surgery team is contacted.

INTRAVENOUS PRESCRIPTION CHART

WARD

CHEMOTHERAPY

SURNAME	FIRST NAME	HOSP NUMBER	D.O.B. / AGE	WEIGHT: / WEIGHT:	DATE: / DATE:	HEIGHT	SURF AREA	ALLERGIES?

DATE	IV FLUID	VOLUME	ADDITIVES	RATE	DURATION	DRS SIG	DATE & TIME	NURSE UNIT	NOTES
	CYCLOPHOSPHAMIDE								
–0:15			Ondansetron_____mg	Slow IV bolus					5mg/m^2 (max 8mg)
–0:15			Mesna_____mg	Slow IV bolus	Over 15 mins				20% Cyclophosphamide dose
0:00			Cyclophosphamide___mg	Slow IV bolus	Over at least 10 mins				Give via 3-way tap into hydration fluids
0:00	Glucose 2.5%/ Sodium Chloride 0.45%	ml	Mesna_____mg (_____mg per 500ml bag or_____mg per 1000ml bag)	ml/hr	12hr				Hydration rate = 85ml/m^2/hr Mesna dose =100% Cyclophosphamide dose

Fig. 24.1 Cyclophosphamide infusion chart.

Personal protective equipment

Personal protective equipment (PPE) is necessary when preparing, handling, and administering cytotoxic drugs, to minimize the risk of accidental contamination.

Further reading

Boumpas I., Austin HA, 3rd, Vaughan EM, et al. (1993). Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Intern Med* **119**: 366–9.

Brogan PA, and Dillon MJ (2000). The use of immunosuppressive and cytotoxic drugs in non-malignant disease. *Arch Dis Child* **83**: 259–64.

Guidelines for the use of basiliximab

Background

Basiliximab is indicated for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation. It is a murine/human chimeric monoclonal antibody that is directed against the interleukin-2 receptor alpha-chain (CD25 antigen), which is expressed on the surface of T-lymphocytes in response to antigenic challenge. Basiliximab specifically binds to the CD25 antigen on activated T-lymphocytes expressing the high affinity interleukin-2 receptor and thereby prevents binding of interleukin-2, the signal for T-cell proliferation. Complete and consistent blocking of the interleukin-2 receptor is maintained as long as serum basiliximab levels exceed 0.2microgram/mL (4–6 weeks). As concentrations fall below this level, expression of the CD25 antigen returns to pretherapy values within 1–2 weeks. Basiliximab does not cause cytokine release or myelosuppression.

The current marketing authorization for basiliximab is for use in adults and for concomitant use with ciclosporin and corticosteroids only, although there is data to support its use in children over the age of 2 years and with other immunosuppressive agents.

Patient selection

Patients receiving a 2nd or 3rd transplant

- Patients who may have developed antibodies precluding further administration of a monoclonal antibody.
- Patients who are deemed unable to tolerate standard triple therapy.
- Patients receiving steroid-free immunosuppressive protocols.
- Patients will be given two infusions of basiliximab.

Dose

- *<40kg:* 10mg infused on Day 0 within 2h prior to surgery and on Day 4 after transplantation.
- *>40kg:* 20mg infused on Day 0 within 2h prior to surgery and on Day 4 after transplantation.

Reconstitution and administration

- Basiliximab is provided as:
  - vial containing 20mg basiliximab powder;
  - + ampoule of water for injections.
- Add 5mL water for injection to the vial containing 20mg basiliximab powder.
- Shake the vial gently to dissolve the powder. After reconstitution the solution should be used immediately (at least within 24h if stored in a refrigerator).

The reconstituted solution is isotonic and must be further diluted:

- 10mg dose must be diluted to at least 25mL (20mg to at least 50mL) with NaCl 0.9% or glucose 5% for infusion.
- Infuse over 20–30min.
- Do not mix with any other preparation.

Contraindications

Known hypersensitivity to basiliximab or any other component of the formulation.

Undesirable effects

- Basiliximab did not increase the incidence of serious adverse events observed in organ transplantation when compared with placebo.
- Acute adverse events suggestive of hypersensitivity were not reported in 363 patients who received basiliximab in two randomized trials:
  - infections occurred at similar rates in patients who received basiliximab or placebo and so did cytomegalovirus (CMV) infections;
  - post-transplant lymphoproliferative disorders occurred in 0.3% and 0.6%, respectively, of basiliximab and placebo patients;
  - in these trials, a total of 13 patients (5 basiliximab and 8 placebo recipients) developed various malignancies in the first 12 months after transplant.
- One study of paediatric renal transplant patients showed a marked decrease in ciclosporin levels within the first 6 weeks when combined with basiliximab, possibly due to interaction on cytochrome P450 metabolism level. This indicates that children receiving basiliximab need to be closely monitored for decreasing ciclosporin levels.

Further reading

Ferguson R. (1994). Acute rejection episodes—best predictor of long-term primary cadaveric renal transplant survival. *Clin Transplant* **8**: 328–31.

Kahan BD, Rajagopalan PR, and Hall M. (1999). Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. United States Simulect Renal Study Group. *Transplantation* **67**: 276–84.

Nashan B, Moore R, Amlot P, et al. (1997). Randomized trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. *Lancet* **350**: 1193–8. Erratum in: *Lancet* 1997; **350**: 1484.

Rigg KM. (1995). Renal transplantation: current status, complications and prevention. *J Antimicrob Chemother* **36**(Suppl B)**:** 51–7.

Protocol for administration of blood to patients with or approaching chronic kidney disease stage 5

The administration of blood products to patients who will need renal replacement therapy should be avoided as far as possible because human leucocyte antigen (HLA) sensitization can occur following transfusion of blood and platelets. Possible options to reduce this risk are as follows:

- Children awaiting planned surgery should have their haemoglobin boosted with erythropoietin, raising it to the upper limit of the normal range, to reduce the risk of the need for blood transfusion.
- Ensure that the iron stores are replete.
- Although blood in the UK is leucocyte depleted, some leucocytes remain. These can be removed by further washing of the red cells, which some centres negotiate with their local transfusion service for children who will need transplantation (after which immunosuppression should decrease their chances of HLA sensitization). However, this increases the cost of the transfusion and the blood has to be used within 2 weeks, increasing the risk of wastage. Moreover, there is no clinical evidence to confirm that the extra washing reduces the risk of sensitization. Leukocyte filters may be used as an alternative.
- Post-transplant CMV negative blood should be prescribed for patients who are CMV negative.
- Anti-HLA antibodies should be measured 10 days after blood or platelets have been given.

Protocol for percutaneous transluminal angioplasty

Introduction

Balloon dilation of stenosed renal arteries is a form of treatment utilized in childhood renovascular hypertension. Most patients who undergo an angioplasty procedure have been fully investigated previously in terms of renal function, differential kidney function by isotope scanning, delineation of significant vascular pathology affecting a kidney or the kidneys via Doppler US, renal arteriography, and renal vein renin studies. In addition, the patients will be receiving anti-hypertensive therapy, usually with several agents involved.

Pre-angioplasty check list

- Detailed history of condition, anatomical sites of pathology, differential renal function, renal vein renin data, site to be dilated, presence or absence of cerebrovascular or other non-renal vascular disease, and cardiac status.
- Details of all drugs being administered, especially anti-hypertensives, their dosages, and schedules of delivery. It is particularly important to identify drugs that might modify cardiovascular responsiveness, such as β blockers.
- Details of BP control i.e. levels of BP usually maintained and requirements concerning range of BP to be aimed at—especially relevant if cerebrovascular disease also present.
- All previous isotope, ultrasonographic and angiographic imaging must be reviewed.
- If no renal isotope study (DMSA or MAG3) has been undertaken within 3 months of the procedure, a repeat must be undertaken prior to the proposed angioplasty.
- Consent must be obtained and risks of the procedure explained in detail to parents.

Bloods

- Haemoglobin, white blood count, and platelet count.
- Clotting screen.
- Urea and electrolytes and plasma creatinine.
- Group and cross-match 1unit blood.

Drugs

- Establish the protocol for each individual child concerning drug administration pre-operatively with anaesthetist and the nephrologist involved with the case. Usually, anti-hypertensives are given at approximately the usual time prior to the procedure, but this may need individual modification.
- Make sure the anaesthetist is aware of each agent, especially those that interfere with cardiovascular responsiveness and if the child has cerebrovascular disease, and agree BP levels to be maintained during the procedure and in the recovery area.

- **NB**. β-blockers may mask the signs of blood loss, i.e. inappropriate bradycardia and other drugs might be associated with tachycardia when volume replete.

Post-procedure

- Post-operative BP and pulse rate agreed limits will have been determined for the individual child prior to procedure being undertaken. Hypotension with or without tachycardia, pallor, or abdominal pain may indicate haemorrhage, and would necessitate urgent evaluation and action. Adequate vascular access must be available for IV fluid administration and/or blood if necessary, as well as for the administration of parenteral anti-hypertensive therapy.
- A follow-up renal isotope scan (DMSA or MAG3 should be undertaken 24–48h following the procedure.
- Further management (e.g. prescription of aspirin) should be decided on an individual basis.

Travel information: guidance for renal patients

It is most important that renal patients are advised to contact their doctor, nurse, or pharmacist before they consider travelling to a country that requires specific vaccinations and/or malaria prophylaxis. For patients on ciclosporin or tacrolimus it is wise to start anti-malarials at least 2 weeks before travelling so that levels can be checked and any dosage adjustments made.

For the most up-to-date information on vaccines and anti-malarials refer to the British National Formulary for telephone numbers and websites.

Vaccines

List of vaccines that may or may not be recommended for immunosuppressed patients may be found in the chapter on renal transplantation (see 📖 'Vaccination after transplantation', p.517).

Anti-malarials for prophylaxis

The correct anti-malarial for the part of the world visited must be prescribed. In addition patients must be told to avoid mosquito bites, take their prophylaxis medicines regularly, and must visit their doctor immediately if they fall ill within 1 year and especially within 3 months of return from holiday.

If mefloquine recommended

The dose is adjusted for age, but no dose changes are required for renal patients.

Tablets 250mg

Started 2–3 weeks before entering endemic area and continued for 4 weeks after leaving:

- *5–19kg:* 62.5mg once a week.
- *20–30kg:* 125mg once a week.
- *31–45kg:* 187.5mg once a week.
- *>45kg and adults:* 250mg once a week.

If doxycycline recommended

The dose is adjusted for age, but no dose changes are required for patients on peritoneal or haemodialysis. For transplant patients doxycycline can alter ciclosporin or tacrolimus levels.

Capsules 50mg, 100mg, dispersible tablets 100mg

Started 1 week before entering endemic area and continued for 4 weeks after leaving. (If on ciclosporin or tacrolimus start 2 weeks before so that levels can be checked and any dose adjustments made).

- *>12 years 25–45kg:* 75mg once a day.
- *Adult:* 100mg once a day.

If chloroquine and proguanil recommended

Chloroquine

The dose is adjusted for age, but no dose changes are required for renal patients unless they are in CKD 5.

- *Tablets (chloroquine base) 150mg:* started 1 week before entering endemic area and continued for 4 weeks after leaving.
- Dose 5mg chloroquine base/kg once a week. Equivalent to:
  - *1–4 years:* half a tablet once a week;
  - *5–8 years:* one tablet once a week;
  - *9–15 years:* one-and-a-half tablets once a week;
  - *adults:* two tablets once a week.
- *Renal impairment:* no dose reduction until GFR <10—give 50% dose.

Proguanil

The dose is adjusted for age and for renal function.

Tablets 100mg

Started 1 week before entering endemic area and continued for 4 weeks after leaving.

- *Infants up to 12 weeks, bodyweight < 6kg:* 25mg once a day.
- *12 weeks to 11 months, 6–10kg:* 50mg od.
- *1–3 years, 10–16kg:* 75mg od.
- *4–7 years, 16–25kg:* 100mg od.
- *8–12 years, 26–45kg:* 150mg od.
- *Over 13 years, >45kg, adult dose:* 200mg od.

In renal impairment

- *GFR >60:* standard dose.
- *GFR 20–59:* 50% dose.
- *GFR 10–19:* 25% dose every 2nd day.
- *GFR <10:* 25% dose once a week.

If proguanil with atovaquone (Malarone®) recommended

The dose is adjusted for age and renal function. Started 1–2 days before entering endemic area and continued for 1 week after leaving.

Tablets proguanil 100mg, atovaquone 250mg

- Adult and child over 40kg: 1 tablet od.

Paediatric tablets proguanil 25mg, atovaquone 62.5mg

- *Child 11–20kg:* 1 tablet od.
- *21–30kg:* 2 tablets od.
- *31–40kg:* 3 tablets od.

In renal impairment

- Malarone® should not be given if GFR <30.
- For GFR 30–60 suggest 50% dose, although there is no data for this.

Guidelines for the treatment of swine flu (H1N1) infection in children with renal disease

Table 24.3 provides information on the dosing of antiviral medications for the treatment of swine flu during pandemics.

Oseltamivir capsules are available in 30, 45, and 75mg strength. Where possible, rounding of doses up/down to the nearest capsule is preferable. Oseltamivir suspension or solution may be used for children under 7 years of age with eGFR ≤30mL/min/1.73m^2. Oseltamivir liquid can be stored at room temperature or in fridge. Discard after 10 days.[2]

Administration information for oseltamivir in patients with swallowing difficulty/enteral feeding tubes

- Contents of capsule can be opened and mixed with chocolate syrup, honey, sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce, or yoghurt.
- The contents of the capsule pour easily, but are granular in nature. Once dispersed in water, care must be taken to draw up the entire dose, and administer and flush well. Although small particles are visible in the dispersion, this flushes via an 8Fr NG tube without blockage.
- No specific site is documented for absorption. Absorption is rapid following oral administration, with peak levels occurring between 1 and 4h. Absorption is not affected by food. Absorption is highly unlikely to be affected by enteral feed.[3]
- For full administration details see monograph.[2]

Further reading

Ashley C and Currie A. (2009). *Renal drug handbook*, 3rd edn. Radcliffe Publishing, Milton Keynes.

Wallace J. and the Scottish Neonatal and Paediatric Pharmacists Group (2009)Treatment and prophylaxis of influenza in children under 1 year of age: guidance for prescribers (April 2009). NHS Scotland/UKMI, Glasgow. Available at: http://www.nelm.nhs.uk/en/NeLM-Area/Community-Areas/Pan-Flu-Resources-for-PCT-Pharmacy-Staff/Clinical-support/Treatment-and-prophylaxis-of-influenza-in-children-under-1-year-of-age-guidance-for-prescribers-April-2009-NHS-Tower-Hamlets-RP18/.

2 Summaries of Product Characteristics - Tamiflu® product range.

3 Monograph for inclusion in Handbook Of Drug Administration via Enteral Feeding Tubes. Advance Release, May 2009. Available at: http://www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q--A/Advice-on-administration-of-oseltamivir-Tamiflu-via-enteral-feeding-tubes/?query=tamiflu&rank=2.

Table 24.3 Guidelines for the treatment of swine flu (H1N1) infection in children with renal disease

Patient type	Drug	Treatment dose and frequency	Prophylaxis dose and frequency	Notes
eGFR >30mL/min/1.73m^2 [1]				
>2 months–1 year	Oseltamivir	2mg/kg/dose[1] bd for 5 days	2mg/kg/dose od for 10 days	
>1 year–3 years (<15kg)		30mg bd for 5 days.	30mg od for 10 days	As per BNFc
>3 years–7 years (15–23kg)		45mg bd for 5 days	45mg od for 10 days	As per BNFc
>7 years–13 years (23–40kg)		60mg bd for 5 days	60mg od for 10 days	As per BNFc
>13 years (>40kg)		75mg bd for 5 days	75mg daily for 10 days	As per BNFc
eGFR 10–30mL/min/1.73m^2				
>5 years and have ***no respiratory*** problems	**Zanamavir**	Two 5mg blisters inhaled (using the disc haler) bd for 5 days	Two 5mg blisters inhaled (using the disk haler) od for 10 days	Poor systemic absorption (10–20%)
>2 months–5 years	Oseltamivir	2mg/kg/dose od for 5 days	2mg/kg/dose on alternate days for 10 days	
Over 2 months of age with respiratory problems		2mg/kg/dose od for 5 days (maximum 75mg per dose)	2mg/kg/dose on alternate days for 10 days (maximum 75mg per dose)	
eGFR <10mL/min/1.73m^2				
Over 2 months of age	Oseltamivir	1mg/kg/dose stat (maximum 30mg per dose)	1mg/kg/dose every 10 days i.e. on days 1 and 10 only. (maximum 30mg per dose)	
Patients on CAPD and CCPD				
Over 2 months of age	Oseltamivir	1mg/kg/dose stat (maximum 30mg per dose)	1mg/kg/dose stat (maximum 30mg per dose)	Dialysed

Table 24.3 (*Contd.*)

Patient type	Drug	Treatment dose and frequency	Prophylaxis dose and frequency	Notes
Patients on haemodialysis				
Over 2 months of age	Oseltamivir	1mg/kg/dose after each dialysis session for 5 days (maximum 30mg per dose)	1mg/kg/dose after each dialysis session for 10 days (maximum 30mg per dose)	Dialysed
Patients on CAV/VVHD				
Treatment and prophylaxis dose as in eGFR 10–30mL/min/1.73m^2				
Unknown dialysability				

Miscellaneous

Calculation of body surface area

$$BSA\ (m^2) = \sqrt{[height\ (cm) \times weight\ (kg)/3600]}$$

Fractional excretion

See also 🕮 'Management: fluid and electrolytes', p.418.

This is most commonly used in calculation of the fractional excretion of sodium (FENa), which may be useful in the assessment of volume status (see 🕮 Chapter 17, p.377).

$$FE_x = [(U_x/P_x) \times (P_{CR}/U_{Cr})] \times 100$$

where FE_x = fractional excretion of solute x (expressed as %); U_x = urine concentration of solute x; P_x = plasma concentration of solute x; P_{Cr} = plasma concentration of creatinine; and U_{Cr} = urine concentration of creatinine.

U_x, P_x, P_{Cr} and U_{Cr} should be in the same units.

Clinical relevance: FENa

In a well child, FENa simply reflects Na intake. However, in the setting of acute oliguria, FENa can be used to define the aetiology: FENa greater than 2.5% suggests established acute tubular necrosis, whereas FENa less than 1% suggests renal hypoperfusion (pre-renal acute kidney injury (AKI)) and the patient would probably benefit from volume expansion. It is important to obtain the urine sample before diuretics are used to increase urine output. Whilst a low FENa after a furosemide challenge would still be consistent with pre-renal AKI, an elevated FENa could be due to the drug or acute tubular necrosis.

Conversion to SI units

Table 24.4 gives the conversion factor required to change from mg/dL (used in North America) to SI units.

Table 24.4 Conversion factor to change from mg/dL to SI units

	Conversion factor
Creatinine	88.4
Urea	0.357
Calcium	0.2495
Phosphate	0.3229
Glucose	0.05551
PTH (pg/mL)	0.106 (pmol/l)

Recipe for 0.45% saline/5% glucose

To a 500-mL bag of 5% glucose add 7.5mL of 30% NaCl. **NB**. In some instances, e.g. the neonate, this recipe can be used to make 0.45% aline/10% glucose by adding the same NaCl to a similar volume of 10% glucose.

SBP by age and height (Tables 24.5 and 24.6)

Table 24.5 Girls SBP by age and height (heights given for age at midyear)

Age	BP Classification	Systolic BP (mmHg)						
3	**Height (cm)**	**91**	**92**	**95**	**98**	**100**	**103**	**105**
	Prehypertension	100	100	102	103	104	106	106
	Stage 1 HTN	104	104	105	107	108	109	110
	Stage 2 HTN	116	116	118	119	120	121	122
4	**Height (cm)**	**97**	**99**	**101**	**104**	**108**	**110**	**112**
	Prehypertension	101	102	103	104	106	107	108
	Stage 1 HTN	105	106	107	108	110	111	112
	Stage 2 HTN	117	118	119	120	122	123	124
5	**Height (cm)**	**104**	**105**	**108**	**111**	**115**	**118**	**120**
	Prehypertension	103	103	105	106	107	109	109
	Stage 1 HTN	107	107	108	110	111	112	113
	Stage 2 HTN	119	119	121	122	123	125	125
6	**Height (cm)**	**110**	**112**	**115**	**118**	**122**	**126**	**128**
	Prehypertension	104	105	106	108	109	110	111
	Stage 1 HTN	108	109	110	111	113	114	115
	Stage 2 HTN	120	121	122	124	125	126	127
7	**Height (cm)**	**116**	**118**	**121**	**125**	**129**	**132**	**135**
	Prehypertension	106	107	108	109	111	112	113
	Stage 1 HTN	110	111	112	113	115	116	116
	Stage 2 HTN	122	123	124	125	127	128	129
8	**Height (cm)**	**121**	**123**	**127**	**131**	**135**	**139**	**141**
	Prehypertension	108	109	110	111	113	114	114
	Stage 1 HTN	112	112	114	115	116	118	118
	Stage 2 HTN	124	125	126	127	128	130	130
9	**Height (cm)**	**125**	**128**	**131**	**136**	**140**	**144**	**147**
	Prehypertension	110	110	112	113	114	116	116
	Stage 1 HTN	114	114	115	117	118	119	120
	Stage 2 HTN	126	126	128	129	130	132	132
10	**Height (cm)**	**130**	**132**	**136**	**141**	**146**	**150**	**153**
	Prehypertension	112	112	114	115	116	118	118
	Stage 1 HTN	116	116	117	119	120	121	122
	Stage 2 HTN	128	128	130	131	132	134	134
11	**Height (cm)**	**136**	**138**	**143**	**148**	**153**	**157**	**160**
	Prehypertension	114	114	116	117	118	119	120
	Stage 1 HTN	118	118	119	121	122	123	124
	Stage 2 HTN	130	130	131	133	134	135	136
12	**Height (cm)**	**143**	**146**	**150**	**155**	**160**	**164**	**166**
	Prehypertension	116	116	117	119	120	120	120
	Stage 1 HTN	119	120	121	123	124	125	126
	Stage 2 HTN	132	132	133	135	136	137	138
13	**Height (cm)**	**148**	**151**	**155**	**159**	**164**	**168**	**170**
	Prehypertension	117	118	119	120	120	120	120
	Stage 1 HTN	121	122	123	124	126	127	128
	Stage 2 HTN	133	134	135	137	138	139	140

(*Continued*)

Table 24.5 (Continued)

Age	BP Classification	Systolic BP (mmHg)						
14	**Height (cm)**	**151**	**153**	**157**	**161**	**166**	**170**	**172**
	Prehypertension	119	120	120	120	120	120	120
	Stage 1 HTN	123	123	125	126	127	129	129
	Stage 2 HTN	135	136	137	138	140	141	141
15	**Height (cm)**	**152**	**154**	**158**	**162**	**167**	**171**	**173**
	Prehypertension	120	120	120	120	120	120	120
	Stage 1 HTN	124	125	126	127	129	130	131
	Stage 2 HTN	136	137	138	139	141	142	143
16	**Height (cm)**	**152**	**154**	**158**	**163**	**167**	**171**	**173**
	Prehypertension	120	120	120	120	120	120	120
	Stage 1 HTN	125	126	127	128	130	131	132
	Stage 2 HTN	137	138	139	140	142	143	144
17	**Height (cm)**	**152**	**155**	**159**	**163**	**167**	**171**	**174**
	Prehypertension	120	120	120	120	120	120	120
	Stage 1 HTN	125	126	127	129	130	131	132
	Stage 2 HTN	138	138	139	141	142	143	144

Data from: http://www.nhlbi.nih.gov/health/public/heart/hbp/bp_child_pocket/bp_child_pocket.pdf

Table 24.6 Boys SBP by age and height (heights given for age at midyear)

Age	BP Classification	Systolic BP (mmHg)						
3	**Height (cm)**	**92**	**94**	**96**	**99**	**102**	**104**	**106**
	Prehypertension	100	101	103	105	107	108	109
	Stage 1 HTN	104	105	107	109	110	112	113
	Stage 2 HTN	116	117	119	121	123	124	125
4	**Height (cm)**	**99**	**100**	**103**	**106**	**109**	**112**	**113**
	Prehypertension	102	103	105	107	109	110	111
	Stage 1 HTN	106	107	109	111	112	114	115
	Stage 2 HTN	118	119	121	123	125	126	127
5	**Height (cm)**	**104**	**106**	**109**	**112**	**116**	**119**	**120**
	Prehypertension	104	105	106	108	110	111	112
	Stage 1 HTN	108	109	110	112	114	115	116
	Stage 2 HTN	120	121	123	125	126	128	128
6	**Height (cm)**	**110**	**112**	**115**	**119**	**122**	**126**	**127**
	Prehypertension	105	106	108	110	111	113	113
	Stage 1 HTN	109	110	112	114	115	117	117
	Stage 2 HTN	121	122	124	126	128	129	130
7	**Height (cm)**	**116**	**118**	**121**	**125**	**129**	**132**	**134**
	Prehypertension	106	107	109	111	113	114	115
	Stage 1 HTN	110	111	113	115	117	118	119
	Stage 2 HTN	122	123	125	127	129	130	131

(*Continued*)

Table 24.6 (Continued)

Age	BP Classification	Systolic BP (mmHg)						
8	**Height (cm)**	**121**	**123**	**127**	**131**	**135**	**139**	**141**
	Prehypertension	107	109	110	112	114	115	116
	Stage 1 HTN	111	112	114	116	118	119	120
	Stage 2 HTN	124	125	127	128	130	132	132
9	**Height (cm)**	**126**	**128**	**132**	**136**	**141**	**145**	**147**
	Prehypertension	109	110	112	114	115	117	118
	Stage 1 HTN	113	114	116	118	119	121	121
	Stage 2 HTN	125	126	128	130	132	133	134
10	**Height (cm)**	**130**	**133**	**137**	**141**	**146**	**150**	**153**
	Prehypertension	111	112	114	115	117	119	119
	Stage 1 HTN	115	116	117	119	121	122	123
	Stage 2 HTN	127	128	130	132	133	135	135
11	**Height (cm)**	**135**	**137**	**142**	**146**	**151**	**156**	**159**
	Prehypertension	113	114	115	117	119	120	120
	Stage 1 HTN	117	118	119	121	123	124	125
	Stage 2 HTN	129	130	132	134	135	137	137
12	**Height (cm)**	**140**	**143**	**148**	**153**	**158**	**163**	**166**
	Prehypertension	115	116	118	120	120	120	120
	Stage 1 HTN	119	120	122	123	125	127	127
	Stage 2 HTN	131	132	134	136	138	139	140
13	**Height (cm)**	**147**	**150**	**155**	**160**	**166**	**171**	**173**
	Prehypertension	117	118	120	120	120	120	120
	Stage 1 HTN	121	122	124	126	128	129	130
	Stage 2 HTN	133	135	136	138	140	141	142
14	**Height (cm)**	**154**	**157**	**162**	**167**	**173**	**177**	**180**
	Prehypertension	120	120	120	120	120	120	120
	Stage 1 HTN	124	125	127	128	130	132	132
	Stage 2 HTN	136	137	139	141	143	144	145
15	**Height (cm)**	**159**	**162**	**167**	**172**	**177**	**182**	**184**
	Prehypertension	120	120	120	120	120	120	120
	Stage 1 HTN	126	127	129	131	133	134	135
	Stage 2 HTN	139	140	141	143	145	147	147
16	**Height (cm)**	**162**	**165**	**170**	**175**	**180**	**184**	**186**
	Prehypertension	120	120	120	120	120	120	120
	Stage 1 HTN	129	130	132	134	135	137	137
	Stage 2 HTN	141	142	144	146	148	149	150
17	**Height (cm)**	**164**	**166**	**171**	**176**	**181**	**185**	**187**
	Prehypertension	120	120	120	120	120	120	120
	Stage 1 HTN	131	132	134	136	138	139	140
	Stage 2 HTN	144	145	146	148	150	151	152

Data from: http://www.nhlbi.nih.gov/health/public/heart/hbp/bp_child_pocket/bp_child_pocket.pdf

Index

A

B

C

D

E

F

G

H

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Z