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Edited by

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Oxford Specialist Handbooks in Paediatrics

Paediatric Rheumatology

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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
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First Edition published in 2012

Impression: 1

British Library Cataloguing in Publication Data
Data available

Library of Congress Cataloging in Publication Data
Data available

ISBN 978–0–19–959263–0

Printed in Great Britain by
Ashford Colour Press Ltd, Gosport, Hampshire

Preface

The purpose of this book

This handbook aims to help you understand and manage virtually any paediatric rheumatology condition that may present to you in clinical practice; it is pocket-sized with a system of bullet points to allow easy reference to up-to-date evidence-based (where possible) and consensus-derived opinion. This first edition of the handbook is written amidst a revolution in clinical genetics and novel therapeutics in the field of multisystemic inflammatory disease, and captures state-of-the-art clinical care and best current practice in this context. Essential further reading, including website links, direct you to sources where more information can be obtained. The handbook is divided into sections to cover essential elements of the clinical assessment, the approach to investigations and management, along with important key facts of knowledge and practical advice. It includes advice on the care of acute emergencies, chronic disorders, and the spectrum of common conditions seen by all paediatricians to those seen rarely and usually cared for in specialized paediatric rheumatology centres, in collaboration with local units. Many of the chapters will be applicable to the day-to-day care of patients on a general paediatric ward or in the outpatient clinic. Acute emergencies that can occur in multisystem disease and issues arising from the use of potent immunosuppressive treatments are dealt with in detail.

This handbook will provide guidance for trainees, the general paediatrician, and the multidisciplinary team specialists (doctors, nurses, physiotherapists, occupational therapists, podiatrists, and psychologists) who care for children with rheumatological conditions. We bring together for the first time practical guidance for the use of outcome measures, clinical scores of disease activity, and drug prescribing relevant to paediatric rheumatology. 'State-of-the-art treatment' of paediatric rheumatology conditions includes an ever increasing number of biologic and novel therapies—we provide practical guidance for the use of such treatments with guidelines, algorithms, and emphasis of the role of the multidisciplinary team to deliver optimal clinical care.

We are very proud of our extensive authorship, including doctors and allied health professionals, many of whom are international leaders in their field. We have successfully engaged with the breadth of the British Society for Paediatric and Adolescent Rheumatology (BSPAR) community, with representation from the majority of centres across the UK and have contributions from all current UK trainees in paediatric rheumatology working in partnership with consultant supervisors. We also have input from parents of children with rheumatic disease to emphasize their role in working together with healthcare professionals—much of what we do in clinical practice lacks a robust evidence base and we emphasize the importance of input from consumers on how to involve and fully engage children and their families with clinical decision-making and research opportunities to facilitate growth of evidence to inform best practice.

This book is a measure of the growing collaboration of paediatric rheumatology both within the UK and with our colleagues further afield to develop and share knowledge, promote highest quality clinical care, education, and training to facilitate access to optimal care for all children with rheumatic disease.

All profits from the sales of the handbook will be donated to BSPAR.

Helen Foster
Paul A. Brogan

Foreword 1

UK's Paediatric Rheumatology Clinical Studies Group

The importance of supporting the very best clinical research to improve the care of children with rheumatic and musculoskeletal health has been exemplified by the establishment by the National Institute of Health Research (NIHR) Medicines for Children Research Network (MCRN)[1] and Arthritis Research UK of the MCRN/Arthritis Research UK Paediatric Rheumatology Clinical Studies Group (CSG).[2] This partnership of expertise has supported a major opportunity and development in recent years of taking forward a comprehensive and long lasting, national clinical research programme for Paediatric Rheumatology.

Following a detailed, widespread consultation and consensus process, involving all relevant stakeholders including consumers (see Foreword 2 for comment on consumer input), the CSG's primary task was to define the key strategic priorities in paediatric rheumatology with respect to:

'What are the key clinical research priorities that will change clinical practice in paediatric rheumatology?'

To achieve this, the CSG:

- Looks to address the gaps in the evidence base in the management of children and young people with rheumatic or musculoskeletal conditions.
- Works with all interested parties towards developing a comprehensive portfolio of key research clinical trials and related studies covering the entire spectrum of major disease areas in paediatric rheumatology in the UK.
- Has a strong multidisciplinary membership including: 4 consumer representatives, clinicians, clinical academics, basic scientists, allied health professionals, and a pharmacist expert in paediatric formulations.

The CSG's 'goal' is that:

- 'All children and young people in the UK with a rheumatological condition may be given the opportunity to be enrolled in a clinical trial or well-conducted clinical study from point of diagnosis onwards, and in so doing improve the care and outcome of them and patients with similar conditions in the future;
- That all children have the option of contributing towards a related, fully informed and consented Biobank (e.g. DNA and serum) for subsequent investigation into the cause of their condition.'

To facilitate this process, the CSG has developed (to date) 9 'topic specific groups' (TSGs) to foster collaboration and support multidisciplinary efforts to address the key priority areas within paediatric rheumatology, as well as organizing ad hoc meetings to focus on specific projects.

- Each TSG has members of the CSG as 'link-persons' to support communication and integration of the activities of the TSGs within the wider CSG research agenda and support structures.

- The 9 TSGs are: Auto-inflammatory diseases; Bone Health; Juvenile Dermatomyositis; Juvenile Idiopathic Arthritis and associated Uveitis; Juvenile-onset Systemic Lupus Erythematosus; Childhood Scleroderma; Non-inflammatory, musculoskeletal disorders; Childhood Vasculitides.

In addition, the CSG supports investigators in the following way:

- Welcoming and publicizing expressions of interest in working towards these priority studies, calling for submission of protocols and proposals to address these priorities.
- Working with stakeholders and funding bodies and to identify barriers to research participation and identifying strategies to facilitate engagement and collaboration in clinical research.
- Supporting protocols where relevant can also include pilot and feasibility studies to provide proof of concept for definitive studies in terms of recruitment, data acquisition.
- Encouraging consideration of research 'add-ons' to bring value-added benefit to the children participating in these studies, e.g. pharmacogenetic and qualitative studies.
- Being advisory to investigators, the MCRN on studies submitted for NIHR Portfolio adoption, including commercial trials, and to the Arthritis Research UK and assist with their development.
- Working in close collaboration with other MCRN and Arthritis Research UK CSGs, as well as other topic specific research networks in all areas of mutual interest.

References

1 http://www.mcrn.org.uk.
2 http://www.arthritisresearchuk.org/research/clinical_study_groups/csg_-_mcrn_paediatric_rheumato.aspx.

Foreword 2

Parent and young person involvement in research—a 'consumer's' perspective

The social and psychological aspects of living with any chronic condition can create a different type of expertise to that of clinicians and researchers. Consumer involvement is concerned with creating a forum where the experience, knowledge, and expertise of both healthcare professionals and the public can come together in an equal partnership to benefit healthcare research. High-quality research, optimal accrual to research projects, and improved patient outcomes are dependent on listening to the voices of children and young people, their families and carers, and taking account of their experiences, priorities, and perspectives. Engaged effectively, consumers can contribute to all aspects of clinical research and clinical service development and including:

- Identifying and prioritizing research ideas that are relevant to clinical practice.
- Commissioning research to highlight topic areas of concern to patients.
- Designing research studies and associated documentation to enhance the feasibility of the project by identifying potential barriers to study participation.
- The management of studies (e.g. as members of steering group).
- Analysis or interpretation of research results to address key issues relevant to patients.
- Dissemination of research results throughout the lay community.

Key principles for the productive involvement of patients, parents, young people and families, (referred to as patient and public involvement or PPI), in partnership for research and clinical service development are discussed in detail. In summary these are:

- All members of the clinical research group should understand the benefits of PPI perspective.
- Participation of new PPI members will be facilitated if they are formally introduced and effort is made to find out about their background/ experiences.
- In advance of meetings, it is important to consider the PPI angle on all agenda items and identify those which may be of particular interest to PPI members so they may prepare for discussions.
- Include introductions at the start of a meeting and clarify the meeting purpose, use plain English, and minimize jargon.
- During the meetings, encourage questions and invite the PPI members to comment on all issues.
- Consumers' contributions are often based on their own experiences of an illness, and wherever possible they should be representative of the broader community.
- After a meeting it is important to minute contributions made by PPI members with a follow-up process for feedback.

Further reading

TwoCan Associates for the UKCRC and NCRI. Patient and public involvement in research groups – Guidance for Chairs. TwoCan Associates, 2010. http://www.twocanassociates.co.uk/pubs.php.

Foreword 3

I am delighted as the current Convenor of The British Society for Paediatric and Adolescent Rheumatology (BSPAR) to provide a Foreword for this *Oxford Handbook of Paediatric Rheumatology*.

BSPAR has evolved over several decades from the multidisciplinary British Paediatric Rheumatology Group to achieve its new charitable status, and is determined and committed to encourage and support clinical care, research, education, and training in paediatric rheumatology in the UK. It was in order to help deliver these goals that in 2010 BSPAR achieved charitable status and I am truly proud of the commitment made by all the contributing authors of this book to donate any fees due and profits made to BSPAR.

This handbook has been produced by a dedicated editorial team and with contributions from a large and truly multidisciplinary authorship. This highlights the fundamental principle that underpins the ethos of BSPAR—namely the sense of teamwork that helps individual teams deliver day-to-day healthcare to children and young people with rheumatologic disorders and also drives us towards our goal of high-quality research continually improving the delivery of clinical care.

Throughout our activities it is our patients and their families who directly benefit from the improved training and dissemination of information that BSPAR provides to the medical and allied health carers with whom they come into direct contact. Through education and training, all healthcare professionals improve the service which they provide to their patients, and I am sure that this handbook will prove invaluable to many working in this field.

Dr Gavin Cleary
Convenor

Foreword 4

Paediatric rheumatology training in the UK

In the UK, training in paediatric rheumatology follows completion of general paediatric training and is overseen by the Royal College of Paediatrics and Child Health (RCPCH) with a Competency Based Framework and a process of assessment. Training in paediatric rheumatology is through the national training programme for the training of specialists in paediatrics (called the 'Grid') with competitive entry organized by RCPCH. This programme of training is a minimum of 2 years, recommended to be in more than one accredited centre, and trainees complete a programme of formative and summative assessments which are competency-based. Ultimately trainees acquire a Certificate of Completion of Training to be eligible to be appointed to Consultant posts working in the National Health Service. Training for general paediatricians with an interest in rheumatology is also encouraged and such trainees do not need to be appointed to the Grid but are recommended to have 1 year's training in a recognized paediatric rheumatology centre. The Competency Frameworks for Speciality Paediatrics form the basis of the curriculum for training and there is a Framework for the Specialist in Paediatric Rheumatology and also for the general paediatrician with an interest in rheumatology. Further details are given on the format of training and the Competency Frameworks are given on the British Society of Paediatric and Adolescent Rheumatology website (http://www.bspar.org.uk/pages/trainees_area_members.asp) and the RCPCH website (http://www.rcpch.ac.uk/Training/Competency-Framework).

Increasingly throughout the UK and elsewhere, there are networks of clinical services working together to deliver paediatric rheumatology care, often across large geographical areas and encompassing various models of care with specialist expertise linking with other, and often smaller units. The role of adult rheumatologists is still very important as part of these clinical networks, although in many areas the focus of the adult rheumatology team is increasingly towards transitional care. There is a great need to raise awareness of paediatric rheumatology and the importance of early and prompt access to appropriate specialist care. There is a shortage of specialist paediatric rheumatology multidisciplinary teams in the UK and further afield. The role of shared care between specialist services with local general paediatric and adult rheumatology teams is increasingly important so that high-quality clinical care can be delivered and equitably. Such clinical networks require personnel with training and support, highlighting the need for training, training positions, and a mechanism for support and teaching resources. This content of this handbook is largely based on the content of the Competency Frameworks for Paediatric Rheumatology and aims to address learning needs of paediatric rheumatology trainees, general paediatricians with an interest in rheumatology, as well as other healthcare professionals working within the specialty and clinical networks. To date there are no competency frameworks or curricula

for allied health professionals working in paediatric rheumatology but through involvement of nurses and therapists as contributors to the handbook, we aim to have addressed some of the learning needs.

Helen Foster
Chair of RCPCH Specialist Advisory Committee for Rheumatology

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Symbols and abbreviations

🕮	cross-reference
↑	increase/d
↓	decrease/d
♂	male
♀	female
~	approximately
±	plus/minus
2D	two-dimensional
3D	three-dimensional
AAV	ANCA-associated vasculitides
ACE	angiotensin-converting enzyme
ACL	anticardiolipin
ACR	American College of Rheumatology
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ALPS	autoimmune lymphoproliferative syndrome
ANA	antinuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
anti-CCP	anti-cyclic citrullinated protein
AP	anteroposterior
aPL	antiphospholipid [antibody]
APS	antiphospholipid syndrome
APTT	activated partial thromboplastin time
ARF	acute rheumatic fever
ASIC	anterior superior iliac crest
ASOT	anti-streptolysin O titre
AZA	azathioprine
BD	Behçet's disease
BJHS	benign joint hypermobility syndrome
BNFC	British National Formulary for Children
BP	blood pressure
BPRG	British Paediatric Rheumatology Group
BSA	body surface area
BSPAR	British Society of Paediatric and Adolescent Rheumatology
CAA	coronary artery abnormality

cANCA	cytoplasmic anti-neutrophil cytoplasmic antibody
CAPS	catastrophic antiphospholid syndrome or cryopyrin associated periodic syndrome
CAU	chronic anterior uveitis
CCP	cyclic citrullinated protein
CD	Crohn's disease
CF	cystic fibrosis
CHAQ	Child Health Assessment Questionnaire
CINCA	chronic infantile neurologic cutaneous and articular syndrome
CNS	central nervous system or clinical nurse specialist
cPACNS	primary angiitis of the central nervous system in children
cPAN	cutaneous polyarteritis nodosa
CRMO	chronic recurrent multifocal osteomyelitis
CRP	C-reactive protein
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
CSS	Churg–Strauss syndrome
CT	computed tomography
CTA	computed tomography angiography
CTD	connective tissue disease
CXR	chest x-ray
CYC	cyclophosphamide
DAS	Disease Activity Score
DD	Degos disease
DDH	developmental dysplasia of the hip
DIRA	deficiency of IL-1 receptor antagonist
DMARD	disease-modifying antirheumatic drug
DXA	dual-emission X-ray absorptiometry
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyography
ENA	extractable nuclear antigen
EOS	early-onset sarcoidosis
ERA	enthesitis-related arthritis
ERT	enzyme replacement therapy
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FBC	full blood count
FCAS	familial cold autoinflammatory syndrome
FII	factitious or induced illness

FMD	fibromuscular dysplasia
FMF	familial Mediterranean fever
G6PD	glucose-6-phosphate dehydrogenase
GAG	glycosaminoglycan
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GI	gastrointestinal
GN	glomerulonephritis
GP	General practitioner
GvHD	graft-versus-host disease
GWAS	genome-wide association study
HA	healthy adults
HC	healthy children
HIV	human immunodeficiency virus
HLA	human leucocyte association
HLH	haemophagocytic lymphohistiocytosis
HSCT	haematopoietic stem cell transplantation
HSN	Henoch–Schönlein nephritis
HSP	Henoch–Schönlein purpura
HUVS	hypocomplementaemic urticarial vasculitic syndrome
IA	intra-articular
IAC	intra-articular corticosteroid
IBD	inflammatory bowel disease
IC	indeterminate colitis
Ig	immunoglobulin
ILAR	International League of Associations for Rheumatology
IM	intramuscular
INR	international normalized ratio
IV	intravenous
IVIG	intravenous immunoglobulin
IVMP	intravenous methylprednisolone
JDM	juvenile dermatomyositis
JIA	juvenile idiopathic arthritis
JSLE	juvenile-onset systemic lupus erythematosus
jSSc	juvenile systemic sclerosis
KD	Kawasaki disease
kg	kilogramme/s
L	litre/s
LDH	lactate dehydrogenase
LFT	liver function test

LMWH	low-molecular-weight heparin
LN	lupus nephritis
LS	localized scleroderma
LTBI	latent tuberculosis infection
LV	livedoid vasculopathy
MAS	macrophage activation syndrome
MC&S	microscopy, culture and sensitivity
MCPJ	metacarpophalangeal joint
MCTD	mixed connective tissue disease
MDT	multidisciplinary team
MED	multiple epiphyseal dysplasia
mg	milligramme/s
MHC	major histocompatibility complex
min	minute/s
MKD	mevalonate kinase deficiency
ML	mucolipidoses
mL	millilitre/s
mm	millimetre/s
MMF	mycophenolate mofetil
MPO	myeloperoxidase
MPS	mucopolysaccharidoses
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MSK	musculoskeletal
MSUS	musculoskeletal ultrasound
MTPJ	metatarsophalangeal joint
MTX	methotrexate
MWS	Muckle–Wells syndrome
NAI	non-accidental injury
NBO	non-bacterial osteitis
NFC	nailfold capillary
NICE	National Institute for Health and Clinical Excellence
NOMID	neonatal onset multisystem inflammatory disease
NTI	narrow therapeutic index
OCD	osteochondritis dissecans
OI	osteogenesis imperfecta
OT	occupational therapist
PA	posterior–anterior
PACNS	primary angiitis of the central nervous system
PAH	pulmonary arterial hypertension

PAN	polyarteritis nodosa
pANCA	perinuclear anti-neutrophil cytoplasmic antibody
PAPA	pyogenic sterile arthritis, pyoderma gangrenosum, and acne [syndrome]
PCR	polymerase chain reaction
PET	positron emission tomography
pGALS	paediatric gait, arms, legs, spine musculoskeletal screening examination
PIPJ	proximal interphalangeal joint
PK	pharmacokinetic
PO	per os (orally)
PR3	proteinase 3
pREMS	paediatric regional examination of the musculoskeletal system
PRT	paediatric rheumatology team
PTH	parathyroid hormone
PUO	pyrexia of unknown origin
PVL	Panton–Valentine leukocidin
PXE	pseudoxanthoma elasticum
QoL	quality of life
RA	rheumatoid arthritis
RCT	randomized control trial
RD	Raynaud's disease
RF	rheumatoid factor
RICE	Rest, ice, compress, elevate
RP	Raynaud's phenomenon
sec	second/s
SAPHO	synovitis acne pustulosis hyperostosis osteitis [syndrome]
SEDC	spondyloepiphyseal dysplasia congenita
SIADH	syndrome of inappropriate anti-diuretic hormone secretion
sJIA	systemic juvenile idiopathic arthritis
SLE	systemic lupus erythematosus
SmPC	summary of product characteristics
SNP	single nucleotide polymorphism
SSc	systemic sclerosis
SSZ	sulphasalazine
TA	triamcinolone acetonide
TB	tuberculosis
TGFβ	transforming growth factor-beta
TH	triamcinolone hexacetonide

TMJ	temporomandibular joint
TNF	tumour necrosis factor
TPMT	thiopurine methyltransferase
TRAPS	TNF receptor-associated period syndrome
TRM	transplant-related mortality
TST	tuberculin skin test
U&E	urea and electrolyte
UC	ulcerative colitis
UK	United Kingdom
US	ultrasound
VAS	visual analogue score
VZIG	varicella-zoster immunoglobulin
VZV	varicella zoster virus
WCC	white cell count
yr	year/s

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Chapter 1

Clinical skills and assessment

Epidemiology of paediatric musculoskeletal conditions

Inflammatory musculoskeletal conditions

- Juvenile idiopathic arthritis (JIA), the most common chronic rheumatic disease of childhood, is a clinically heterogeneous group of disorders characterized by chronic inflammatory arthritis. JIA is considered to be an autoimmune disease, which is thought to result of an immune reaction caused or triggered by environmental factors such as infectious agents in a genetically susceptible host, although the exact aetiology has yet to be determined.
- Determining the incidence and prevalence, both within the UK and internationally, has been challenged by changing classification criteria (American College of Rheumatology [ACR] versus European League Against Rheumatism [EULAR] versus League of Associations for Rheumatology [ILAR]) as well as differences in case ascertainment.
- The earliest epidemiological studies of JIA performed in populations from Western Europe and North America showed an incidence varying between 1.3 per 100,000 person-years in France and 22.6 per 100,000 person-years in Norway. The prevalence of JIA was reported as between 7 and 148 per 100,000 person-years, in France and Norway respectively. However, comparison of these studies is difficult, because different diagnostic criteria, e.g. EULAR vs. ACR, and different study designs were used.
- More recent population-based studies data have shown a higher prevalence of JIA, between 167 and 400 per 100,000 person-years; this difference is likely due to undiagnosed cases being identified in 'healthy' children when they underwent examination by trained paediatric rheumatologists. A recent population-based multicentre study performed in southeastern Norway found the annual incidence of childhood arthritis was 71 per 100,000 children; however this study included transient arthritis, postinfectious arthritis, and infectious arthritis as well as JIA.
- A diagnostic register was established in the UK in 1989 with the objectives of describing the demography and diagnostic classification of children referred to paediatric rheumatology clinics and also to estimate the incidence of juvenile arthritis in the UK. The annual incidence rate for juvenile arthritis from 2 centres in 1996 was 10 per 100,000, and for all rheumatic disorders was 32–42 per 100,000 children under age 16.
- Ethnicity has also been found to play a role. Children of European ancestry have been found to be at the highest risk of developing all types of JIA compared to other ethnic groups, except rheumatoid factor (RF)+ve polyarticular JIA. Also, native North American children are at a higher risk than children of European descent of developing a polyarticular course of disease, such as extended oligoarticular JIA, RF−ve polyarticular JIA, and RF+ve polyarticular JIA.

Juvenile-onset systemic lupus erythematosus

- Childhood-onset juvenile systemic lupus erythematosus (SLE) was found to account for <1% of patients in paediatric rheumatology clinics in a UK Registry, compared to 1.5–3% in Canada and 4.5% in the USA. In a Canadian study from a national Registry, the mean annual incidence of SLE was estimated at 0.36 per 100,000 children.

Juvenile dermatomyositis

- The incidence of juvenile dermatomyositis in the UK and Ireland is reported at a rate of 0.19 per 100,000 children. This compares with rates of 0.25–0.41 per 100,000 for children in a US registry.

Juvenile scleroderma

- Scleroderma in childhood remains very rare. A recent UK study has estimated the annual incidence to be 3.4 per million children for localized scleroderma; and 0.27 per million for systemic disease.

Non-inflammatory musculoskeletal conditions

Hypermobility

- The prevalence of hypermobility in children as a phenomenon, as opposed to benign joint hypermobility syndrome (BJHS), has been measured in a number of studies previously and, depending on the age or ethnicity of the study population or the inclusion criteria, has been reported to be between 2.3% and 30%.
- However, the presence of hypermobility in children does not equate to having BJHS. The latter is defined as the presence of a degree of joint hypermobility measured by a prearranged and validated scoring system, associated with musculoskeletal symptoms and signs, and other connective tissue problems likely to be attributable to it.
- There is wide divergence in the joint laxity observed amongst different ethnic groups. The Europeans are most stiff; the Bantu tribes of intermediate joint laxity; and those originally from the Indian subcontinent of most marked joint laxity.
- Considerable overlap between benign hypermobility and mild variants of Ehlers–Danlos syndrome, Marfan syndrome, and osteogenesis imperfect has been reported.

Complex regional pain syndrome

- The incidence of complex regional pain syndrome (CRPS) in children is unknown. In a population study in the USA, the overall risk of CRPS was 5.46 per 100,000 person years. However, this mainly reflected adult CRPS, as the median age at diagnosis was 46yr.
- In large paediatric series CRPS is more common in girls (70%), and the mean age at diagnosis is 13yr of age (range 5–17yr).

Further reading

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Malleson PN, Fung MY, Rosenberg AM. The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association Disease Registry. *J Rheumatol* 1996; **23**:1981–7.

Symmons DP, Jones M, Osborne J, *et al.* Pediatric rheumatology in the United Kingdom: data from the British Pediatric Rheumatology Group National Diagnostic Register. *J Rheumatol* 1996; **23**:1975–80.

History taking, physical examination, and approaches to investigation

- The differential diagnosis of musculoskeletal pain in children is broad (Box 1.1). Taking a history and performing a physical examination (general and musculoskeletal) are integral to making an accurate diagnosis.
- In history taking it is worth asking open questions (Table 1.1), probing for features that may suggest mechanical or inflammatory pathology (Table 1.2), seeking any suggestion of systemic disease and 'red flags' (Box 1.2) to warrant urgent concern or clues in the history to suggest inflammatory musculoskeletal disease (Box 1.3).
- Appropriate clinical assessment requires knowledge of normal development, normal variants (see 🕮 Normal variants of lower limb development, p 9), normal and abnormal gait patterns (see 🕮 The gait cycle and abnormal gait patterns, p 11), clinical presentations at different ages (e.g. the hip, see 🕮 Hip pain and hip problems in children and adolescents, p 106), and an approach to initial investigations. Further details are given in chapters relating to individual diseases.

Key points to note in the clinical assessment:

- A common pitfall in making a diagnosis is to inappropriately attribute a child's problem to trauma (which is a common event in the life of all ambulant children).
- The history (often given by the parent or carer), may be based on observations and interpretation of events made by others (such as teachers or friends), and may be rather vague and ill-defined with non-specific complaints such as 'my child is limping' or 'my child is not walking quite right'.
  - Consider the age and development of the child and modify the questioning and consultation style accordingly.
  - The young child may deny having pain when asked directly, and this should not be taken to mean that the child does not have any pain.
- Physical examination needs to be comprehensive:
  - Assessment of pain is important (see 🕮 Pain syndromes and the assessment of pain, p 87) and can result in physical examination being challenging for everyone present.
  - A musculoskeletal screening examination (e.g. pGALS—see 🕮 pGALS, p 18) will identify areas of significant joint abnormality which may not be apparent from the history alone. Some aspects of pGALS, such as gait observation may be modified or need to be postponed in the acutely unwell child.
  - A more detailed regional musculoskeletal examination (see 🕮 pREMS, p 23) is an adjunct to the screening examination and the possibility of referred pain needs to be considered.
  - Indolent presentations of chronic musculoskeletal disease can impact on growth (either localized or generalized). It is important to assess height and weight, review growth charts in the Parent Held Record where available, and look for evidence of disproportionate growth (e.g. asymmetrical leg length) or muscle wasting.

- Additional clinical skills are required pending the clinical scenario and include capillaroscopy (see 🕮 Nailfold capillaroscopy in rheumatic disease, p 37) and muscle testing (see 🕮 Juvenile dermatomyositis, p 266).
- Musculoskeletal ultrasound is increasingly being used as an adjunct to clinical examination (see 🕮 Musculoskeletal ultrasound in juvenile idiopathic arthritis, p 28).

Box 1.1 The differential diagnosis of musculoskeletal pain in children and adolescents

Life-threatening conditions
- Malignancy (leukaemia, lymphoma, bone tumour)
- Sepsis (septic arthritis, osteomyelitis)
- Non-accidental injury (NAI).

Joint pain with minimal or no swelling
- Hypermobility syndromes
- Orthopaedic syndromes (e.g. Osgood–Schlatter disease, Perthes disease)
- Idiopathic pain syndromes (reflex sympathetic dystrophy, fibromyalgia)
- Metabolic (e.g. hypothyroidism, lysosomal storage diseases)
- Tumour (benign and malignant).

Joint pain with swelling
- Trauma (haemarthrosis)
- Infection
- Septic arthritis and osteomyelitis (viral, bacterial, mycobacterial):
  - Reactive arthritis (post-enteric, sexually acquired)
  - Infection related (rheumatic fever, post-vaccination)
- JIA
- Arthritis related to inflammatory bowel disease
- Connective tissue diseases (SLE, scleroderma, dermatomyositis, vasculitis)
- Metabolic (e.g. osteomalacia/rickets, cystic fibrosis)
- Haematological (e.g. haemophilia, haemoglobinopathy)
- Tumour (benign and malignant)
- Chromosomal (e.g. Down's related arthritis)
- Auto-inflammatory syndromes (e.g. periodic syndromes, chronic recurrent multifocal osteomyelitis)
- Sarcoidosis
- Developmental/congenital (e.g. achondroplasia).

Table 1.1 Key questions to ask when taking a musculoskeletal history

Questions to parent/carer (and the child as appropriate)	Points to check for	Comments
What have you or anyone else noticed?	Behaviour, mood, joint swelling, limping, bruising	Limping, whether intermittent or persistent, **always** warrants further assessment. Deterioration in school performance (e.g. sport, handwriting) is always significant. Joint swelling is always significant but can be subtle and easily overlooked by the parent (and even healthcare professionals!), especially if the changes are symmetrical Rather than describing stiffness, the parents may notice the child is reluctant to weight-bear or limps in the mornings or 'gels' after periods of immobility (e.g. after long car rides or sitting in a classroom)
What is the child like in him/herself?	Irritability, grumpy, 'clingy', reluctant to play, systemic features (e.g. fever, anorexia, weight loss)	Young children in pain may not verbalize pain but may present with behavioural changes or avoidance of activities previously enjoyed Systemic features including 'red flags' to suggest malignancy or infection
Where is the pain? (Ask the child to point) and what is it like?	Take a pain history and focus on locality, exacerbating/relieving factors, timescale pattern	Asymmetrical persistent site of pain is invariably a cause for concern. Referred pain from the hip may present with non-specific pain in the thigh or knee
How is he/she in the mornings and during the day?	Diurnal variation and daytime symptoms (e.g. limping, difficulty walking, dressing, toileting, stairs?)	Pain on waking or daytime symptoms suggestive of stiffness or gelling (after periods of inactivity), are indicative of inflammatory joint (or muscle) disease
What is he/she like with walking and running? Has there been any **change** in his/her activities?	Motor milestones and suggestion of delay or regression of achieved milestone, including speech and language. Avoidance of activities that previously enjoyed (e.g. sport, play) are noteworthy	Regression of achieved motor milestones, functional impairment or avoidance of activity (including play, sport, or writing), are more suggestive of acquired joint or muscle disease (and especially inflammatory causes). An assessment of global neurodevelopment is indicated with delay or regression in speech, language, or motor skills. 'Clumsiness' is a non-specific term but may mask significant musculoskeletal or neurological disease

Table 1.1 (*Contd.*)

Questions to parent/carer (and the child as appropriate)	Points to check for	Comments
How is he/she at school/ nursery?	School attendance (any suggestion of school avoidance, bullying)	Behavioural problems in the young child may manifest as non-specific pains (headaches, tummy aches, or leg pains). Sensitive questioning may reveal stressful events at home or school
Does he/she wake at night with pain?	Pattern of night waking	Night waking is a common feature of growing pains (and usually intermittent, and often predictable). Conversely persistent night waking, especially if there are other concerns (such as unilaterality, limping, unusual location, or systemic features) are of concern and invariably necessitate further investigation
Can you predict when the pains may occur?	Relationship to physical activity (including during or after sporting activities)	Growing pains tend to be worse later in the day, evenings and often after busy days
What do you do when he/she is in pain?	Response to analgesics, anti-inflammatory medication, massages, and reaction of parent	Lack of response to simple analgesia is a concern. Vicious circle of reinforced behaviour can occur
What is your main concern?	Sleep disturbance, cosmesis, anxiety about serious disease (arthritis, cancer, family history), pain control.	A family history of muscle disease, arthritis or autoimmune disease may indicate a predisposition to muscle or joint disease. Observed 'abnormalities' (such as flat feet, curly toes) may be part of normal development. The parent or carer will undoubtedly have anxieties and concerns about the child, often fear severe illness and both child and parent have an expectation of investigations (i.e. blood tests!)

Table 1.2 Distinguishing mechanical from inflammatory musculoskeletal presentations

	Mechanical	Inflammatory
Pain	Worse on weight bearing and after activity such as walking	Often eased by movement and may be seemingly absent in young children and manifest as behavioural change or avoidance of activity
Joint swelling	Usually mild and maybe transient	Tends to be persistent
Morning stiffness or gelling after rest	Usually absent	Often marked
Instability *(giving way)*	May be present	Usually absent
Locking	May be present	Usually absent
Loss of full movement	May be present	Often present

Box 1.2 RED FLAGS (to raise concern about infection or malignancy or non-accidental malignancy)

- Fever, systemic upset
- Bone/joint pain with fever
- Weight loss, sweats, persistent night waking
- Incongruence between history and clinical presentation pattern of physical findings.

Box 1.3 Important points when considering inflammatory joint or muscle disease

- The lack of reported pain does not exclude arthritis.
- There is need to probe for symptoms such as:
  - Gelling (e.g. stiffness after long car rides).
  - Altered function (e.g. play, handwriting skills, writing, regression of milestones).
  - Deterioration in behaviour (irritability, poor sleeping).
- There is need to examine all joints as often joint involvement may be 'asymptomatic' or illocalized.
- There is need to assess muscle strength (e.g. proximal muscle weakness).

Normal variants of lower limb development

Table 1.3 Normal variants of lower limb development

	Indications for concern and referral to physiotherapy or paediatric orthopaedics unless specified	Comments (see 🕮 Foot and ankle problems, p 121, 🕮 The role of the podiatrist, p 385, and 🕮 Joint hypermobility, p 124)
Tip-toe walking Common in healthy young children	• Toe walking is persistent or asymmetrical • Associated developmental delay • Child unable to squat or stand with their heels on the floor (tightness of calf muscles) • Child >3yr old, and unable to stand from floor sitting without using hands	• Can associate with clubfoot or neurological disease (e.g. muscular dystrophy, cerebral palsy, poliomyelitis). Careful neuromuscular/ assessment required. Check for gastrocnemius contracture and shoes for sole wear. Physiotherapy may help mild cases but surgery may be required
Flat feet Common and normal for babies and toddlers, resolves with development of longitudinal arch usually by 4–6yr of age	• Signs of pressure on the foot, e.g. blistering • The longitudinal arch does not form normally when the child stands on tip toe • The foot is stiff (i.e. the normal arch does not form when the child stands on tip toe or the big toe is passively extended)	• Persistence often familial, more common in hypermobility • Insoles may help but shouldn't be worn all the time—walking in bare in feet helps promote foot development • A non-flexible flat foot may indicate tarsal coalition (often teens) • In newborn exclude vertical talus
Pes cavus Not common—the opposite of flat feet and is when the arch is extremely pronounced	• Often associated with toe clawing, calluses, heel varus, and pain with difficult to fit footwear • May be physiological (familial—so check parents' feet!), residual from clubfoot abnormality, or associated with neurological abnormalities. Paediatric neurology/orthopaedics referral usually needed	• Careful neuromuscular/ musculoskeletal assessment required. Neurological conditions to consider include—spina bifida, spinal dysraphism, poliomyelitis, Charcot–Marie–Tooth, Friedrich's ataxia • Insoles may help and surgery may be required
Curly toes Most resolve by 4yr	• Surgery rarely needed	• Check shoes are well fitting

(*continued*)

Table 1.3 (*Contd.*)

	Indications for concern and referral to physiotherapy or paediatric orthopaedics unless specified	Comments (see 🕮 Foot and ankle problems, p 121, 🕮 The role of the podiatrist, p 385, and 🕮 Joint hypermobility, p 124)
Knock knees Usually resolve by the age of 6yr	• Associated with pain or asymmetrical • Extreme (>6cm intermalleolar distance at ankles) or persistent (>6yr)	• A gap of 6–7cm between the ankles is normal (between 2–4yr) • Late feature of arthritis of knee (e.g. JIA)
Bow legs Common and normally seen in children until the age of 2yr	• Associated with pain or asymmetrical or the child is short in stature or has other medical problems • Extreme (>6cm intercondylar distance at knees) or persistent (>6yr)	• Conditions to exclude include rickets, skeletal dysplasias, syndromes associated with dwarfism (e.g. achondroplasia), Blount's disease • Late feature of arthritis of knee (e.g. JIA)
Out-toeing Feet point outwards and usually resolves by 4yr	• Recent onset in a teenager—check hips for a slipped upper femoral epiphysis.	

JIA, juvenile idiopathic arthritis.

Further reading

Staheli, L.T. *Fundamentals of Pediatric Orthopedics—Foot and lower limb.* Philadelphia, PA: Lippincott-Raven, 2008.

The gait cycle and abnormal gait patterns

A child with an abnormal gait is a common presentation and can be due to many different causes (Tables 1.4 and 1.5). Clearly there is considerable overlap with neurological problems and careful clinical assessment, recognition of different gait patterns, and knowledge of potential differential diagnoses is very helpful (Table 1.6).

General effects of neuromuscular disease on joint action

- Muscle weakness reduces stability.
- Muscle weakness and spasticity reduces range of motion.
- Muscle weakness and spasticity reduces efficiency.
- Muscle weakness and spasticity encourages compensatory movements.
- Longstanding weakness and spasticity may cause joint contracture.
- Longstanding contracture and compensatory movements may cause bone deformities (lever arm dysfunction).

Indications for neuromuscular assessment

- To study abnormal inefficient gait or gait that is deteriorating.
- To identify specific targets for surgical correction, e.g. osteotomies, muscle lengthening.
- Allows detailed assessment of gait by multidisciplinary team.
- Assess outcomes of intervention, i.e. orthoses, physiotherapy, or surgery.

Limitations of gait analysis

- Expense, training, and operator experience dependent.
- Variation between observers, of assessments and recommendations.

Table 1.4 The normal gait cycle and abnormal patterns observed in neuromuscular disease

Gait cycle phase	Normal characteristics	Abnormal characteristics in neuromuscular disease	Examples of abnormality in musculoskeletal disease
 Loading response	• Dorsiflexed ankle for weight acceptance • Heel strike (for shock absorption)	• Lack of dorsiflexion range due to weakness, contracture or calf muscle spasticity • High stepping gait (no heel strike), e.g. poliomyelitis and other paralytic disorders	• Tip-toe walking with short gastrocnemius muscles or painful hindfoot (e.g. Sever's disease)

(*continued*)

Table 1.4 (*Contd.*)

Gait cycle phase	Normal characteristics	Abnormal characteristics in neuromuscular disease	Examples of abnormality in musculoskeletal disease
 Mid stance	• Stable ankle • Dorsiflexors contract, plantar flexors relax • Knee extends • Hip extends	• Peroneal weakness may reduce ankle stability, e.g. common peroneal nerve palsy • Hamstring contracture or spasticity may reduce knee extension	• Painful ankle (e.g. JIA)
 Terminal stance	• Full hip extension • Full knee extension • Allows contralateral limb clearance	• Pelvic lurch due to abductor weakness affects hip stability (Trendelenburg gait) • Psoas spasticity and contracture prevents hip extension, e.g. spastic diplegia	• Leg-length discrepancy (longer leg scuffs the ground or circumducts)
 Pre/early swing	• Ankle plantar flexion • Power generation for propulsion	• Weak calf muscle generates less power, e.g. poliomyelitis	• Restricted ankle (e.g. JIA)
 Mid swing	• Hip max flexion • Knee max flexion • Ankle dorsiflexion for clearance	• Poor clearance due to tibialis anterior and peronei weakness e.g. Charcot–Marie–Tooth and other peripheral neuropathies	• Loss of full extension due to inflammatory joint (knee) or muscle (quadriceps) disease
 Terminal stance	• Knee extends (allows adequate step length) • Ankle dorsiflexes for heel strike (foot pre-positioning)	• Lack of full extension due to quads weakness, e.g. spastic diplegia • Lack of dorsiflexion range due to weakness, contracture or calf muscle spasticity e.g. spastic hemiplegia	• Pain inhibition of hip abductors in Legg–Calve–Perthes disease

Table 1.5 Neuromuscular assessment

Component	Risk factors	Examples
History	Prenatal infection or bleeding	Varicella zoster, abruption
	Postnatal special care	Postnatal respiratory distress
	Family history of neuromuscular disorder	Charcot–Marie–Tooth disease
	Deteriorating mobility	Deteriorating gait, fatigue
	Milestones not achieved	Poor head control, not sitting unsupported by age 12 months
Examination	Muscle weakness	
	↑ muscle tone	Spasticity
	Joint contracture	Tip toeing, hamstring tightness
	Bone deformity	Femoral neck anteversion, cavovarus or plano valgus feet
Gait analysis	Abnormal gait	High stepping or crouch gait
	Slow motion playback	Lack of heel strike (calf muscle spasticity)
	Force plate studies	Loss of knee extension (hamstring spasticity)
	Joint motion sensors	Loss of hip extension
	Electromyography	Abnormal muscle contraction

Table 1.6 Abnormal gait patterns seen in musculoskeletal disease

	Description	Potential causes
Antalgic gait	Due to pain on the affected side, where the stance phase (the length of time spent bearing weight) on the affected side is shorter. May present with limp or non-weight-bearing	• Multiple causes and sites, including trauma, sepsis, JIA, Legge–Calve–Perthes disease
Trendelenburg gait	Results from hip abductor muscle weakness and whilst weight-bearing on ipsilateral side, the pelvis drops on contralateral side, rather than rising as is normal. With bilateral hip disease—a waddling 'rolling sailor' gait with hips, knees and feet externally rotated. This gait is also observed secondary to painful hip conditions due to pain inhibition of normal muscle activity	• Hip joint disease (e.g. Legge–Calve–Perthes disease, slipped capital femoral epiphysis, developmental dysplasia of the hip, JIA involving the hip). • Muscle disease (juvenile Dermatomyositis or inherited myopathies) • Neurological conditions (spina bifida, cerebral palsy, and spinal cord injury)
Circumduction gait ('peg leg')	A circular movement of the leg with excessive hip abduction as the leg swings forward	• A lack of full knee extension (JIA, trauma)—in JIA may be due to leg-length discrepancy • Unilateral spasticity as in hemiplegic cerebral palsy
Waddling gait	A wide-based gait suggests proximal muscle weakness	• Inflammatory myopathies
Spastic gait	Refers to stiff walking with foot-dragging and the foot inverted	• Upper motor neuron neurologic disease (e.g. diplegic or quadriplegic cerebral palsy, stroke)
Ataxic gait	Due to instability with an alternating narrow to wide base of gait	• Neurological disease (e.g. ataxic cerebral palsy affecting the cerebellum, cerebellar ataxia and Friedreich's ataxia)
Toe-walking gait ('equinus')	Absent heel contact	• Habitual toe walking (common and associated with normal foot examination and normal walking on request) • Persistent toe walking (spastic upper motor neuron neurologic disease (e.g. diplegic cerebral palsy), JIA, and mild lysosomal storage disorders

Normal gait and musculoskeletal development

- It is important to be aware of normal motor milestones (Table 1.7) and normal variants in gait and leg alignment (see 📖 Normal variants of lower limb development, p 9).
- Patterns of abnormal gait are important to recognize and are based on understanding of the gait cycle (see 📖 The gait cycle and abnormal gait patterns, p 11).
- There is considerable variation in the way normal gait patterns develop—such variation may be familial (e.g. 'bottom-shufflers' often walk later) and subject to racial variation (e.g. African black children tend to walk sooner and Asian children later than average).
- The normal toddler has a broad-base gait for support, and appears to be high stepped and flat footed with arms outstretched for balance.
- The legs are externally rotated with a degree of bowing. Heel strike develops around 15–18 months with reciprocal arm swing.
- Running and change of direction occur after the age of 2yr, although this is often accompanied by frequent falls until the child acquires balance and coordination.
- In the school-age child, the step length increases and step frequency slows. Adult gait and posture occur around the age of 8yr.

The approach to investigation

- The approach to investigation is based on the differential diagnosis derived from the clinical setting; details of investigations required and their interpretation are given in this handbook for the various diseases.
- With regard to suspected inflammatory joint disease, it must be remembered that JIA is a diagnosis of exclusion, there is no diagnostic test and pending the clinical scenario the child may undergo multiple tests to confirm the diagnosis (Table 1.8).
- It is important that the child is referred for a paediatric rheumatology assessment as soon as the diagnosis is suspected and certainly before invasive tests such as arthroscopy or procedures requiring general anaesthetic (e.g. magnetic resonance imaging [MRI] in the young child) are contemplated.
- Delay in making a diagnosis of JIA is well reported and often exacerbated through waiting for procedures that may be unnecessary.

Table 1.7 Normal musculoskeletal development

Sits without support	6–8 months
Creep on hands and knees	9–11 months
Cruise/or bottom shuffle	11–12 months
Walk independently	12–14 months
Climb up stairs on hands and knees	~15 months
Run stiffly	~16 months
Walk down steps (non-reciprocal)	20–24 months
Walk up steps, alternate feet	3yr
Hop on one foot, broad jump	4yr
Skipping	5yr
Balance on one foot for 20sec	6–7yr
Adult gait and posture	8yr

Table 1.8 Investigations in the child with suspected JIA—cautionary notes

FBC and blood film	May be normal in JIA, especially oligo-articular subtype Anaemia of chronic disease may be present in polyarticular JIA and systemic onset JIA Raised white cell count and raised platelets a feature of systemic onset JIA A blood film is helpful to exclude leukaemia but suspicion of this requires a bone marrow examination
Acute phase reactants ESR, CRP	May be raised, and often very high in systemic JIA
Ferritin	May be raised and often extremely high in systemic JIA or macrophage activation syndrome
Antinuclear factor	May be absent in 50% of JIA and may be found in viral illnesses, non-rheumatic disease, and many healthy children as well as connective tissue disease (such as SLE) In the presence of JIA, ANA indicates high risk of chronic anterior uveitis, which affects 30% of children with JIA and is potentially blinding if undetected and untreated
Rheumatoid factor	Rarely found in children with JIA (<10% of cases) but associates with poor prognosis
Slit lamp examination	**All children with suspected JIA require prompt referral to ophthalmology for eye screening for uveitis** which is invariably asymptomatic in the early stages and if undetected and untreated, can lead to blindness
Synovial fluid examination	Not required to make a diagnosis of JIA but is mandatory to exclude sepsis in the child with a single hot swollen joint (and any suspicion of tuberculosis).
Arthroscopy and synovial biopsy	Not required to make a diagnosis of JIA. **Seldom indicated and not recommended before child has been assessed by a paediatric rheumatologist.**
Radiographs	May be normal in early JIA—loss of joint space and joint damage occur in severe or untreated disease. Useful to exclude other pathology (and tumour).
Ultrasound	Ultrasonography is sensitive to early changes, is well tolerated by young children, and is increasingly more available
MRI	MRI is sensitive to early changes of inflammatory arthritis but may not be available and in young children invariably requires sedation. Referral to paediatric rheumatology should not be delayed whilst awaiting MRI scanning. **Gadolinium contrast should be remembered—often not given to children who have MRI prior to paediatric rheumatology assessment, resulting in need for repeat scans.**

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBC, full blood count; MRI, magnetic resonance imaging.

pGALS: paediatric gait, arms, legs, spine musculoskeletal screening examination

- The pGALS screening assessment (Box 1.4) is a simple evidence-based approach to musculoskeletal assessment based on the adult GALS (gait, arms, legs, spine) screen and has been shown to have high sensitivity to detect significant joint abnormalities.
- Key to distinguishing normal from abnormal is a knowledge of ranges of movement in different age groups and ethnicity, looking for asymmetry, and careful examination for subtle changes.
- pGALS is primarily aimed at the school-aged child, but younger children will often comply with pGALS, especially if they copy the examiner and see this as a game.
- pGALS incorporates a series of simple manoeuvres, takes an average of 2min to perform and simple practical tips facilitate the examination (Box 1.5 and Tables 1.9 and 1.10).
- The pGALS screen includes 3 questions relating to pain and function although a negative response does *not* exclude significant musculoskeletal disease and at a minimum the screening examination should be done in all clinical scenarios where musculoskeletal disease is a concern (Box 1.6).
- It is essential to perform all parts of the pGALS screen as joint involvement may be apparently 'asymptomatic', symptoms may not be localized, and it is important to check for verbal and non-verbal clues of joint discomfort such as facial expression or withdrawal of limb.
- The information needs to be interpreted in the context of the physical examination elsewhere (e.g. chest, abdomen, neurological examinations in the case of the limping child) or in the presence of any 'red flags' in the unwell child.
- Documentation of findings in the case notes is simple, using a grid (Fig. 1.1).

Box 1.4 The pGALS musculoskeletal screening examination

Screening questions
- 'Do you (or does your child) have any pain or stiffness in your joints, muscles, or your back?'
- 'Do you have any difficulty getting yourself dressed without any help?'
- 'Do you have any difficulty going up and down stairs?'

Gait
- Observe the child walking.
- 'Walk on your tip-toes/walk on your heels.'

Arms (see Table 1.9)
- 'Put your hands out in front of you.'
- 'Turn your hands over and make a fist.'
- 'Pinch your index finger and thumb together.'
- 'Touch the tips of your fingers with your thumb.'
- Squeeze the metacarpophalangeal joints.
- 'Put your hands together/put your hands back to back.'
- 'Reach up and touch the sky.'
- 'Look at the ceiling.' (*assesses neck*)
- 'Put your hands behind your neck.'

Legs (see Table 1.10)
- Feel for effusion at the knee.
- 'Bend and then straighten your knee' (active movement of knees and examiner feels for crepitus).
- Passive flexion (90°) with internal rotation of hip.

Spine (see Table 1.10)
- 'Open your mouth and put 3 of your [*child's own*] fingers in your mouth.'
- Lateral flexion of cervical spine—'Try and touch your shoulder with your ear.'
- 'Look at the ceiling.'
- Observe the spine from behind.
- 'Can you bend and touch your toes?' Observe curve of the spine from side and behind.

Box 1.5 Practical tips: while performing the pGALS screening examination

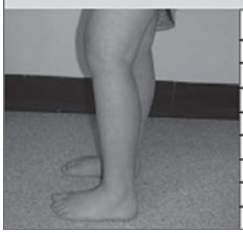
- Get the child to copy you doing the manoeuvres.
- Look for verbal and non-verbal clues of discomfort (e.g. facial expression, withdrawal).
- Do the full screen as extent of joint involvement may not be obvious from the history.
- Look for asymmetry (e.g. muscle bulk, joint swelling, range of joint movement).
- Consider clinical patterns (e.g. non-benign hypermobility and Marfanoid habitus or skin elasticity, and association of leg-length discrepancy and scoliosis).

Box 1.6 Practical tips: when to perform pGALS in the assessment

- Child with muscle, joint, or bone pain.
- Unwell child with pyrexia.
- Child with limp.
- Delay or regression of motor milestones.
- The 'clumsy' child in the absence of neurological disease.
- Child with chronic disease and known association with musculoskeletal presentations.

Documentation of the pGALS screen

Documentation of the pGALS screening assessment is important and a simple pro forma is proposed with the following example–a child with a swollen left knee with limited flexion of the knee and antalgic gait.



pGALS screening questions		
Any pain?	Left knee	
Problems with dressing?	No difficulty	
Problems with walking?	Some difficulty on walking	
	Appearance	Movement
Gait		✗
Arms	✓	✓
Legs	✗	✗
Spine	✓	✓

Fig. 1.1 Documentation of the pGALS screen findings. Reproduced with permission by Arthritis Research UK (see Free educational resources.)

Further reading and resources

Foster HE, Kay LJ, Friswell M, Coady D, Myers A. Musculoskeletal screening examination (pGALS) for school-age children based on the adult GALS screen. *Arthritis Care Res* 2006; **55**(5):709–16.

Free educational resources (DVD and handouts) to demonstrate pGALS and the manouvres are available: http://www.arthritisresearchuk.org/files/6535_05032010155008.pdf. http://www.arthritisresearchuk.org/arthritis_information/information_for_medical_profes/medical_student_handbook.aspx.

Table 1.9

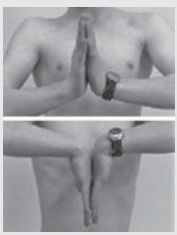
Figure	Screening manoeuvres	What is being assessed?
	'Touch the tips of your fingers'	• Manual dexterity • Coordination of small joints of fingers and thumbs
	Squeeze the metacarpophalangeal joints for tenderness	• Metacarpophalangeal joints
	'Put your hands together palm to palm' and 'put your hands together back to back'	• Extension of small joints of fingers • Wrist extension • Elbow flexion
	'Reach up,"touch the sky"' and 'Look at the ceiling'	• Elbow extension • Wrist extension • Shoulder abduction • Neck extension
	'Put your hands behind your neck'	• Shoulder abduction • External rotation of shoulders • Elbow flexion

Table adapted and used with permission by Arthritis Research UK (see Free educational resources).

Table 1.10

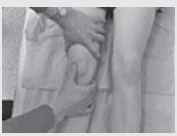
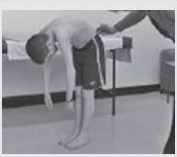
Figure	Screening manoeuvres	What is being assessed?
	'Try and touch your shoulder with your ear'	• Cervical spine lateral flexion
	'Open wide and put three (*child's own*) fingers in your mouth'	• Temporomandibular joints (and check for deviation of jaw movement)
	Fell for effusion at the knee (patella tap, or crossfluctuation)	• Knee effusion (small effusion may be missed by patella tap alone)
	Active movement of knees (flexion and extension) and feel for crepitus	• Knee flexion • Knee extension
	Passive movement of hip (knee flexed to 90°, and internal rotation of hip)	• Hip flexion and internal rotation
	'Bend forwards and touch your toes'	• Forward flexion of thoraco-lumbar spine (and check for scoliosis)

Table adapted and used with permission by Arthritis Research UK (see Free educational resources).

pREMS: paediatric regional examination of the musculoskeletal system

- Following the musculoskeletal screening examination (pGALS), the observer is directed to a more detailed examination of the relevant area, based on the 'look, feel, move,' principle described in the adult regional examination of the musculoskeletal system (called REMS), with active movements performed first and then passively by the examiner.
- A paediatric version of REMS (called pREMS) has been developed from observation of clinicians in clinical practice and is the first consensus-based regional musculoskeletal examination for school-aged children.
- pREMS is similar to adult REMS using the same general principles (Box 1.7) although it differs by anatomical region reflecting different pathologies from those observed in adults (Box 1.8).

Box 1.7 General principles

Introduction
- Introduce yourself to child and parent/carer.
- Explain what you want to examine, gain verbal consent to examine.
- Be aware of normal variants in leg alignment, joint range, gait, developmental milestones.

Look for:
- Swellings, rashes (e.g. psoriasis/vasculitis), muscle wasting, scars, leg-length discrepancy.
- Deformity/dysmorphism/'disproportions'/discomfort, i.e. non-verbal signals.

Feel for:
- Temperature, swelling, tenderness (along bones and joint line).

Movement
- Full range of movement—active and passive (note any asymmetry).
- Restriction—mild, moderate, or severe.

Function and measure
- Functional assessment of joint/anatomical region to include power of muscles and stability.
- Measurement of height/leg length.

Box 1.8 Examination schedules by anatomical region

The options refer to additional manoeuvres suggested pending common clinical scenarios. Details on the examination techniques used are available (see 📖 'Further reading', p 27).

Examination of the hand and wrist

- Inspect hands (palms and backs) for muscle wasting, skin, and nail changes.
- Feel for radial pulse, tendon thickening, and bulk of thenar and hypothenar eminences.
- Feel for skin temperature.
- Squeeze metacarpophalangeal joints (MCPJs).
- Bimanually palpate swollen or painful joints, including wrists.
- Look and feel along ulnar border.
- Assess full finger extension and full finger tuck.
- Assess wrist flexion and extension, abduction and adduction—active and passive.
- Assess function: grip and pinch, picking up small object, writing/drawing.
- Options—assess for hypermobility syndromes, muscle power, capillaroscopy, peripheral neuropathy.

Examination of the elbow

- Look for carrying angle, scars, swellings or rashes, deformity.
- Feel for skin temperature.
- Palpate over head of radius, joint line, medial and lateral epicondyles.
- Assess full flexion and extension, pronation and supination—actively and passively.
- Assess function—e.g. hand to nose or mouth, hands behind head.
- Options—assess for hypermobility syndromes, muscle power, instability tests, enthuses.

Examination of the shoulder

With the patient standing or sitting:

- Inspect shoulders, clavicles, and sternoclavicular joints from the front, side, and behind, and assess shoulder height.
- Inspect skin in axillae and palpate for lymphadenopathy.
- Assess skin temperature.
- Palpate bony landmarks and surrounding muscles.
- Assess movement and function: hands behind head, hands behind back.
- Assess (actively and passively) external rotation, flexion, extension, and abduction.
- Observe scapular movement.
- Options—assess for hypermobility syndromes, muscle power, instability.

Examination of the hip

With the patient supine lying on couch:

- Look for flexion deformity and leg-length discrepancy.
- Check for scars, rashes.

Box 1.8 (*Contd.*)

- Feel the greater trochanter for tenderness.
- Assess full hip flexion, internal and external rotation, abduction and adduction.
- Perform Thomas' test.
- Hip abduction (lying on side).

Patient lying prone on couch:

- Sacroiliac joint palpation.
- Hip internal (and external) rotation.

With the patient standing:

- Assess posture and leg alignment.
- Look for gluteal muscle bulk.
- Perform the Trendelenburg test.
- Assess function (gait with turning and running, ancillary movements).
- Options—assess for hypermobility, muscle power, enthesitis, thigh–foot angle (child with in-toeing).

Examination of the knee

With the patient standing:

- Look for varus/valgus deformity, hyperextension and popliteal swellings.
- Inspect skin for pattern of bruising and rashes.
- Assess gait (see Examination of the hip, this Box).

With the patient lying on couch:

- Look from the end of the couch for varus/valgus deformity, muscle wasting, scars, and swellings.
- Look from the side for fixed flexion deformity.
- Check for passive hyperextension and leg-length discrepancy.
- Feel skin temperature.
- With the knee slightly flexed palpate the joint line and the borders of the patella.
- Feel the popliteal fossa.
- Perform a patellar tap and cross fluctuation (bulge sign).
- Assess full flexion and extension (actively and passively).
- Option: assess stability of knee ligaments—medial and lateral collateral—and perform anterior draw test.
- Option: tests for anterior knee pain/patellar maltracking/apprehension/patella glide.
- Option—assess for hypermobility, enthesitis, hamstring tightness, iliotibial band tightness/thigh–foot angle.

Examination of the foot and ankle

With the patient lying supine on couch:

- Look at dorsal and plantar surfaces of the foot.
- Feel the skin temperature.
- Palpate for peripheral pulses.
- Squeeze the MTPJs.
- Palpate the midfoot, ankle joint line, and subtalar joint.

(*continued*)

Box 1.8 (*Contd.*)

- Assess movement (actively and passively) at the subtalar joint (inversion and eversion), the big toe (dorsi- and plantar flexion), the ankle joint (dorsi- and plantar flexion), and mid-tarsal joints (passive rotation).
- Look at the patient's footwear.
- Option: assess for hypermobility, thigh–foot angle, enthesitis, muscle power, capillaroscopy.

With the patient standing:

- Look at the forefoot, midfoot (foot arch), and the hindfoot.
- Assess gait cycle (heel strike, stance, toe off), running and turning, ancillary movement.
- Assess muscle bulk (calves).

Examination of the spine

With the patient standing:

- Inspect from the side and from behind.
- Inspect skin and natal cleft.
- Inspect limb/trunk proportions.
- Inspect facial and jaw profile.
- Palpate the spinal processes and paraspinal muscles and temporomandibular joints (TMJs).
- Assess movement: lumbar flexion and extension and lateral flexion; cervical flexion, extension, rotation and lateral flexion, thoracic rotation.
- Assess TMJ opening.
- Options: Schober's test, 'stork test'.*

With the patient sitting on couch (standing in younger child):

- Assess thoracic rotation.

With the patient lying on couch:

- Perform straight leg raising and dorsi-flexion of the big toe.
- Assess limb reflexes.
- Options: assess for leg-length discrepancy, hypermobility, sacroiliac joint irritation on palpation.

'Stork test'—standing on one leg and extension of spine causes pain (suggestive of spondylolysis)—see 🕮 Back pain in children and adolescents, p 100.

Further reading

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Musculoskeletal ultrasound in juvenile idiopathic arthritis

Musculoskeletal ultrasound (MSUS) is becoming increasingly used at the bedside by clinicians (Table 1.11). MSUS is valuable in guiding intra-articular steroid injections and detecting subclinical disease. MSUS helps to identify the structures involved in a clinically swollen joint allowing the operator to distinguish between joint and or tendon or tendon sheath involvement. Key points to note making MSUS very practical for use in children:

- MSUS provides images in real time and allows the operator to examine the joint during motion.
- It provides both anatomical and pathological information.
- It is cheap and quick to perform.
- It is well tolerated by children.
- It is an important adjunct to clinical examination.
- It frequently avoids the need for examinations such as MRI which require sedation for the younger child, are costly and not always readily available.

Table 1.11 Musculoskeletal ultrasound in paediatric rheumatology

MSUS is valuable for the identification of:	MSUS is not useful for:	MSUS is less useful for:
• Joint effusions • Synovial hypertrophy • Synovitis • Enthesitis • Tendonitis • Tenosynovitis • Bursa and bursitis	• Bone pathology	• Deep structures

Getting started

- Current ultrasound (US) machines are very user friendly, with images that are easily recognizable with some practice. However, it is strongly advised to begin with a basic MSUS course (see 📖 Further reading, p 31), often available within adult rheumatology and refresh musculoskeletal anatomical knowledge to enable interpretation of the images.
- Once the basic technique is mastered then it is important to practise and become familiar with the US machine as each tends to have its own unique features.
- Briefly, the probe transmits and receives the US signal. Low frequency probes (5–10Hz) are useful for large or deep joints such as the hip and knee, however resolution is lower. High frequency probes >15Hz have limited penetration and are thus only useful in small joints and superficial structures. However, they have excellent resolution. The latter is thus invaluable in paediatric examination of children's joints.

- Scans are usually performed along the longitudinal and transverse axis of structures to give a '3D' (three-dimensional) image of the joint and soft tissues.
- Grey scale refers to the processed images received by the probe. Here hypoechoic (black) structures such as cartilage and joint fluid can be identified. Hyperechoic (white) structures such as the interface with bone and intermediate (grey) structures such as muscle, tendon, and synovial tissue can be seen.
- Power Doppler signal represents blood flow. With the right settings synovial blood flow representing synovitis can be identified. However, power Doppler signal is prone to artefact so it is important that the user is aware of these to avoid erroneous diagnoses.
- The knee joint is a good starting point. It is a commonly involved joint and the images easy to interpret with a little practice.
- Fig. 1.2 represents a longitudinal scan of the knees of a child aged 8yr, normal and abnormal. Note the appearance of the partially ossified patella with the large cartilage halo, the growth plates, the longitudinal striations of the quadriceps tendon, and the potential space of the suprapatellar pouch.

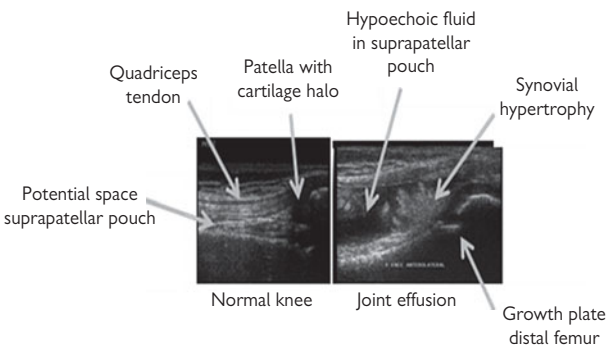

Fig. 1.2 MSUS appearance of knee arthritis compared to normal.

- Fig. 1.3 demonstrates positive power Doppler signal in the tendon sheath of the tibialis posterior tendon.
- Even deeply seated joints such as the hip are easily viewed in children—MSUS can distinguish between a limited range of movement in a hip due to damage and that due to active inflammation which can be difficult to do clinically.

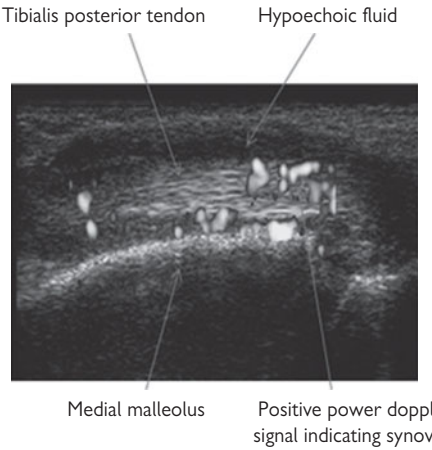

Fig. 1.3 Doppler signal indicating active synovitis in the tibialis posterior tendon at the ankle joint.

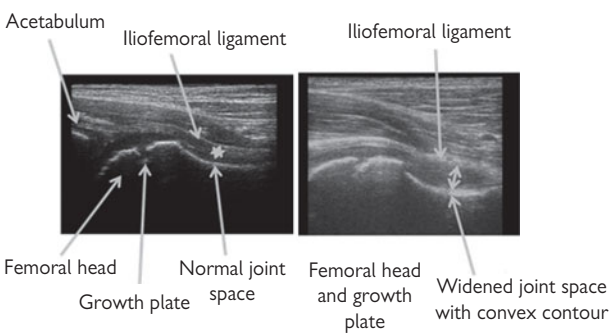

Fig. 1.4 Effusion at the hip joint compared to a normal hip.

- Fig. 1.4 demonstrates an effusion in a hip joint compared to the normal contra-lateral normal hip. Note the convex appearance of the Iliofemoral ligament and the ↑ joint space.

Pitfalls of MSUS in children

- Cartilage appears hypoechoic, similar to joint fluid. Thus pathology can be over diagnosed; the non-compressibility of cartilage compared to fluid is an important difference to help discriminate.
- The hypoechoic appearance of growth plates can mimic fractures and erosions; knowing anatomy relative to age and always viewing in 2 planes is essential.
- Nutrient arteries, especially around growth plates, can mimic synovitis; knowing the normal appearance of epiphysis and comparing the contralateral side can be very helpful.
- MSUS findings are user dependent; standardizing procedures and comparing findings between observers is therefore important. More work is needed in this area of research.
- There is currently limited published information on the appearance of joints in healthy children; normative data and images are being collated in research studies.

Further reading

British Society for Rheumatology ultrasound courses: http://www.rheumatology.org.uk/education.
EULAR musculoskeletal imaging and courses: http://www.eular.org.
Mc Nally EG. *Practical Musculoskeletal Ultrasound.* Philadelphia, PA: Elsevier, 2005.
Wakefield RJ, D'Agostino MA. *Essential Applications of Musculoskeletal Ultrasound in Rheumatology.* Philadelphia, PA: Saunders, 2010.

Autoantibodies

Antibodies are immunoglobulins produced in response to an antigen and form an important part of the adaptive immune system and our humoral response to infection. Autoantibodies are formed in response to self-antigens. The presence of autoantibodies does not imply or inevitably result in autoimmune diseases, although in some autoimmune diseases the associated antibodies are directly involved in the pathogenesis e.g. anti-glomerular basement membrane (GBM) disease; myasthenia gravis; and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. This chapter describes some of the important and/or frequently observed autoantibodies in paediatric rheumatology.

Anti-neutrophil cytoplasmic antibodies

(see 🕮 The ANCA-associated vasculitide, p 188)

- Antibodies against lysosomal enzymes in neutrophils and (to a lesser extent) monocytes.
- The main enzymes targeted are myeloperoxidase (MPO) and proteinase 3 (PR3), however other antigens may also be targeted.
- There are 2 main patterns of staining detectable by indirect immunofluorescence: perinuclear (pANCA) and cytoplasmic (cANCA).
- About 90% of cANCA is directed against PR3 (PR3-ANCA) and 70% of pANCA is against MPO (MPO-ANCA).
- PR3-ANCA is commonly seen in Wegener's granulomatosis; although it can be detected in some cases of microscopic polyangiitis.
- MPO-ANCA is typically associated with:
  - Microscopic polyangiitis.
  - Churg–Strauss syndrome (occasional).
  - Idiopathic renal limited pauci-immune glomerulonephritis.
- ANCAs are not 100% specific for the ANCA-associated vasculitides: they can also be positive in chronic infections or malignancy including tuberculosis, HIV, and Hodgkin's lymphoma. Atypical ANCA (BPI-ANCA) are sometimes observed in cystic fibrosis, and are not necessarily associated with vasculitis in that scenario.
- Atypical pANCA are detected in some forms of inflammatory bowel disease and may be associated with sclerosing cholangitis, and can also be drug induced.

Antinuclear antibodies (ANAs)

- ANAs are directed against the cell's nuclear contents. Titres vary between laboratories but are usually reported to be 'positive' at 1:40–1:80. In clinical practice titres may be significant at 1:320 or higher.
- A positive ANA titre alone is not diagnostic of a specific condition, nor is ANA necessarily a useful screening test for autoimmune disease. A positive ANA can be found in up to 15% of normal children.
- A positive ANA can be associated with a variety of conditions including:
  - SLE
  - Drug-induced lupus
  - Undifferentiated connective tissue disease
  - Sjögren's syndrome

  - Juvenile dermatomyositis
  - Scleroderma and systemic sclerosis
  - Morphoea
  - JIA, particularly those who have (or may develop) uveitis.
- Positive ANA is rare in systemic juvenile idiopathic arthritis (sJIA).
- ANA can also occur in immunoglobulin A (IgA) deficiency, viral infections, neoplasias and may also be drug-induced.

Anti ds-DNA antibodies

- These autoantibodies are highly specific for SLE and are seen in the majority of children with lupus nephritis. Titres can be useful in monitoring disease activity however they do not always correlate with disease activity in all patients.

Rheumatoid factor and anti-cyclic citrullinated protein (anti-CCP) antibodies

- Classic RF is IgM directed against IgG. RFs of other immunoglobulin isotypes have been reported but their significance is uncertain.
- <10% of children with JIA are RF+ve. Those who are positive, are usually older girls with a polyarticular disease course.
- RF can also be positive in SLE and in a minority of patients with systemic sclerosis.
- RF may also be elevated as an acute phase reactant, for example in bacterial endocarditis, and so a positive result should be confirmed by repeating.
- Anti-CCP antibodies are also found in children with RF+ve polyarthritis.
  - Anti-CCP antibodies are less prevalent in JIA than adult RA but are detectable in a significant proportion of RF+ve patients with polyarticular-onset JIA.
  - There may be a significant relation between anti-CCP positivity and erosive joint disease in polyarticular RF+ve JIA.

Antiphospholipid antibodies (see 🕮 Antiphospholipid syndrome (APS), p 279)

- These are a heterogeneous group of antibodies which bind to phospholipids in the cell membrane and include IgG and IgM anticardiolipin (ACL) Ab, and beta 2-glycoprotein 1 antibodies. The lupus anticoagulant (LAC) is typically measured using the dilute Russell viper venom assay (see 🕮 Antiphospholipid syndrome (APS), p 279).
- May be positive in 1° antiphospholipid syndrome, SLE, some vasculitides, viral infections (often associated with transient ACL positivity), drug induced, and up to 8% of the normal population.
- Not all ACL are pathogenic, nor is the mechanism of ACL pathogenicity fully understood. This is an area of ongoing research.

Anti-C1q antibodies

- Cause low C1q and are seen in almost all patients with hypocomplementaemic urticarial vasculitic syndrome (HUVS), but also in a variety of other autoimmune conditions such as SLE.

Extractable nuclear antigens (ENAs)

- A number of ENAs have been identified. In fact not all ENAs are truly nuclear, some can be directed against cytoplasmic components. The following may be present in paediatric rheumatology patients (Table 1.12).

Table 1.12 Common ENAs in paediatric rheumatology

Antibody	Common disease association
Anti-RNP	mixed connective tissue disease (MCTD), SLE, scleroderma
Anti-histone	Drug-induced lupus
Anti-Smith	SLE—possible association with central nervous system (CNS) disease when present along with anti U1 RNP
SS-A/anti-Ro	SLE, Sjögren's syndrome
SSB/anti-La	Anti-Ro and anti-La are associated with recurrent spontaneous abortions, heart block in neonatal lupus and may be detectable in ANA−ve lupus.
Anti-SCL-70	Diffuse systemic sclerosis.
Anti-centromere	Systemic sclerosis and related disorders; may be associated with an ↑ risk of developing calcinosis and telangiectasia. May be a risk factor for developing pulmonary hypertension, gastrointestinal involvement, and Raynaud's phenomenon.
Anti-LKM	Some forms of autoimmune hepatitis
Smooth muscle antibodies	Post-viral infection; some forms of autoimmune hepatitis

Other autoantibodies

- There are many other organ-specific and non-organ-specific autoantibodies associated with paediatric autoimmune disease beyond the scope of this chapter.
- These include antibodies against components of the nephron and lung (notably anti-GBM antibodies); renal tubules; striated muscle; endocrine and reproductive organs; components of the brain (associated with the emerging and increasingly described autoimmune encephalopathies); peripheral nervous system (including myasthenia gravis); the gastrointestinal tract; skin; and many others.
- Not all of these fulfil Koch's postulates as the defined cause of the disease, although some are directly involved in the pathogenesis of the associated disease.

Thermography in rheumatic disease

Introduction

Thermography is a non-invasive technique able to detect infrared radiation and provide an image of the temperature distribution across the body surface. The skin temperature is influenced by the skin vasculature or by the conduction of heat generated in structures deeper to the skin surface and this can be detected by thermography.

Indications

- Assessment of inflamed joints.
- Response to cold challenge of the hands in Raynaud's phenomenon.
- Detection of disease activity and monitoring of treatment in scleroderma.

Preparation

- The environmental temperature should be 22–24°C.
- Patients should remove their clothing from the area to be examined for at least 15min prior to examination to balance the body temperature with the environment.
- The infrared camera should be allowed to acclimatize with the room temperature and be calibrated.

Techniques

- The infrared camera should be focused and the distance from the camera to patient should be recorded.
- A thermograph (static, single image) of the relevant lesion is taken.
- For comparison, images of the matching opposite site or surrounding skin are also taken.

Images and interpretation

- Images are analysed for skin asymmetries with corresponding opposite sites or surrounding skin. Lesions are considered active (or positive) on thermography and appear red when the affected area is more than 0.5°C warmer than the matching opposite limb or body site. Alternatively this can be 0.5°C warmer than the surrounding skin if bilateral sites are involved.
- In Fig. 1.5 the lesion on the right leg as indicated by the 3 arrowheads was clinically causing limb-length discrepancy. The corresponding thermal image prior to treatment shows ↑ temperature on the affected area representing an active lesion.
- Thermography can also be used after the onset of treatment, in which you would expect to see cooling of the initial 'hot', active lesion.

Limitations

- Changes in heat conduction through the skin from deep tissues in lesions associated with extensive subcutaneous atrophy can lead to 'false-positive' thermograms so older scleroderma lesions can often appear 'active' despite their clinical inactivity.
- Thermography is only a substitute measure of blood flow, laser Doppler techniques provides a direct measure of blood flow.

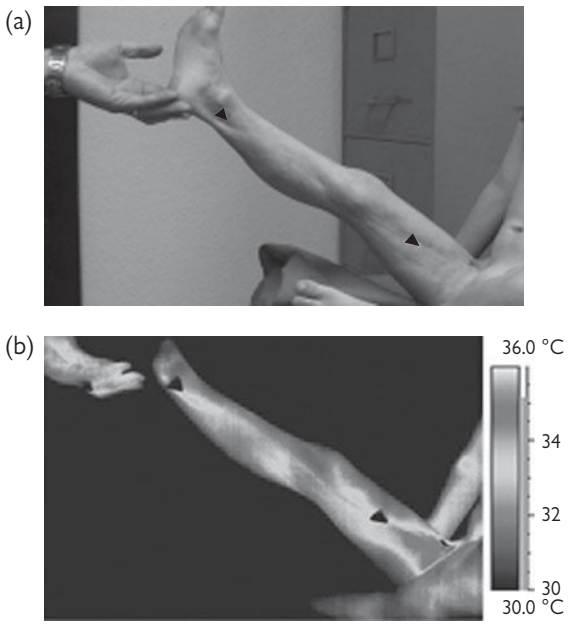

Fig. 1.5 (a) Clinical and (b) thermographic images of a patient with linear morphoea.

Nailfold capillaroscopy in rheumatic disease

Introduction

- Nailfold capillaroscopy is a useful, non-invasive investigation.
- Morphological changes of the finger nailfold capillaries (NFCs) can be directly visualized with magnification and appear to reflect microvascular abnormalities in many rheumatological conditions.
- Nailfold capillaroscopy can be employed when clinical features suggest an underlying connective tissue disease (CTD) or vasculopathy (Table 1.13).

Table 1.13 When to consider nailfold capillaroscopy

Underlying cause	Clinical features
Non-specific/ constitutional	Fever, anorexia, nausea, lethargy, easy fatiguability, non-specific pain, weakness
Raynaud's phenomenon (RP)	Primary Raynaud's disease: if RP occur in the absence of a definable underlying disease Secondary Raynaud's syndrome: if RP is associated with a connective tissue disease/vasculopathy
Juvenile dermatomyositis (JDM)	Muscle weakness, heliotrope rash, Gottron's papules
Progressive systemic sclerosis/scleroderma	Raynaud's syndrome, peripheral skin tightening and ulceration, respiratory symptoms, abdominal pain, malabsorption
Other vasculopathy/ vasculitis	(Although many do not appear to have prominent nailfold capillaroscopy abnormalities)
SLE and undifferentiated CTD	Fever, malaise, joint pain, myalgia, fatigue, malar rash

Preparation

- The environmental temperature should be 20–24°C.
- Both hands must be uncovered at least 30min before the examination to balance the body temperature with the environment.
- Place a drop of water, immersion oil or aqua gel over the edge of the nailfold and look through this to reduce the reflections of the keratin layer.

Techniques

- Hand-held ophthalmoscope:
  - Set the magnification (dioptres) to at least +20 or preferably +40.
  - Use the 'non-ophthalmoscope' hand to hold the patient's fingertip and bring the ophthalmoscope to within about 0.5cm of the nailfold with the drop of fluid (typically KY-jelly) on it.
  - Small adjustments in the distance between the ophthalmoscope head and the nailfold will bring the capillaries into sharp focus.

- Hand-held dermatoscope:
  - Easier to use than a hand-held ophthalmoscope and can be attached to a digital camera, but does not give as much magnification (×10)
  - 2 types: either an oil immersion (technique as for ophthalmoscope) or cross-polarized dermatoscope which can be placed directly on the nailfold.
- Direct capillaroscopy using a dissecting stereomicroscope (such as an Olympus SZ-40).

Images and interpretation

6 parameters aid more precise definition:

- Capillary density, capillary width, capillary tortuosity, visible avascular areas, capillary disarrangement, number of abnormal vessels (Fig. 1.6a–e).

Healthy children (HC) have a lower density of capillaries than healthy adults (HA) (Fig. 1.7). JDM and scleroderma (grouped as CTD) demonstrate significantly reduced capillary density compared with HC and other childhood rheumatological diseases (JIA, SLE, primary Raynaud's disease, (RD) and vasculitis).

Limitations

- If the patient has 'vertical capillary loops,' as marked abnormalities can only be visualized if present in the horizontal plane.
- Fingernail/cuticle biters may traumatize the nailfold and disrupt the capillary appearance.
- It is unclear whether nailfold capillaroscopy is useful for disease monitoring. Some patients with a previous CTD may continue to have abnormal NFCs for years after disease remission.

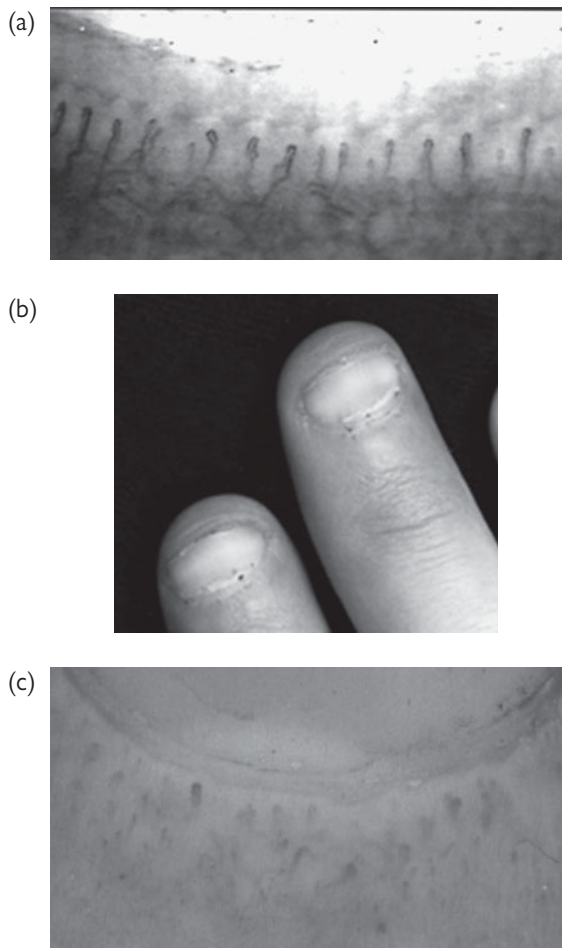

Fig. 1.6 (a) Nailfold capillaries. Normal pattern of NFCs (original magnification ×66). Regular pattern of thin 'hairpin' loops. There is an uncommon normal anatomical variation where the capillaries loop more vertically up towards the surface of the skin, so the horizontal 'hairpin' appearance may not always be seen. (b) Naked eye view. Note the tiny red dots on the nailfolds. (c) Hand-held ophthalmoscope at +40 dioptres. Note irregular size and pattern of capillaries.

(d)

(e)

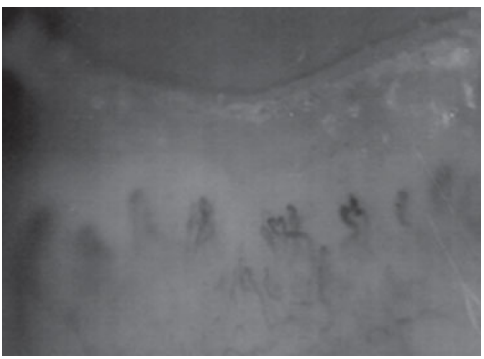

Fig. 1.6 (*continued*) (d) Abnormal NFCs (original magnification x66). Dilated capillaries with reduced number in the field of view.
(e) Abnormal NFCs (original magnification x66). Abnormal 'bushy' shapes and bare areas suggesting capillary drop out.

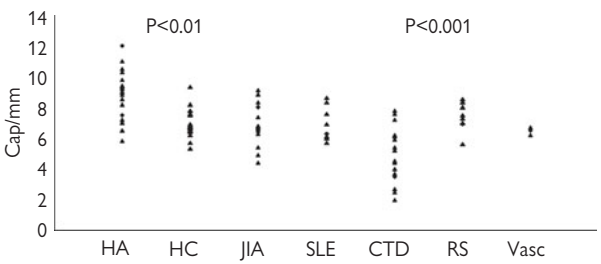

Fig. 1.7 Differences in nailfold capillary density in childhood rheumatic diseases. Reproduced from Dolezalova P, Young SP, Bacon PA, *et al*. Nailfold capillary microscopy in healthy children and in childhood rheumatic diseases: a prospective single blind observational study. *Ann Rheum Dis* 2003; **62**:444–9.

Outcome measures in paediatric rheumatology

When it is not possible to cure a disease, it is important to determine how far treatment and disease compromise the child's quality of life (QoL). Measures of disease activity and pain guide immediate intervention, but broader holistic assessments of mental, physical, family, and social functioning, life satisfaction, and well-being are outcomes ultimately valued by the patient and family. Since there is a degree of subjectivity, each measure has to be reliable (repeatable on more than one occasion), valid (asks the right questions), and responsive (sensitive to true changes in patient's condition to guide effective care). A summary of the outcome measure often used in paediatric rheumatology is given in Table 1.14.

The ***American College Rheumatology (ACR) Core Outcome Variables*** are the standard composite measure for disease activity in juvenile arthritis, used successfully in most drug trials of JIA since defined in 1997. The 6 variables are:

- Active 71-joint count
- Restricted 71-joint count
- CHAQ
- Patient global and physician global assessments (10cm visual analogue scales: 0cm = well; 10cm = unwell)
- ESR.

Improvement is defined as 30% improvement from baseline in 3 of 6 variables (so called ACR30) with no more than one of the remaining variables deteriorating by more than 30%. ACR50 and ACR70 represent greater levels of improvement and the criteria can be used to define flares of arthritis (worsening in 2 variables by 40%). The most responsive measure is the physician global assessment of disease activity, and active joint count. Least responsive is the CHAQ and ESR/CRP. The JADAS, a modification of the variables, provides a numeric score.

Table 1.14 Outcome measures in paediatric rheumatology

Outcome measure	Components/scope	Comments
Disease activity		
ACR core outcome variables	Standard assessment in JIA assessing 6 variables (see 🕮 Outcome measures in paediatric rheumatology, p 41)	
Juvenile Arthritis Disease Activity Score (JADAS-27)	Composite score of physician VAS, parent/patient VAS, active 27-joint count and normalized ESR	Scored out of 57. Other JADAS versions available (see 🕮 Disease activity scores in rheumatoid arthritis and JIA, p 165)

(*continued*)

Table 1.14 (*Contd.*)

Outcome measure	Components/scope	Comments
Childhood myositis assessment scale (CMAS)	14-item quantitative assessment of muscle strength and endurance. Used in JDM along with global assessments of activity and CHAQ	Scored out of 53. Requires trained personnel. Manual myometry testing may be an alternative (see 🕮 Juvenile dermatomyositis, p 266)
British Isles Lupus Assessment Group index (BILAG)	Scoring based on the physicians intention to treat and used in association with biological data and global assessments	BILAG has been adapted for paediatric use. An alternative is to use SLEDAI (see 🕮 British Isles Lupus Assessment Group (BILAG) 2004 Index, p 248 and Table 4.11)
Paediatric vasculitis activity score (PVAS)	Scoring based on the physicians intention to treat	Adapted from the adult BVAS (Birmingham Vasculitis Activity Score) tool and validity is being assessed
Damage measures		
Juvenile arthritis damage index (JADI)	Assesses articular (36 joints) and extra-articular (5 organs including eyes) damage	
Systemic Lupus International Collaborative Clinics (SLICC)	See lupus section (🕮 SLICC/ACR Damage Index (paediatric), p 258)	
Paediatric vasculitis damage index (pVDI)	Cumulative index of items persisting for 3 months or more	Adapted from VDI and validity is being assessed
Physical function		
Childhood health assessment questionnaire (CHAQ)	Standard tool. Takes 10min to complete 8 domains, focusing on disability and discomfort. Easy to score and interpret (see 🕮 The Child Health Assessment Questionnaire (CHAQ), p 45)	Translated in to many languages. Forms for child (8–19yr) & parent (patient 2–19yr). Insensitive to short term changes in children.
Juvenile arthritis functional assessment scale (JAFAS)	Comprehensive assessment of function in children >7yr using 10 timed tasks	Requires standardized equipment and trained health professionals. Responsiveness not known

Table 1.14 (*Contd.*)

Outcome measure	Components/scope	Comments
Juvenile arthritis functional assessment report (JAFAR)	23-item evaluation of both child (>7yr) and parent reports	
Juvenile arthritis functionality scale (JAFS)	Short 15-item questionnaire of function in lower limbs, hand/wrist and upper segment	Responsive and discriminative
Functional status measure FSII (R)	Health status (eating, play behaviour, sleep, and emotional health) of children 0–16yr	
Child activity limitations interview (CALI)	Assesses impairment due to recurrent pain in school age children and adolescents	
Health status and quality of life		
Child health questionnaire (CHQ)	Domains in health perception, function, behaviour, mental health, impact on parents, family cohesion, limitations in family activity, activities with friends, change in health, bodily pain, school, work, self-esteem	Adapted from the SF-36. Sensitive to clinical change in children with JIA
Paediatric Quality of Life Inventory (PedsQoL)	A quick (23-item) measure for healthy and sick children aged 2–18yr assessing physical, emotional, social and school functioning	Versions for both parents and children. A PedsQL rheumatology module takes 10–15min
Juvenile arthritis quality of life questionnaire (JAQQ)	Disease specific measure of physical and psychosocial function	Successful in adolescents
EQ5D (EuroQoL)	Generic health utility index extensively used in adult studies	Valid for JIA

VAS, visual analogue score.

Interpretation of outcome measures needs to consider a child's changing cognitive skills, needs, and expectations and a parent's physical and emotional well-being, relationships, and adjustment. Parents are used as proxy respondents and the level of parent/child agreement varies for disability, pain and QoL with good correlation for CHAQ. Adolescents are less positive than parents about health and well-being. Parent and physician reports tend to agree in 70% of cases with over-rating by parents in 20% (typically due to pain intensity) and over-rating by physician in 12% (typically rated to CRP and a number of active joints). Other problems include ceiling and floor effect, e.g. a patient may continue to improve or deteriorate but the test does not capture this change.

Further reading

Moorthy LN, Peterson MG, Harrison MJ, *et al.* Physical function assessment tools in pediatric rheumatology. *Pediatr Rheumatol Online J* 2008; **6**:9.

Ruperto N, Ravelli A, Falcini F, *et al.* Performance of the preliminary definition of improvement in juvenile chronic arthritis patients treated with methotrexate. Italian Pediatric Rheumatology Study Group. *Ann Rheum Dis* 1998; **57**:38–41.

The Child Health Assessment Questionnaire (CHAQ)*

* Adapted from Singh G, Athreya B, Fries J, *et al*. Measurement of health status in children with juvenile rheumatoid arthritis. 1994. *Arthritis Rheum* **37**:1761–9.

CHAQ scoring (see Table 1.15)

1. Each of the 8 sections or scored for the highest value tick in its own section

- 0 for 'without any difficulty' or 'not applicable'
- 1 for 'with some difficulty'
- 2 for 'with much difficulty'
- 3 for 'unable to do'

2. Then look at the section that refers to help required by aids or devices or another person

- If any of these are ticked look at the section that the comment refers to.
- If that section is scored a 0 or 1 than increase it to a 2.
- If that section scored 2 leave it as a 2.
- If that section scored 3 leave it as a 3.

3. Add the eight totals and divide that total by 8 (see Table 1.16) to derive the CHAQ score (0–3)

4. In addition, pain and general evaluation are scored on a 10cm visual analogue score were 0 signifies no pain and normal functioning, and 10 signifies severe pain and severe limitation of functioning.

Table 1.15 Childhood Health Assessment Questionnaire

PATIENT HOSP NO: DATE:
NAME:

In this section we are interested in learning how your child's pain affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please tick the one response which best describes your child's usual activities OVER THE PAST WEEK. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable". For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but not because he/she is RESTRICTED BY PAIN or ILLNESS, please mark it as "NOT Applicable".

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
DRESSING & PERSONAL CARE					
Is your child able to:					
- Dress, including tying shoelaces and doing buttons?	o	o	o	o	o
- Shampoo his/her hair?	o	o	o	o	o
- Remove socks?	o	o	o	o	o
- Cut fingernails?	o	o	o	o	o
GETTING UP					
Is your child able to:					
- Stand up from a low chair or floor?	o	o	o	o	o
- Get in and out of bed or stand up in a cot?	o	o	o	o	o

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
EATING					
Is your child able to:					
- Cut his/her own meat?	o	o	o	o	o
- Lift up a cup or glass to mouth?	o	o	o	o	o
- Open a new cereal box?	o	o	o	o	o
WALKING					
Is your child able to:					
- Walk outside on flat ground?	o	o	o	o	o
- Climb up five steps?	o	o	o	o	o

* **Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

- Walking stick	o	- Devices used for dressing (button hook, zip pull, long-handled shoe horn, etc.)	o
- Walking frame	o	- Built up pencil or special utensils	o
- Crutches	o	- Special or built up chair	o
- Wheelchair	o	- Other (Specify:_____)	o

* **Please tick any categories for which your child usually needs help from another person BECAUSE OF PAIN or ILLNESS:**

- Dressing and personal care	o	- Eating	o
- Getting up	o	- Walking	o

HYGIENE					
Is your child able to:					
- Wash and dry entire body?	o	o	o	o	o
- Take a bath (get in and out of bath)?	o	o	o	o	o
- Get on and off the toilet or potty?	o	o	o	o	o
- Brush teeth?	o	o	o	o	o
- Comb/brush hair?	o	o	o	o	o
REACH					
Is your child able to:					
- Reach and get down a heavy object such as a large game or books from just above his/her head?	o	o	o	o	o
- Bend down to pick up clothing or a piece of paper from the floor?	o	o	o	o	o
- Pull on a jumper over his/her head?	o	o	o	o	o
- Turn neck to look back over shoulder?	o	o	o	o	o
GRIP					
Is your child able to:					
- Write or scribble with pen or pencil?	o	o	o	o	o
- Open car doors?	o	o	o	o	o
- Open jars which have been previously opened?	o	o	o	o	o
- Turn taps on and off?	o	o	o	o	o
- Push open a door when he/she has to turn a door knob?	o	o	o	o	o

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To do	Not Applicable
ACTIVITIES					
Is your child able to:					
- Run errands and shop?	o	o	o	o	o
- Get in and out of a car or toy car or school bus?	o	o	o	o	o
- Ride bike or tricycle?	o	o	o	o	o
- Do household chores (e.g. wash dishes, take out rubbish, hoovering, gardening, make bed, clean room)?	o	o	o	o	o
- Run and play?	o	o	o	o	o

* **Please tick any AIDS or DEVICES that your child usually uses for any of the above activities:**

- Raised toilet seat	o	- Bathrail	o
- Bath seat	o	- Long-handled appliances for reach	o
- Jar opener (for jars previously opened)	o	- Long-handled appliances in bathroom	o

* **Please tick any categories for which your child usually needs help from another person BECAUSE OF PAIN:**

- Hygiene	o	- Gripping and opening things	o
- Reach	o	- Errands and chores	o

PAIN

- How much pain do you think your child has had IN THE PAST WEEK?
- Place a mark on the line below, to indicate the severity of the pain

No pain 0 _____ 100 Very severe pain

GENERAL EVALUATION: Considering all the ways that your child's pain or illness affects him/her, rate how he/she is doing by placing a single mark on the line below **(* Core assessment*)**

Very well 0 _____ 100 Very poor

Person/s completing questionnaire:- SCORE:

Mother ☐
Father ☐
Child ☐ Other ☐ Date of completion: _____

Table 1.16 Converting the CHAQ responses into a final score

Eighths	CHAQ score	Eighths	CHAQ score	Eighths	CHAQ score
1	0.125	9	1.125	17	2.125
2	0.25	10	1.25	18	2.25
3	0.375	11	1.375	19	2.375
4	0.5	12	1.5	20	2.5
5	0.625	13	1.625	21	2.625
6	0.75	14	1.75	22	2.75
7	0.875	15	1.875	23	2.875
8	1	16	2	24	3

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Chapter 2

Common and important clinical problems

Musculoskeletal presentations and non-accidental injury

Child maltreatment is common, serious, and can be fatal. The true incidence of child abuse is difficult to ascertain (and it is probably under-diagnosed and under-reported) but a national survey amongst 18–24yr-olds conducted in the UK reports a prevalence of 7% describing 'serious physical abuse' in their childhood years. Early detection and intervention may help to prevent further abuse and limit resulting damage to the child. It is therefore important that *all* medical staff who have contact with children are aware of the possibility of non-accidental injury (NAI) and consider this where there are features of concern and that professionals are familiar with the procedures to be followed if abuse or neglect is suspected.

Possible musculoskeletal presentations of NAI include:

- A child with a limp or loss of function of a limb, which may result from a fracture or soft tissue injury with no history of trauma or an inadequate history.
- Joint swelling which may be due to haemarthrosis resulting from trauma (although JIA is a much more common cause of joint swelling in childhood).
- Direct impact injury to fingers may cause fusiform swelling which may mimic symmetrical small-joint arthritis.
- Cold injury may produce redness and swelling of hands and feet.
- A history of inconsistent or unexplained symptoms or clinical findings may be indicative of factitious or induced illness (FII).

Conversely, NAI may occasionally be suspected in cases where the underlying cause is a rheumatological disease:

- Vasculitis or panniculitis presenting with bruising, purpura, or soft tissue swelling in the absence of a history of trauma.
- Henoch–Schönlein purpura should be identifiable by its characteristic evolution from urticarial lesions to purpura and by the associated abdominal pain and arthritis. The typical distribution is a symmetrical rash on the buttocks and lower limbs but the rash may occur elsewhere.
- Chilblains have been misdiagnosed as NAI.
- Infantile cortical hyperostosis or Caffey's disease may present with multiple areas of soft tissue swelling, bone lesions, and irritability in a young infant and has been mistaken for NAI.
- Degos disease is a rare occlusive vasculopathy that can present with subdural effusions and an ulcerative skin rash which may mimic cigarette burns.
- Remember children with rheumatological disease may also be subjected to abuse and considering safeguarding issues is an important role of the paediatric rheumatology MDT (see 🕮 The multidisciplinary team, p 378).

Features in the presentation suggestive or supportive of a diagnosis of NAI

- Usually, one single feature is not diagnostic of abuse, but it is the overall pattern of presentation that is suspicious.
- Vague, unwitnessed, inconsistent, discrepant history.
- Inappropriate carer response, e.g. delayed presentation.
- Previous or ongoing social concerns.
- Repeated presentations to A&E departments with episodes of poorly explained trauma.
- Features which may indicate ***neglect*** such as:
  - Inappropriate or dirty clothing
  - Failure to thrive,
  - Developmental impairment
  - Behavioural difficulties.
- ***Bruises*** in children should be assessed in the context of the child's medical and social history, developmental stage, and explanation given. Maltreatment may be suggested by bruises:
  - In children who are not independently mobile
  - Away from bony prominences
  - To particular sites, e.g. face, back
  - That are multiple and in clusters (e.g. fingertip bruises)
  - With imprint of implement.
- ***Fractures:*** no fracture in isolation is pathognomonic of child abuse. Features of concern include:
  - Fractures inconsistent with the developmental stage of the child or where there is an inadequate explanation as to cause.
  - Multiple fractures of different ages.

Principles of management of suspected NAI

- The child's welfare is paramount. In particular, the child's best interests over-ride other considerations such as confidentiality and the carer's interests.
- Discuss concerns with senior colleagues or the lead or designated professional for child protection.
- Record history and observations carefully.
- If you have concerns that a child may be being abused or neglected you have a responsibility to refer to children's social care so that a multi-agency assessment can take place.

Further reading

Cawson P, Wattam C, Brooker S, *et al. Child maltreatment in the United Kingdom: A study of the prevalence of abuse and neglect.* London: NSPCC, 2000. http://www.nspcc.org.uk/inform/research/findings/childmaltreatmentintheunitedkingdom_wda48252.html.

HM Government Department for children, schools and families. *Working together to safeguard children: A guide to inter-agency working to safeguard and promote the welfare of children.* London: DfE, 2010.

Welsh Child Protection Systematic Review Group. *Core-info: Bruises on Children.* Available at: http://www.core-info.cf.ac.uk.

Welsh Child Protection Systematic Review Group. *Core-info: Fractures in Children.* Available at: http://www.core-info.cf.ac.uk.

Malignancy and musculoskeletal presentations

- In childhood malignancies, it is estimated that up to 2/3 of children have musculoskeletal manifestations at initial presentation.
- Bone pain, myalgia, and articular symptoms such as arthritis and arthralgia are all well described.
- Malignancy can occasionally present with arthritis, mimicking JIA and should be excluded in all children with musculoskeletal complaints to avoid diagnostic delay.
- An incorrect diagnosis of JIA and resulting pre-treatment with corticosteroids or cytotoxic agents such as methotrexate (MTX) may cause difficulty with bone marrow interpretation and may even lead to a poor response to chemotherapeutic agents.
- It is reported that neoplasia accounts for 1% of referrals to paediatric rheumatology services. The majority of these malignancies are accounted for by leukaemias and lymphomas, but occasionally such musculoskeletal findings may occur as a result of solid tumours.

Leukaemia

- Leukaemia is by far the commonest form of cancer in children, accounting for 30% of all childhood malignancies, with acute lymphoblastic leukaemia (ALL) representing the majority.
- Arthritis is noted in >25% at presentation. Large joints are more frequently involved than small joints and an oligoarticular course more commonly reported than a polyarticular course.
- Distinguishing ALL from JIA can be difficult. Clinical and laboratory features that may help discriminate ALL from JIA are outlined in Box 2.1.
- Children with ALL and joint or bone disease often report intense continuous pain that is often out of context with clinical findings.
  - Affected children typically have exquisite tenderness across the metaphysis of the surrounding bones of the swollen joints.
- Progressive anaemia is the most common haematological change, with changes in platelet count and white cell counts (WCCS) less frequently seen.
- It is imperative to be aware that a normal/low WCC and normal blood film can be seen, especially in the early stages of ALL, and may remain normal for weeks and months after onset of joint symptoms.
- The pathognomonic leukaemic cells or blast cells are typically absent at the onset of the disease.
- Systemic features such as daily fever and hepatosplenomegaly can occur with all types of neoplasia and can mimic childhood rheumatic diseases such as systemic onset JIA and connective tissue disorders.

Box 2.1 Red flags! Features suggestive of malignancy rather than JIA

- Severe metaphyseal tenderness or other non-articular bone pain.
- Intense continuous pain and immobility.
- Nocturnal pain (especially if unilateral).
- Back pain.
- Absence of early morning stiffness.
- Low/normal WCC; low/normal platelet count; dropping Hb; normal serum ferritin with systemic features (rash, fever).
- Arthritis with raised LDH levels.*
- Abnormal blood film (not always present).
- Radiological findings of metaphyseal radiolucent bands, periosteal reaction, sclerotic and osteolytic lesions.

Presence of abnormal blood count and nocturnal pain has a sensitivity and specificity ≥85% for ALL.

*Raised LDH alone has a low sensitivity in distinguishing JIA from ALL.

Investigations

- Routine blood tests including: FBC and blood film, routine clinical chemistry (U&Es, LFTs, bone biochemistry), ESR, CRP.
- Serum LDH, uric acid.
- Plain film X-rays (Fig. 2.1).
- Bone marrow aspirate and trephine.

Management

- With the initiation of appropriate treatment for ALL, the associated arthritis will usually quickly resolve.
- The use of analgesia in the form of NSAIDs and supportive measures from physiotherapy and occupational therapy is beneficial particularly in the acute state of the illness, and can be particularly useful symptomatically whilst investigations are completed and definitive treatment started.

Lymphoma

- Musculoskeletal symptoms in association with lymphoma are less commonly seen than with ALL.
- Bone pain is the commonest feature described and a true arthritis is rarely seen.
- Non-Hodgkin and Hodgkin lymphomas can cause bone pain as a result of direct invasion of the cortex or marrow by the tumour leading to bone infarction.
- Other causes of bone pain result from hypertrophic osteoarthropathy that stimulates an acute and painful periostitis.
- Lymphomas need in particular to be excluded in those with suspected systemic onset JIA, as many overlapping clinical features exist such as arthralgia, fever, malaise, splenomegaly, and lymphadenopathy.
- The lymphadenopathy in lymphomas is often described as matted and may be more rubbery than that of systemic onset JIA, although these are not reliable distinguishing features.
- Abdominal/thoracic imaging (US/CT scan).

- Lymph node biopsy: ***lymph node removal by excision is preferred over needle biopsy, and should be performed in all patients where possible.***

Neuroblastoma

- The commonest solid tumour in toddlers and also the commonest tumours to occur outside the CNS in children are neuroblastomas.
- As 75% of children have metastatic disease including bone involvement at diagnosis, musculoskeletal symptoms (in particular bone pain) are frequently reported.
- Back pain in any young child or toddler is a cause for alarm and urinary catecholamines and catecholamine metabolites (VMA and HVA) are warranted in addition to imaging such as MRI.
- Lytic lesions may be visible on plain film x-ray as well as the other red flags outlined in Box 2.1.

Osteoid osteoma

See 🕮 Bone tumours, p 60.

Osteosarcoma

See 🕮 Bone tumours, p 60.

Further reading

Barbosa CM, Hilario MO, Terreri MT, *et al.* Musculoskeletal manifestations at the onset of acute leukaemias in childhood. *J Pediatr (Rio J)* 2002; **78**:481–4.

Cabral DA, Tucker LB. Malignancies in children who initially present with rheumatic complaints. *J Pediatr* 1999; **134**:53–7.

Robazzi TC, Mendonca N, Silva LR, *et al.* Osteoarticular manifestations as initial presentation of acute leukemias in children and adolescents in Bahia, Brazil. *J Pediatr Hematol Oncol* 2007; **29**:622–62.

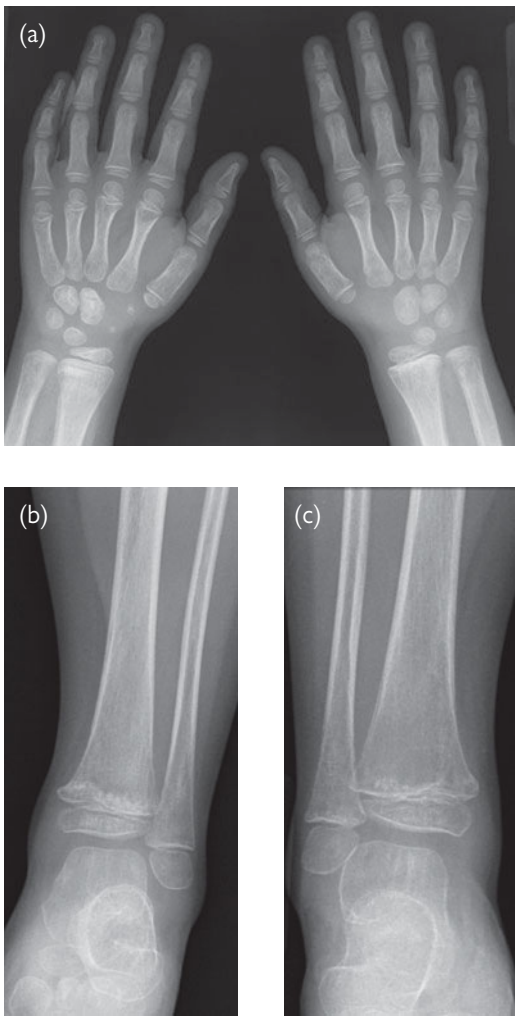

Fig. 2.1 X-ray images of ALL. The bones are osteopenic. There is periosteal reaction along both distal radius and ulna (a). There is patchy metaphyseal sclerosis and lucency of both wrists (a), also at both ankle joints (b, c). Faint periosteal reaction is visible along the lateral distal tibia (c).

Bone tumours

Presentation

Bone tumours (benign or malignant) can present with unexplained pain and swelling. Malignant bone tumours are rare but life threatening and early detection is important. The following clinical features may be present:

- Pain—worse at night.
- Swelling—initially soft-tissue oedema; later bony enlargement and soft tissue extension.
- Cachexia and weight-loss.
- Coincidental injury. Not causative but may bring attention to swelling.
- Pathological fracture through the lesion (5–10%).
- Rarely, symptoms of metastases to lung. Shortness of breath, chest pain, haemoptysis.

Principles of investigation and management

- Patients with suspicious lesions should be referred urgently to a specialist bone tumour MDT for biopsy (which requires careful planning) and further treatment. *Referral should not wait for further imaging investigations.*
- Blood tests may show raised inflammatory markers (but not always), serum alkaline phosphatase or lactate dehydrogenase (LDH).
- Imaging:
  - Plain x-ray is mandatory and detects most 1° bone tumours.
  - MRI—delineates local extent of tumour, size of associated soft tissue mass, involvement of critical anatomical structures, skip lesions in malignant tumours, and allows biopsy planning.
  - CT and whole body isotope bone scan aid staging for malignant 1° bone and soft tissue tumour. Metastases occur most frequently in the lungs or lymph nodes.
  - US—helpful screening investigation for soft tissue masses, can confirm a diagnosis of benign lipoma or vascular malformation, and may also show intralesional calcification, e.g. in synovial sarcomas.
- Biopsies provide a histological diagnosis and tumour grading; they should be performed by the surgical team who will perform the definitive resection.
- Staging systems depend on the diagnosis, histological grade of the tumour, size of the tumour, and the presence or absence of metastases. Staging determines future management.

Malignant bone tumours (Fig. 2.2)

Most common malignant bone tumours are osteosarcoma (55%) and Ewing's sarcoma (35%). Chondrosarcoma is extremely rare in children (<5%).

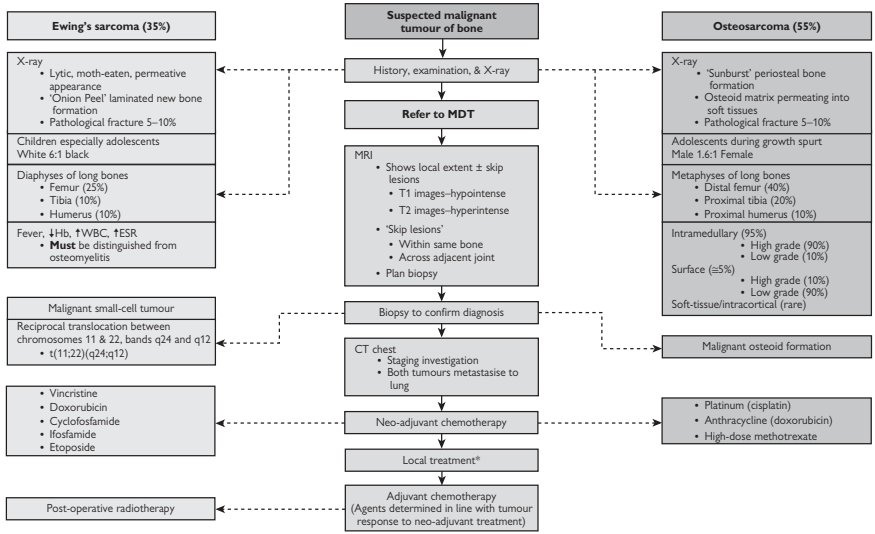

Fig. 2.2 Treatment algorithm for suspected malignant tumour of bone. *Surgery as mainstay of local treatment and the aim being complete removal of the tumour with a surrounding cuff of normal tissue. Limb-salvage surgery rather than amputation is performed in 90% of cases. Major long-bone defects are most often reconstructed with massive endoprostheses, and these can extend to accommodate for growth in children. Radiotherapy can be used as an adjunct to surgery in Ewing's sarcoma, or as the sole local treatment if surgical resection is not feasible.

Benign bone tumours (Fig. 2.3)

Benign bone tumours are more common than malignant lesions. However, urgent investigation and referral to an MDT must be initiated for any suspicious lesion.

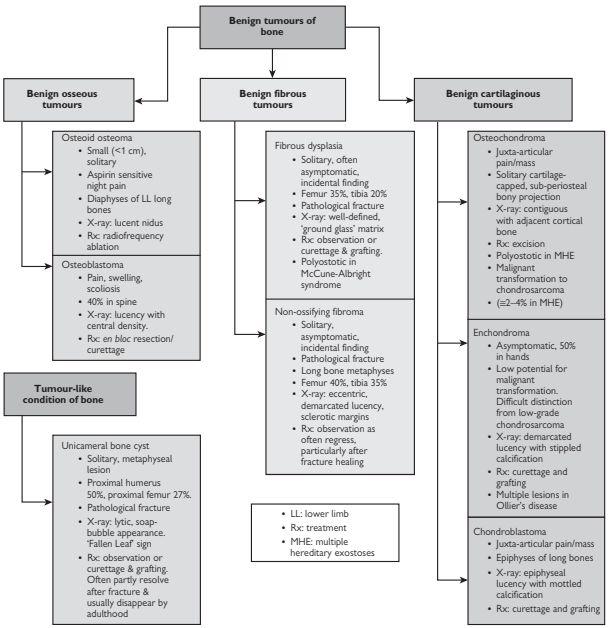

Fig. 2.3 Treatment algorithm for benign tumours of bone.

Soft-tissue sarcomas (Fig. 2.4)

- Although most soft tissue masses are benign, the following are 'red flags' suggestive of malignancy:
  - Lump increasing in size, lump deep to fascia, lump >5cm diameter.
  - Pain, often worse at night.
  - Lump recurring after previous excision.
- Paediatric soft tissue sarcomas are usually classified as rhabdomyosarcomas or non-rhabdomyosarcomas.
- Non-rhabdomyosarcomas are a rare but heterogenous group of tumours in children. Chemotherapy is usually given for malignant tumours.

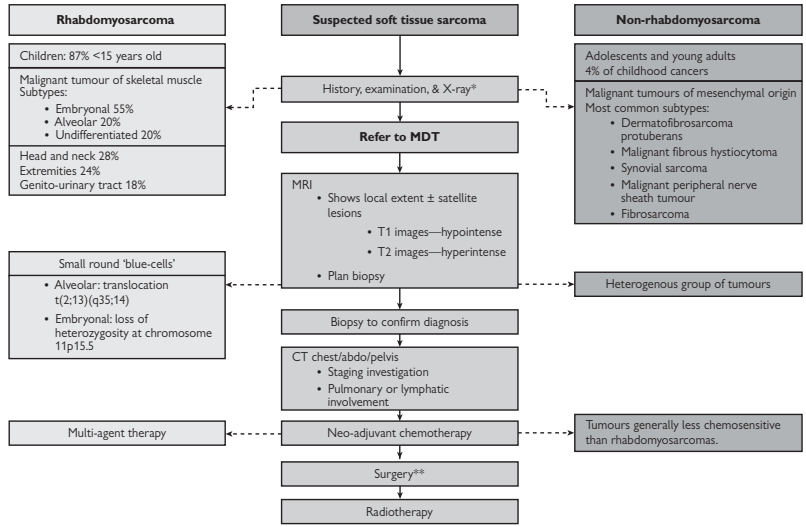

Fig. 2.4 Treatment algorithm for suspected soft tissue sarcoma. *X-rays are mandatory to rule out soft tissue extension of bony tumours and may also show intralesional calcification, e.g. in synovial sarcomas. **The aim of surgery must be complete removal of the tumour with a surrounding cuff of normal tissue. In extremity tumours, limb-salvage surgery is usual but complete removal must not be jeopardized to achieve this.

Bone and joint infections

Septic arthritis and osteomyelitis

- Incidence—2–10 per 100,000 in the general childhood population.

Bacterial infection of the bone or joint should be suspected in infants or children with acute onset of:

- Fever
- Unexplained limp (see 📖 The limping child, p 80) and/or abnormal posture/gait and/or reluctance to use the limb, inability to weight bear, and complete or partial limitation of movement on examination.
- Musculoskeletal pain ± presence of local bone or joint tenderness, bone or joint swelling, erythema ('hot, swollen, joint'), or pain on passive motion of the joint.

- Septic arthritis and osteomyelitis may occur separately or together, may affect 1 or many joints, and the clinical presentation depends on the organism and host immunity. Infants may not appear unwell, and may not always have a high fever. Careful comprehensive examination must be undertaken by a clinician experienced in the assessment of joints.
- Prognosis: usually good unless the diagnosis is delayed.

Septic arthritis

- Septic arthritis is an infectious arthritis of a synovial joint, and is a ***medical emergency***.
- The frequency is highest in young children; 50% of all cases present in first 2 years of life with a greater tendency in boys (2:1). Most common joints (75%) affected in lower limb (knee >hip >ankle). Approximately 25% infections affecting the upper limbs.
- Bacteria may reach the joint:
  - Through haematogenous spread (most common route for bacterial joint infection).
  - By direct penetration (e.g. through the skin).
  - Or by local spread from an adjacent infected site.
- Neonates and infants are at high risk of ***septic arthritis*** developing from osteomyelitis, as infection can spread easily from the metaphysis via the patent transepiphyseal vessels.

Most common pathogens for both septic arthritis and osteomyelitis

- <12 months old: *Staphylococcus aureus*, Group B *Streptococcus*, Gram-negative bacilli.
- 1–5 years: *Staphylococcus aureus*, Group A *Streptococcus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Enterobacter (osteomyelitis)*.
- 5–12yr: *Staphylococcus aureus*, Group A *Streptococcus*.
- 12–18yr: *Staphylococcus aureus*, *Neisseria gonorrhoea*.

Osteomyelitis

- Osteomyelitis is infection of bone.
- The frequency of osteomyelitis is greatest in infants. 1/3 of all cases occur in the first 2 years of life. Half of all cases occur by 5 years of age. Boys >girls (2:1)
- Often preceded by history of trauma in the affected extremity.
- Infection is usually seen in the metaphyseal region of bones.
- Most infections are spread via the haematogenous route from a 1° site of entry (e.g. respiratory, ear, nose, or throat, skin). Infection may also occur by direct inoculation (open fractures, penetrating wounds) or local extension from adjacent sites.
- In the neonate or infant ***transepiphyseal*** vessels are patent and infection may spread to the adjacent joint causing a septic arthritis.
- Organisms are not always isolated. The yield for bacterial growth from synovial fluid and bone aspirate is usually poor.

Types of osteomyelitis

- Acute.
- Subacute (2–3 weeks' duration).
- Chronic: may develop sequestrum and involucrum.
- *Bone abscesses* may develop with surrounding thick fibrous tissue and sclerotic bone (Brodie's abscess).
- Chronic recurrent multifocal osteomyelitis (CRMO, see 🕮 Chronic recurrent multifocal osteomyelitis, p 297).

General principles of management for bone and joint infections

- Prompt diagnosis, adequate and urgent washout, and drainage of joint is required followed by immediate institution of appropriate antibiotics are important to optimize outcome.
- Assessment and management should involve on-call teams for paediatrics, orthopaedics, and microbiology and be guided by local policy for clinical service and antibiotic use. Consideration of antibiotics to cover MRSA or Panton–Valentine leukocidin (PVL) producing *Staphylococcus aureus* may be warranted in certain clinical situations.
- Early referral to orthopaedic team for consideration of irrigation and debridement of the affected joint, and drainage of any associated osteomyelitis. Joint washout and drainage generally always requires a general anaesthetic. Orthopaedic opinion should be sought early to clarify if an aspiration of bone or bone biopsy should be taken, *before* instituting IV antibiotics.
- Empirical IV antibiotics (penicillin and cephalosporin) while awaiting cultures. General current practice is IV antibiotics for up to 3 weeks (until inflammatory markers normalize), followed by oral antibiotics for a total of 4–6 weeks. There is no evidence comparing long versus short courses of antibiotics.
- Appropriate analgesia and anti-inflammatory medication is required. The affected joint should be rested until there is clinical improvement and pain has settled.

- Early physiotherapy assessment is important to guide mobilization as appropriate.
- Investigations:
  - Joint aspiration with Gram-stain microscopy and culture of synovial fluid. (Consider mycobacterial infection; see 📖 Tuberculosis and mycobacterial disease, p 356.)
  - Inoculating blood culture bottles directly with synovial fluid improves yield and may be helpful for isolating certain bacteria.
  - PCR (polymerase chain reaction) on synovial fluid or of synovial tissue may be useful if other cultures have been negative.
  - Blood cultures (ideally, 3 sets over 3 days, always worthwhile; repeat blood cultures if reinserting a cannula in a child).
  - FBC, ESR, CRP can be helpful in the assessment; for bacterial infections, expect WCC to be raised with neutrophilia, and moderately raised CRP. CRP is a better predictor than ESR for acute infection. If high at beginning as a baseline marker, they may be helpful with assessment of progress (resolution towards normal indicating improvement); however, blood tests are *not* diagnostic of septic arthritis, they can only guide management with assessment of the clinical situation.
- Imaging:
  - X-ray—may be normal initially; may show fluid or soft tissue swelling; or widened joint space. Bony changes may not be evident for 14–21 days.
  - USS joint—may show effusion and can guide joint aspiration.
  - MRI—useful if diagnosis unclear or osteomyelitis suspected. Sensitive to early changes and very useful in suspected vertebral osteomyelitis.
  - Radionuclide bone scan (showing ↑ uptake) can be useful if MRI unavailable.

Pointers towards septic arthritis

Kocher proposed clinical prediction scores based on 4 independent factors to differentiate septic arthritis from transient synovitis (Box 2.2).

Box 2.2 Four factors used to predict septic arthritis*

- Fever >38.5°C.
- Non-weight-bearing *or* pain with passive motion of the joint.
- ESR: >40mm/h.
- WCC: >12 × 10^9.

Probability of septic arthritis with the number of predictors present:

Number of factors	*Probability*
0	<0.2%
1	3.0%
2	40.0%
3	93.1%
4	99.6%

*Kocher MS, Zurakowski D, Kasser JR Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. *Bone Joint Surg Am* 1999; **81**(12):1662–70.

Reactive arthritis

- Definition—reactive arthritis is an aseptic acute inflammatory arthritis occurring with, or following, an intercurrent infection, without evidence of the causative organism in the joint. Should be suspected where >1 joint affected and clinical presentation includes potential source of extra-articular infection.
- The infectious agent responsible for triggering the arthritis is generally outside the joint. For agents commonly associated with reactive arthritis, see Table 2.1.
- Reactive arthritis can occur at any age. Reactive arthritis typically follows 7–10 days after an episode of gastroenteritis (young children), typically involves lower limb large joints (knee >ankle >hip) and there is an association of this type of arthritis with HLA B-27 positivity. Acute phase reactants are usually raised (often very high), blood cultures and autoantibodies are negative and the diagnosis may rest on serology or urethral or stool cultures.
- In adolescents, it is important to differentiate reactive arthritis (following an episode of sexually-acquired urethritis from gonococcal arthritis or *Chlamydia* infection. Reiter's disease/syndrome is former terminology used to describe the triad of urethritis, conjunctivitis, and arthritis. Patients may have multiple infections (*Chlamydia*, *Gonococcus*, and HIV).
- Investigations in suspected reactive arthritis:
  - Acute phase reactants
  - Cultures:
    - — Blood
    - — Stool (*Shigella*, *Salmonella*, *Yersinia*, *Campylobacter*)
    - — Urethral (*Gonococcus* [Gram negative], *Chlamydia*)
    - — Synovial fluid (Gram stain and culture)
    - — Throat swab (*Streptococcus*)
  - Serology:
    - — *Salmonella*, *Yersinia*, *Campylobacter*
    - — ASOT and anti-DNAseB (streptococcal infection) seeTables 2.1 and 2.9.
  - HLA B27.
- Management involves establishing a diagnosis and excluding infection, symptoms control with NSAIDS, analgesia, and early physiotherapy involvement. Intra-articular steroid injection will be helpful with persistent arthritis (and once septic arthritis excluded).

Gonococcal arthritis

- Gonococcal arthritis may present as a septic arthritis associated with fever, rigors, skin lesions (macular rash, pustules, or blisters), tenosynovitis, and polyarthritis.
- The knee is the most commonly affected joint, but any joint may be involved.
- If suspected, Gram stain, and culture of synovial fluid, blood cultures, and any exudative lesions will be useful. The possibility of sexual abuse should be considered in a child with gonococcal arthritis.

Table 2.1 Pathogens associated with arthritis

Type	Organism	Organism associated with condition		
		Septic arthritis	**Osteomyelitis**	**Reactive arthritis**
Bacteria	*Staphylococcus aureus*	√	√	
	Streptococcus spp	√	√	√
	Group A	√	√	
	(Group B Strep in neonate)	√	√	√
	Streptococcus pneumoniae	√	√	√
	Salmonella			√
	Shigella			√
	Campylobacter			√
	Neisseria meningitidis, N. gonorrhoeae	√	√	√
	Brucella melitensis, canis	√	√	
	Chlamydia			√
	Mycoplasma pneumoniae (ureaplasma)	√		√
Mycobacteria	*Mycobacterium tuberculosis* (see 🕮 Tuberculosis and mycobacterial disease, p 356)	√	√	
Atypical mycobacteria*	*M. avium complex*	√		
	M. malmoense	√		
	(see 🕮 Tuberculosis and mycobacterial disease, p 356)			
Spirochaete	*Borrelia burgdorferi* (see 🕮 Lyme disease p 368)	√		√
Viruses	Parvovirus B19			√
	Rubella			√
Protozoa	*Toxoplasma**			√
	Giardiasis			√
Helminths	*Toxocara*	√		√
	Dracunculus			√
	Schistosoma	√		√
Fungi*	*Histoplasma*	√		√
	Cryptococcus	√		

*In the immunosuppressed patient (see 🕮 Tuberculosis and mycobacterial disease, p 356).

Further reading

Frank G, Mahoney HM, Eppes SC. Musculoskeletal infections in children. *Pediatr Clin North Am* 2005; **52**(4):1083–6, ix.

Mathews CJ, Kingsley G, Field M, *et al*. Management of septic arthritis: a systematic review. *Ann Rheum Dis* 2007; **66**(4):440–5.

Infections in the immunocompromised

Background

- Chronic inflammatory diseases are managed with a combination of immunosuppressive and anti-inflammatory agents, including steroids and disease modifying anti-rheumatic drugs (DMARDs) and recent novel biological agents have had significant impact on symptom relief and quality of life.
- However, in order to reduce inflammation, they inhibit innate and adaptive immune pathways, making patients increasingly susceptible to both serious and opportunistic infections.
- Although the benefits usually outweigh the risks, infectious complications need to be minimized by careful assessment prior to their commencement and close monitoring whilst on them.

- ***Serious infection:*** requiring treatment with IV antibiotics, needing hospitalization, or causing death.
- ***Opportunistic infection:*** causing infection only in the immunocompromised host or causing mild disease in normal hosts but disseminated, severe infection in the immunocompromised host.

At-risk populations

A lack of high-quality epidemiological data limits our current knowledge about the relative risks (RR) of serious and opportunistic infections in children receiving immunosuppressive and anti-inflammatory regimens. In addition, it is difficult to determine the relative contributions of the underlying disease itself, comorbidities, and immunosuppressive treatment. The following statements are consensus derived:

Corticosteroids

- Immunosuppressive if >2mg/kg given for over 1 week or 1mg/kg for over 4 weeks.
- Mechanism of action by inhibition of inflammatory transcription factors (NFκB), resulting in downregulation of proinflammatory cytokines and genes encoding T-cell growth factors.
- Cause broad cellular immunodeficiency, resulting in susceptibility to viral, bacterial, and fungal infections.
- Infection risk ↑ with higher doses and longer duration of treatment.
  - *It is important to use the lowest dose for shortest duration.*

DMARDs

- May be associated with significant risk of infection, particularly if neutropenia occurs.
- Numerous case reports of opportunistic infections:
  - PCP, reactivation of viruses (EBV, CMV, HSV, VZV).
- In descending order, the risk of infection is greatest with cyclophosphamide >corticosteroids >azathioprine >MTX >cyclosporine/mycophenolate mofetil (MMF).
- The infection risk ↑ when DMARDs are used in combination and/or neutropenia occurs.

Novel biological agents

- Various agents, including TNF-α inhibitors, IL-1 and IL-6 antagonists, T-cell co-stimulation modulators (CTLA-4 fusion proteins), and anti-CD20 agents are increasingly used (see 📖 Biologic therapies for paediatric rheumatological diseases, p 393), with well-defined mode of action of these agents allows potential infectious complications to be anticipated (Table 2.2).
  - The RR of infection associated with these agents is unknown in children although adult epidemiological data suggest higher rates of infection with novel biological agents compared to DMARDs. In descending order the risk is greatest with TNF-α inhibitors > IL-1R/IL-6R antagonists/anti-CD20 agents > T cell co-stimulation modulators.
  - The risk highest in the 1st year of treatment and markedly ↑ when used in combination and/or with conventional immunosuppressive therapy.
  - Infections include TB reactivation/infection (see 📖 Tuberculosis and mycobacterial disease, p 356), fungal infections, severe pyogenic bacterial infections, PCP, virus reactivation.

Strategies for managing severe and opportunistic infections (Fig. 2.5)

- Fever—may arise from infection or be caused by the underlying inflammatory pathology itself.
- Clinical presentation of infection may be altered by underlying disease/immunomodulatory therapy.
- Opportunistic infections—hard to recognize by virtue of their rare presentation but can cause significant morbidity and mortality.

Screening

- Prior to starting immunosuppressive therapy, patients should be screened for latent infections, especially TB.
- Thorough history to evaluate TB risk, varicella immunity, immunization status, and future travel plans; clinical examination to exclude active infections, including dental status and investigations including TB screening as per local guidelines, VZV serology, and FBC to exclude neutropenia or lymphopenia.

Vaccination

- Ideally vaccinate prior to commencing immunosuppressive therapy.
  - Vaccinate if varicella antibody status negative.
  - Consider vaccinating 1st-degree family members (history and/or serologically negative).
  - Ensure vaccination with Prevenar-13 as per the recommended childhood schedule.
  - Immunocompromised children should also receive a single dose of Pneumovax (23-valent polysaccharide vaccine) when aged >2yr.
  - Influenza vaccination recommended annually in the autumn.
- Avoid live vaccines; rest of childhood immunization schedule should be followed.
  - Live vaccines can be given once off steroid treatment for >3 months or other immunosuppression for >6 months.

- Give zoster immunoglobulin (ZIG) if significant exposure to chickenpox in non-immune patients, up to 7 days post-exposure. Immunoglobulin if significant contact with measles, irrespective of antibody status.

Prophylactic antimicrobials

- Treat active or latent TB prior to starting immunosuppressive therapy.
- Prophylaxis should be considered if the patient is neutropenic, lymphopenic, or living in an 'endemic' area (e.g. *Histoplasma*). Seek specialist paediatric infectious diseases advice.

Education

- Avoid foods associated with *Listeria* and *Salmonella* infection (unpasteurized milk, soft cheeses and undercooked eggs and meat). Avoid visits to zoo/animal farms.
- Ensure that parents recognize the early signs of infection and understand that urgent medical assessment is required (see 📖 Biologic therapies for paediatric rheumatological diseases, p 393 and 📖 The role of the clinical nurse specialist, p 380).

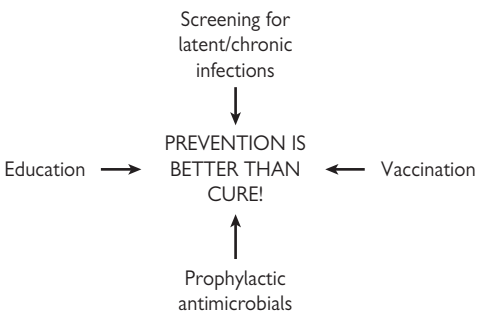

Fig. 2.5 Prevention of infection.

Table 2.2 The infectious complications and organisms associated with novel biological agents

Drug	TNF-α inhibitors	IL-1 antagonists	Anti-CD20 agents	T cell costimulation modulators	IL-6 antagonists
Most commonly used	Etanercept Infliximab Adalimumab	Anakinra Rilonacept Canakinumab	Rituximab	Abatacept	Tocilizumab
Infectious complications	Pneumonia UTI URTI incl. sinusitis Skin + soft tissue infections Musculoskeletal infections	URTI Pneumonia Cellulitis	Pneumonia UTI URTI Shingles	URTI inc. sinusitis Pneumonia Septicaemia Skin+soft tissue inf.	URTI Gastroenteritis
Organisms	*M. tuberculosis* NTM *Salmonella* spp. *Listeria* *Nocardia* *Candida* *Aspergillus* *Histoplasma* *Coccidioides* *Blastomyces* *Cryptococcus* Hepatitis B VZV CMV Toxoplasma	Bacteria ?VZV	Bacteria including *Staphylococcus* and *Pseudomonas* Enterovirus Hepatitis B Hepatitis C JC virus (risk of progressive multifocal leukoencephalopathy) VZV	VZV HSV Aspergillus Candida	EBV PCP

TNF, tumour necrosis factor; UTI, urinary tract infection; URTI, upper respiratory tract infection; NTM, non-tuberculous mycobacteria; VZV, varicella zoster virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; PCP, *Pneumocystis jiroveci* pneumonia.

The approach to the immunocompromised child presenting with fever

- Fever may be the only sign of serious infection, especially in the child with neutropenia.
  - ***Beware:*** TNF-α and IL-1/IL-6 inhibitors may 'mask' fever and an inflammatory response (i.e. CRP may be normal or only mildly elevated).
- Serious bacterial infections, invasive fungal infections, and disseminated viral infections must be distinguished from self-limiting viral infections.
  - Empirical treatment is often initiated until this distinction is made.
- The profile of infection (organism, severity) varies with the immunosuppressive therapy being used (especially for combinations).
  - The highest risk is in haematopoietic stem cell transplantation.
- The algorithm in Fig. 2.6 provides an approach for managing the immunocompromised child presenting with fever.

Important notes

Children with persistent musculoskeletal pain should have the following work-up considered:

- Complete/FBC with differential.
- Acute phase reactants (ESR, CRP).
- Routine serum chemistries (including creatinine, liver, and muscle enzymes).
- Urinalysis.
- Imaging studies (plain x-rays of involved area, other studies as indicated in the algorithm(s)).
- Testing for mycobacterial infection.

Caveats

- Minor trauma and infections are common in children and may not necessarily be related to the diagnosis.
- Remember infection, malignancy and non-accidental injury (child abuse) at each stage.

Further reading

RCPCH. Immunisation against infectious disease—'The Green Book', 2006; Best Practice Guidelines, Immunisation of the Immunocompromised Child. London: RCPCH, 2002. Available at: http://www.RCPCH.ac.uk/guidelines.

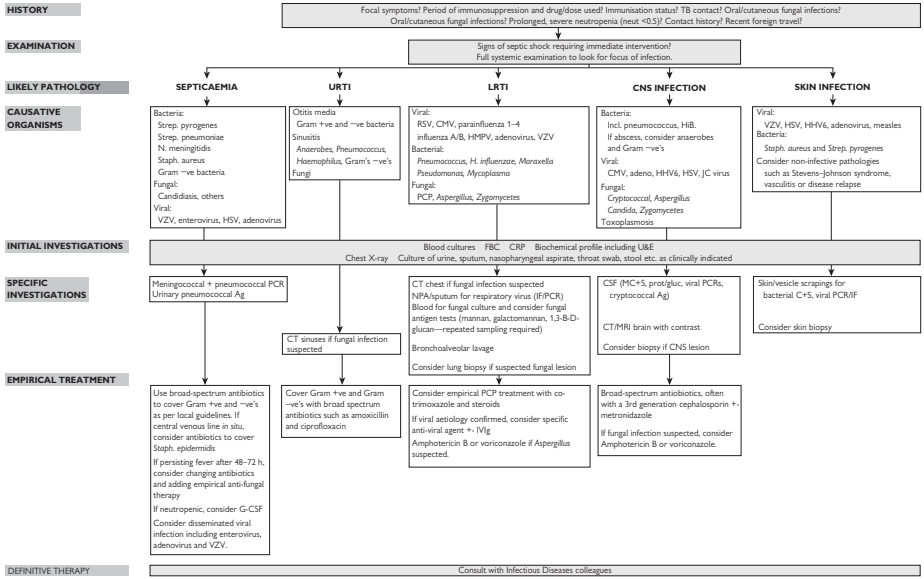

Fig. 2.6 The approach to the immunocompromised child presenting with fever.

Fractures in children and adolescents

See Tables 2.3–2.5.

Excluding fractures as a cause of pain

- Check for a history of injury, e.g. witnessed fall, pain immediately after fall.
  - Be alert for potential of NAI (see 📖 Musculoskeletal presentations and non-accidental injury, p 54)
  - Be alert for fragility fractures (see 📖 Metabolic bone diseases, p 330)
- In school age children and older, accurate palpation to determine site of pain, e.g. periarticular versus shaft of long bones, supracondylar humerus versus epicondyles, distal radius versus scaphoid.
- Imaging appropriately—focal x-rays are better than whole, long-bone x-rays. US scan and bone scan are not useful for detection of acute fractures. In young children with unossified epiphyses, an arthrogram under general anaesthesia is useful to exclude displaced intra-articular fractures.
- Interpret radiographs appropriately for the age—fractures can be confused with physes (growth plates), e.g. is the physis at the site of tenderness? Compare with normal age specific radiographs and x-ray contralateral limb for comparison.
- Growth arrest and subsequent deformity are most common following direct physeal trauma.
- The rate of complications is dependent on the type of fracture, the actual physis involved and the age of the patient (Fig. 2.7).
- Salter-Harris type IV and V fractures are more likely to cause bone bridge formation than types I–III (Fig. 2.8).
- The distal femur and proximal tibia are the most susceptible physeal plates to develop bone bridges following trauma.
- Peripheral growth arrest usually causes angular deformity and the management depends on the extent of the bone bridge. Whereas, central growth arrests usually cause leg-length discrepancy and 50% of the physeal plate may be resected and still allow continued longitudinal growth.

Table 2.3 Fractures in children: epidemiology

Age groups (yr)	Incidence number per 1000 children per year	Common mechanisms	Common fractures (prevalence %)*	
0–1 (infants and pre -walkers)	3.6	Non accidental injury (NAI) Fall below bed height	Clavicle	22.2
			Distal humerus	22.2
			Distal radius	11.1
			Radius & ulna shaft	11.1
			Tibia	8.9
2–4 (pre-school)	12.9	Fall below bed height NAI Falls down stairs	Distal humerus	22.0
			Distal radius	21.3
			Clavicle	15.0
			Radius & ulna shaft	9.5
			Finger phalanges	7.1
5–11 (school children)	23.2	Fall below bed height Sports blunt trauma Falls down stairs Trauma (road traffic accident [RTA])	Distal radius	40.3
			Finger phalanges	14.4
			Distal humerus	7.5
			Radius & ulna shaft	5.9
			Metacarpus	5.3
12–16 (adolescents)	26.6	Sports Fights Blunt trauma RTA Fall below bed height	Distal radius	28.0
			Finger phalanges	20.3
			Metacarpus	14.3
			Clavicle	7.0
			Metatarsus	5.3

*Rennie L, Court-Brown CM, Mok JY, *et al.* The epidemiology of fractures in children. *Injury* 2007; **38**(8):913–22.

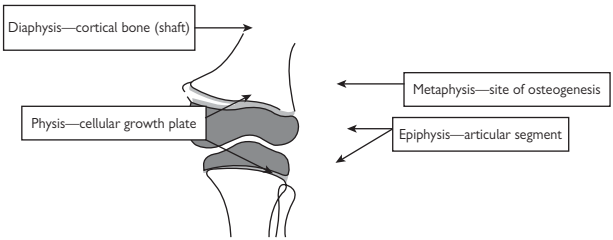

Fig. 2.7 Sites of fracture.

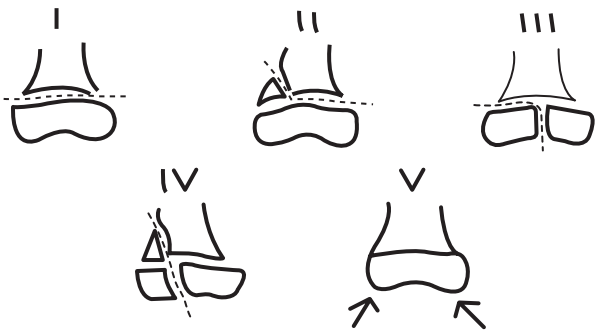

Fig. 2.8 Salter and Harris classification of fractures.

Table 2.4 Fractures in children: management

Principles of fracture management	Objectives	Options (depends on fracture site, rehabilitation requirements and surgeon's preference)
Reduction	Restores alignment and function Reduces pain	*Closed reduction*: general anaesthetic or local anaesthetic manipulation *Open reduction:* especially for intra-articular fractures.
Immobilization	Maintains alignment (after reduction) Reduces pain	*Non operative:* casts/splints *Operative*: percutaneous wires, plate & screws, intramedullary fixation, external fixation
Rehabilitation	Restores strength, range of motion and function	Mobilization Gradual return to activity Physiotherapy

Table 2.5 Fractures in children and adults: comparison of complications

Differences	Adult	Child
Angular deformity	Due to malunion at fracture	Due to malunion or eccentric physeal injury <50%. Depends on age of child and site of fracture.
Shortening	Due to bone loss	Due to bone loss or central physeal injury >50%. Depends on age of child and site of fracture
Healing time	Longer	Shorter due to cellular periosteum
Fragility fractures	Due to osteoporosis	Osteogenesis imperfecta or rickets—check for short stature, family history, serum calcium and PTH

The limping child

- Limping is a symptom and not a diagnosis. Acute limping invariably results from pain and the antalgic (painful) gait refers to the child minimizing weight bearing on the sore limb, with a shortened stance phase and increasing the swing phase of the gait cycle (see 🕮 The gait cycle and abnormal gait patterns, p 11). When assessing gait in the young child, especially the preschool age, it is important to be aware of the normal process of gait development, normal variants, and age-related gait changes (see 🕮 Chapter 1).
- Epidemiological studies are sparse—in one study children with an acute limp accounted for <2% of all paediatric emergency department attendances, although may well be more common in the primary care setting.
- The age of the child is most helpful in establishing a differential diagnosis (Table 2.6). Trauma is the commonest cause of limping and in the case of atraumatic limp, many will resolve spontaneously. However common pitfalls in the assessment of limp are important to note (Box 2.3).
- Most cases of limp are *acquired* abnormality of gait. However, in the child who has 'always had a limp' from initial weight bearing it is important to consider a 'missed' diagnosis of developmental dysplasia of the hip (DDH) or neurological conditions such as cerebral palsy. Furthermore, limping typically affects one leg but in some instances *bilateral* involvement can occur (e.g. Perthes' disease, DDH, slipped capital femoral epiphysis) and makes clinical assessment particularly difficult. See 🕮 Hip pain and hip problems in children and adolescents, p 106.
- It is important to assess limping children very carefully for 'red flags' suggestive of potentially life-threatening causes (including sepsis, malignancy, and NAI)—all of which must not be missed (Table 2.7).
- The discrimination between septic arthritis and reactive arthritis (transient synovitis) at the hip is a common clinical scenario. Kocher's clinical prediction rules (see Box 2.4) can be helpful but should not replace experienced clinical judgement (see also 🕮 Chapter 6 and 🕮 Hip pain and hip problems in children and adolescents, p 106).
- It is also worth remembering that children with established conditions such as JIA or cerebral palsy, can develop acute limp from causes such as slipped upper femoral epiphysis (SUFE) or Perthes' disease. Septic arthritis can occur although is a rare complication post intra-articular steroid injection in JIA management, but must be considered in the era of increasingly immunosuppressive treatments (see 🕮 Infections in the immunocompromised, p 70).
- It is important that children presenting with a limp are followed-up with clear instructions (e.g. parent information leaflet) on when to re-seek medical attention. Children with persistent or intermittent limp warrant further assessment to establish the diagnosis.
- Suggested approaches to the limping child (according to presence or absence of fever) are given (Figs. 2.9 and 2.10).

Indications for urgent assessment of limp

- The very young (under 3 years of age).
- The ill and febrile.
- The non-weight bearing.
- Children with painful restricted hip movements.
- The child who is immunosuppressed.

Table 2.6 Causes of limp by age

	0–3 years	4–10 years	11–16 years
Most common	• Trauma (including toddler's fracture)	• Trauma • Transient synovitis • Perthes' disease	• Trauma • Osgood–Schlatter disease
Conditions requiring urgent intervention	• Osteomyelitis • Septic arthritis • NAI • Malignancy (*e.g. neuroblastoma)* • Testicular torsion • Inguinal hernia	• Osteomyelitis • Septic arthritis • NAI • Malignant disease (*e.g. acute lymphocytic leukaemia)* • Testicular torsion Appendicitis • Inguinal hernia	• Osteomyelitis • Septic arthritis • Slipped upper femoral epiphysis • Malignancy (*e.g. bone tumours)* • Testicular torsion Appendicitis • Inguinal hernia
Other important conditions to consider	• Developmental dysplasia of the hip • JIA	• JIA	• JIA
	• Metabolic (e.g. rickets) • Haematological disease (e.g. sickle cell anaemia) • Reactive arthritis • Lyme arthritis		

Box 2.3 Common pitfalls observed in the assessment of the limping child

- Ascribing limp to trauma and overlooking features that suggest other causes.
- Referred pain (e.g. from the abdomen [and testes in boys], back, or chest and hip pathology manifesting as knee pain).
- Think beyond the hip (!) and examine the child comprehensively.
- Classical clinical features of sepsis may be masked in the immunosuppressed child.
- Mycobacterial infection can be easily missed.
- Synovial fluid may be sterile in partially treated septic arthritis.
- Labelling children with daytime symptoms as having 'growing pains'.
- Medically unexplained limp or physical symptoms warrant specific management and referral (i.e. discharge without a diagnosis and follow-up plan is not advised).
- The blood film may be normal in children with malignancy.
- Radiographs are often normal in children with early sepsis or arthritis.
- Acute phase reactants may be normal in children with arthritis.
- RF is usually negative in children with arthritis.
- ANA and RF may be false positives in children without inflammatory joint or muscle disease.

Table 2.7 The limping child and features that suggest severe life-threatening conditions

Malignancy	Non-accidental injury	Sepsis
• Night pain • Pain severe and non-remitting • Bone pain • Pallor • Bruising • Lymphadenopathy • Hepatosplenomegaly • Anaemia, thrombocytopenia • Systemic symptoms (lethargy, weight loss, night sweats, fever) • Complete non-weight bearing • Back pain in the unwell child • Weight loss	• Delay in seeking medical attention • Changeable history inconsistent with pattern of injury • Explanation of injury incongruent with developmental stage of child • Repeated presentations • Un-witnessed injury • Patterns of injury suggestive of NAI (e.g. bruising over soft tissue areas, multiple bruises, bruises that carry the imprint of an implement) • Distinctive burns, e.g. round cigarette burn, forced immersion burn • Complete non-weight bearing with occult fracture • Type of fracture, e.g. metaphyseal • Multiple injuries • Unkempt appearance and poor hygiene	• Complete non-weight bearing • Pseudo-paralysis of limb • Any attempt to passively move the limb is resisted and causes extreme distress • Pain severe and non-remitting • Limb held in a position which accommodates ↑ joint volume due to effusion • Night pain and waking • Fever • Immunocompromised child—due to 1° disease or medications • Back pain in the unwell child

Box 2.4 Kocher's clinical prediction rule for septic arthritis at the hip in the presence of confirmed hip effusion on US

Factors
- Fever >38°C.
- Unable to weight bear.
- ESR >40mm/h or CRP >20mg/L.
- Serum WCC >12 x 10^6/L.

Probability of septic arthritis
- 0 factors present: <0.2%.
- 2 factors present: 40%.
- 3 factors present: 93%.
- 4 factors present: >99%.

Further reading

Fischer SU, Beattie TF. The limping child: epidemiology, assessment and outcome. *J Bone Joint Surg* 1999; **81B**:1029–34.

Kocher MS, Mandiga R, Zurakowski D, *et al.* Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. *J Bone Joint Surgery of Am* 2004; **86A**(8):1629–35.

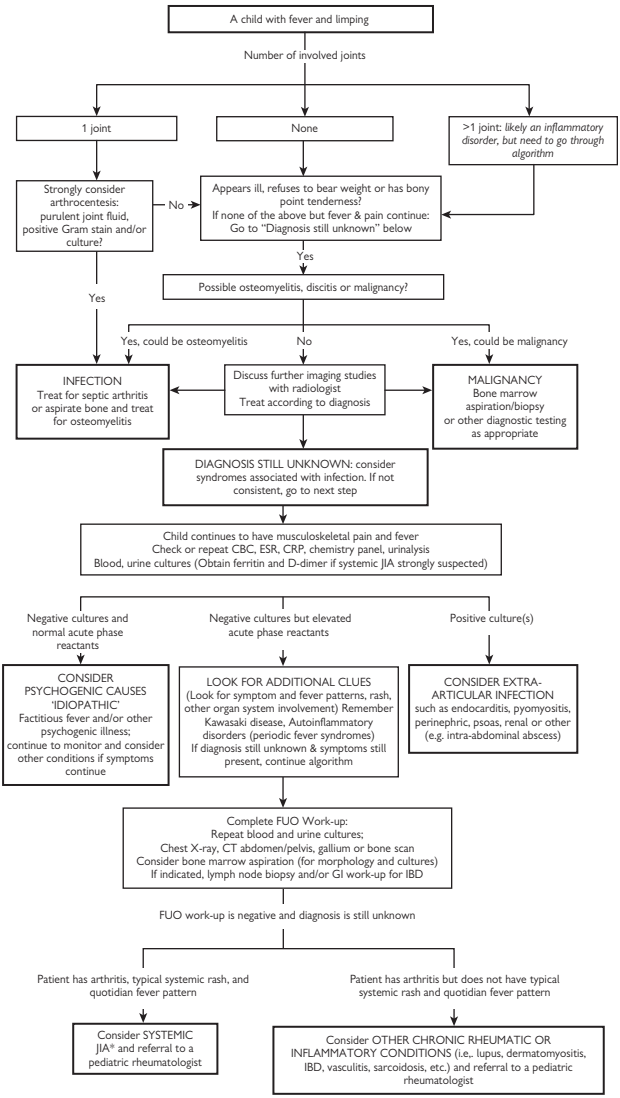

Fig. 2.9 Treatment algorithm for a child with fever and limping. Reproduced with permission from Oxford University Press (and adapted from the original version with permission from the author). Y Kimura. Common presenting problems. In Szer IS, Kimura Y, Malleson PN, *et al.* (eds) *Arthritis in Children and Adolescents*. Oxford: Oxford University Press, 2006.

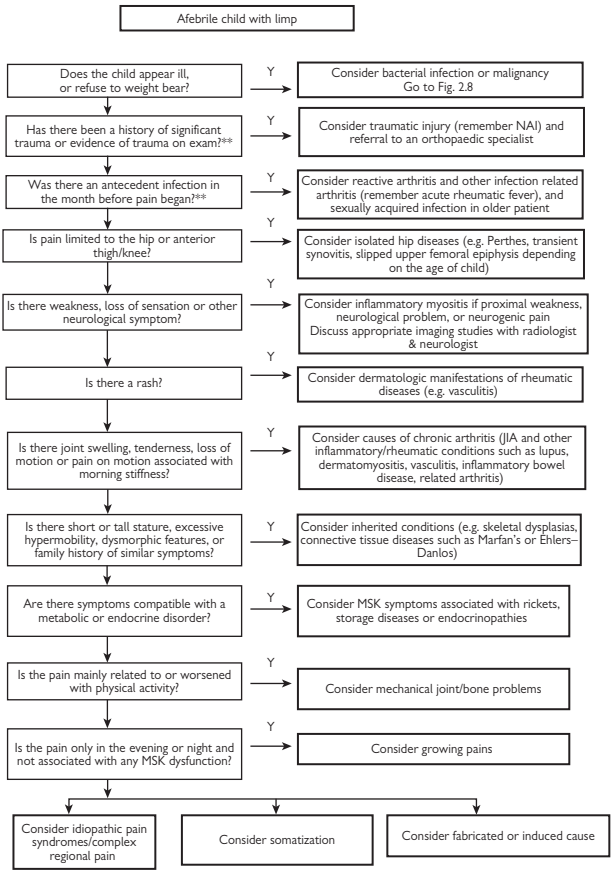

Fig. 2.10 Treatment algorithm for an afebrile child with a limp. Reproduced with permission from Oxford University Press (and adapted from the original version with permission from the author). Y Kimura. Common presenting problems. In Szer IS, Kimura Y, Malleson PN, *et al.* (eds) *Arthritis in Children and Adolescents*. Oxford: Oxford University Press, 2006.

Pain syndromes and the assessment of pain

The chronic experience of pain often has a large and wholly negative impact on the physical and psychological well-being of a young person and their family. Both the child and family may be distressed, fearful, and hoping for cure. There may be feelings of being doubted and past experiences of failed and pain-exacerbating interventions.

The pain assessment (Table 2.8) should aim to:

- Exclude serious possible causes of pain (identification of 'red flags'—see 🕮 Chapter 1, p 8).
- Identify key problems (the physical, social, and psychological impact of pain).
- Identify a treatment plan (acknowledging aetiological factors, environmental stressors and factors that convey resilience), and
- Commence the therapeutic process, building trust and understanding.

Table 2.8 History: important areas to cover in the assessment of pain

Onset of pain	When/where/how pain started
	Important factors in the history, e.g. preceding infection, trauma, operation, or persisting disease
Characteristics of the pain	Nature/site/severity/variation
	Getting better/worse
	Aggravators/ameliorators
	Specific symptoms, e.g. paraesthesia, allodynia (extreme hypersensitivity), skin changes, nocturnal pain
Other symptoms	Systemic/abdominal/genito-urinary/neurological symptoms, e.g. fever, rash, weight loss, appetite change, fatigue, change in mood
Effect of pain on daily living	Sleep disturbance, daytime naps, concentration/memory/mood
	Activity: on bad/good days, school attendance, fitness, hobbies
	Affects on independence and family dynamics
Past and family history of illness	Past illness/operations; family history of illness or pain, e.g. history of painful conditions/fatigue/anxiety/sleep disturbance
Family, emotional, and social circumstances	Family environment/occupations/changes since onset of pain, e.g. any stressors in school, family or peer groups

Examination

Full examination at the beginning may prevent repetition and unnecessary investigations later. Any concerns regarding the diagnosis should be followed-up at this point, avoiding delays that can lead to a worsening of fear, pain symptoms, and associated disability.

Assessing the impact of pain

The history will outline the impact that the pain is having on the individual and their family (e.g. affect on sleep, mood, appetite and fitness, disruption to schooling, social isolation, loss of independence, and widespread family disruption, including financial hardship).

Assessment tools

- *Visual analogue scale (VAS)*—a simple tool for measurement of pain severity as perceived by the child or carer; useful for assessing pain intensity experienced; patients mark their level of pain on a continuous scale from 0 to 10.
- *Faces pain scale*—pictures of faces depicting expressions showing various levels of a pain response; often used in younger children.
- *Bath Adolescent Pain Questionnaire* & *Bath Adolescent Pain Questionnaire for Parent*—2 multidisciplinary tools developed specifically for use in measuring the impact of pain on adolescents with chronic pain and their parents.

Clinical features associated with chronic pain conditions

Pain may start in a localized area with an associated avoidance of movement, and may lead to radiation to other areas of the body, ↑ pain intensity, muscle spasms, abnormal posture, reduced fitness, and pain-associated anxiety. Affects on other body systems include:

- Hypersensitivity or allodynia—unbearable pain on minimal contact; heightened fear of being touched.
- Thermodysregulation—cool and mottled or red and hot skin, especially limbs; abnormal perception of temperature.
- Autonomic dysfunction—sympathetic nervous system stimulation by continuous pain and anxiety signals.
- Musculoskeletal disequilibrium—changes to gait and resting postures of the trunk and limbs; muscle and tendon tightening; altered mechanical load associated with adaptive, protective positioning.

Recognized pain conditions

The most common chronic pain conditions reviewed in paediatric rheumatology settings are:

- ***Diffuse idiopathic musculoskeletal pain (juvenile fibromyalgia):*** generalized pain, often with gradual onset and may follow a period of illness or hypermobility. Fatigue, poor sleep, and low mood are often prominent.
- ***Chronic pain related to hypermobility:*** ligamentous laxity of joints presenting in association with diffuse pain conditions such as lower-limb. With arthralgia, anterior knee pain, and back pain; not all hypermobile individuals will be symptomatic.
- ***Complex regional pain syndrome (CRPS):*** see 🕮 Complex regional pain syndrome, p 89.

- ***Chronic back pain*** (see 📖 Back pain in children and adolescents, p 100): low back pain common in adolescence; may be associated with posture, load bearing, and sedentary activity.
- ***Persistent joint pain following previous or controlled inflammation:*** the degree of disabling pain does not always mirror inflammatory joint activity; environmental and cognitive behavioural factors influence the experience of pain.

Principles of management

- The focus is on symptom management and psychosocial rehabilitation rather than cure.
- Education—to support the rationale for rehabilitation: understand how the body works to maintain pain that is no longer useful, challenge misconceptions of pain always signifying pathology and reduce pain-associated fear.
- Pharmacotherapy—simple analgesics can be tried; gabapentin and pregabalin may be helpful in neuropathic pain, as well as amitriptyline; medication should be used alongside multidisciplinary therapy. Medicine review is often an essential task in this population. Polypharmacy, risk of dosing and combination errors, and confusion over the utility of previously and currently prescribed medication is common. Drug withdrawal, detoxification, and replacement should be carefully managed.
- Physical therapy—early intensive physiotherapy is the treatment of choice to accelerate mobilization; psychological support is important.
- Psychological therapy—should ideally be delivered by a paediatric psychologist who may use therapies such as cognitive-behavioural therapy, acceptance and mindfulness to help the young person and family move forward with rehabilitation and support engagement with normal life activities.

Complex regional pain syndrome (CRPS)

CRPS type I (CRPS I) is a potentially incapacitating syndrome which can occur after a minor injury or operation to a limb. CRPS I has an impact on all tissues and can impair all functions of that extremity, possibly resulting in severe impairment and therapy-resistant pain. In children it is seen more commonly in adolescent girls and not infrequently in young people who are premorbidly very physically active and able. Much academic attention in this condition is targeting the neurophysiological changes that are now evident and the mechanisms of central sensitization.

Clinical features

In children the lower limb is more commonly involved than the upper limb. The pain is usually out of proportion to the inciting event and accompanied by allodynia.

The International Association for the Study of Pain (IASP) has diagnostic criteria for adults with CRPS but not children. Although these diagnostic criteria hold true for children and adolescents, it is widely believed that the dystrophic changes and long-term disability are less common when compared with adults. Occasionally >1 limb may be affected at presentation. It is not unusual for a hand or other leg to develop CRPS months after a leg has been affected.

Features commonly seen in CRPS

- Unexplained diffuse pain (although occasionally very localized).
- Difference in skin colour in relation to the healthy symmetrical limb.
- Oedema (may be transient).
- Difference in skin temperature in relation to the healthy symmetrical limb.
- Limited range of movement and impaired function.
- Worsening of symptoms during exercise.

Rehabilitation

- Key to rehabilitation is reversing the unusual positioning of the limb and returning children to a more active lifestyle while the pain, altered proprioception, and thermodysregulation are still present. Many young people find gentle physical therapy intolerable and continue to hold the affected limb in a fixed position and this further ↑ pain-associated disability with heightening anxiety and low mood.
- Medical therapies are limited but, in addition to regular analgesics, gabapentin and pregabalin may help neuropathic pain. Amitriptyline may have a specific role to help the burning sensation. The true efficacy of these treatments in CRPS is unknown; the consensus is that they are to be used only as an adjunct with ongoing physical and psychological therapy. Other interventions (e.g. pain-relieving blocks/topical patches) are still used albeit with little evidence for their effect.
- Early recognition of CRPS is key. At this stage multidisciplinary input including pain education, targeted physical rehabilitation, psychological support, and analgesia should be instigated. In the majority the condition becomes less bothersome with children returning to normal activities, often leading to complete cessation of symptoms. A few continue to have long-term problems with escalating pain associated disability.

The role of the psychologist in the multidisciplinary team

- Persistent pain brings distress, disability, adult attention, and widespread family disruption. Young people with chronic pain report sleep disturbance, disordered mood, appetite disruption, low feelings, social isolation and unwelcome dependency on parents. When maintained, these factors perpetuate pain and disability.
- Routines of normal schooling can become unmanageable and further strained by interpersonal problems in explaining confusing problems. School absence commonly occurs, further removing the child from their normal social environment. This contributes to the impact on their developmental trajectory, especially around adolescence: usually a time of change, experimentation, social maturation, and development of independence.
- Parental stress is also significant—parents experience distress and conflict in parenting their child. They report struggling to cure and comfort their child, recognizing that the desire to protect may be counterproductive.

Delivering psychological support

It is important that psychological support is integrated in the overall management of patients with chronic pain as early as possible. Once the diagnosis is made the emphasis can move from investigation and cure to symptom management, functional improvement, and psychosocial rehabilitation. This should be delivered by all members of the MDT with a consistent approach.

Components of psychological intervention

- Pain education, pacing, and activity management.
- Communication and managing social interactions.
- Peer relationships and friendships, family support and parenting.
- Goals and ambitions, integration with school and learning.

Key principles

- Disengagement from the pursuit of pain relief and engagement with normal life activities.
- Focus on goals that are important to the individual child.
- Exercise and physical therapy is key to the rehabilitation of young people with persistent pain and psychological support is crucial to provide motivation, reduce fear of damage, and support engagement despite persistent pain.
- Involvement of the parents in the rehabilitation process.

Specific psychological therapies

Cognitive behavioural therapy, mindfulness, acceptance, motivational counselling.

Further reading

Clinch J, Eccleston C. Chronic musculoskeletal pain in children: assessment and management. *Rheumatology* 2009; **48**:466–74.

Eccleston C, Jordan A, McCracken LM, *et al.* The Bath Adolescent Pain Questionnaire (BAPQ): development and preliminary psychometric evaluation of an instrument to assess the impact of chronic pain on adolescents. *Pain* 2005; **118**:263–70.

Growing pains

Overview

- A 'lay term' encompassing non-specific musculoskeletal pains commonly experienced by many healthy young children (with equal gender ratio), characterized by poorly localized aches and pains in the calves, shins, feet, and ankles, usually relieved with massage or simple analgesics, and often predictable to occur later in the day, evenings, and after periods of activity.
- The cause is unknown but there is no clear association with growth (thus the term is a misnomer). Children with growing pains often have features of hypermobility although not all hypermobile children have pain; the causal association of hypermobility with pain in children remains controversial. There is often a family history of growing pains.
- There is no specific test to positively confirm the diagnosis and clinical assessment is integral to excluding potential causes of MSK pains (see 📖 Chapter 1).
  - The 'rules' (red flags) of growing pains (Table 2.9) are important—where the clinical pattern 'does not fit' these rules, further investigation is required.
  - The history should focus on the pattern, predictability, and site of pain—it is important to probe for indicators of concern (Table 2.9).
  - Physical examination requires a comprehensive MSK examination (see 📖 Chapter 1) and general examination.
  - Nocturnal pain is common in growing pains—concern is warranted if night waking is becoming more frequent, unremitting, or localized to one site. Response to NSAIDS is common but (benign) bone tumours need to be considered (see 📖 Bone tumours, p 60).

Management

- Investigation is not needed unless concern has been raised (Box 2.5). Investigations are summarized in Box 2.6.
- Reassurance and explanation is paramount:
  - Growing pains are likely to improve as the child gets older.
  - Advice on footwear (supportive and well fitting); trainers with arch supports are ideal (note shoelaces are best tied and 'Velcro' fastened firmly). Specialist orthotics rarely needed.
  - Given the predictability of pains and to prevent night waking, analgesics before physical activities or at bedtime may be helpful.
- It is important to address parental concerns and give clear instructions when to seek medical attention again (e.g. limping, joint swelling, asymmetrical involvement 1 leg being affected or pains elsewhere (e.g. fingers), or daytime symptoms, systemically unwell avoidance of previously enjoyed activities).
- A parent information leaflet is available: 🖱 http://www.arthritisresearchuk.org/files/6541_20022010162934.pdf.

Box 2.5 The 'rules' of growing pains

'Rules' of growing pains

- Pains *never* present at the start of the day after waking.
- Child doesn't limp.
- Physical activities not limited by symptoms.
- Pains symmetrical in lower limbs and not limited to joints.
- Physical examination normal (joint hypermobility may or may not be detected).
- Systemically well and major motor milestones normal.
- Age range 3–12yr.

Indications for concern

- Systemic upset (*red flags* to suggest sepsis or malignancy).
- Abnormal growth (height and weight).
- Abnormal developmental milestones:
  - *Delay* (especially major motor skills) suggestive of neurological disease or metabolic bone disease ***or***
  - *Regression* of achieved motor milestones (consider inflammatory joint or muscle disease).
- Impaired functional ability (ask about play, sport, schoolwork, 'clumsiness').
- Limping (intermittent or persistent).
- Morning symptoms (other than tiredness after disturbed sleep) or mood changes may suggest inflammatory arthritis.
- Widespread pain (such as upper limbs and back).
- School absenteeism.

Box 2.6 Investigations that may be indicated

- FBC (and film), acute phase reactants (ESR, CRP).
- Biochemistry (bone biochemistry and vitamin D) to exclude metabolic bone disease including osteomalacia (see 🕮 Metabolic bone diseases, p 330).
- Thyroid function, muscle enzymes to exclude inflammatory muscle disease (see 🕮 Juvenile dermatomyositis, p 266).
- X-ray of legs (hips with frog views) to exclude hip pathology, e.g. Perthes disease (seeTable 2.13).
- Radioisotope bone scan to exclude local hot spots (e.g. osteoid osteoma, occult fracture)—see 🕮 Bone tumours, p 60.

Further reading

Foster HE, Boyd D, Jandial S. *Growing Pains. A Practical Guide for Primary Care.* ARC, 2008. Available at: 🖱 http://www.arthritisresearchuk.org/files/6541_20022010162934.pdf.

Pyrexia of unknown origin

Definition

Several definitions have been proposed: essentially this is a term for persistent or recurrent pyrexia that persists for longer than you would expect from a self-limiting viral illness (e.g. 5 days) and has evaded diagnosis from reasonable 1st-line history, examination, and investigation.

One useful working definition of pyrexia of unknown origin (PUO) is: pyrexia >38.0°C on several occasions, >3 weeks' duration of illness, and failure to reach diagnosis despite 1 week of inpatient investigations.

Key points

- Always consider incomplete Kawasaki disease, especially if faced with an irritable young child with fever ± any other suggestive history, signs, or suggestive blood results (see 🕮 Kawasaki disease, p 183). Missing out on early treatment of this can ↑ risk of significant coronary artery aneurysms.
- In the immunosuppressed child (e.g. neonate, neutropenic, HIV+ve, on immunosuppressive treatment, or 1° immunodeficiency), different causes (especially infections, e.g. fungal, cryptosporidium) are more likely and treatment against relevant possible infection should be given alongside investigation.
- Antibiotics have often been tried and no benefit seen, especially in young children.
- 1st-line investigation usually includes:
  - Blood cultures when pyrexial.
  - Urine microscopy and culture.
  - Chest x-ray (CXR).
  - Cerebrospinal fluid (CSF) microscopy, culture, and PCR analysis for herpes simplex virus (HSV).

Assessment

The approach includes investing time in carefully reviewing the history including:

- Detailed review of all systems including rashes, weight loss, bowel symptoms, joint symptoms, mouth ulcers.
- Foreign travel, history of tick bites.
- Health of family members recently and family history of unexplained fever.
- Pets and their health.
- Drug and medication history.
- Hobbies (e.g. camping/trekking), swimming in lakes or rivers, and especially recently.
- Sexual history when relevant.

Detailed examination of all systems and repeated examination including:

- Examining skin for rashes, especially when pyrexial.
- Lymphadenopathy.
- Mouth for ulcers.
- Auscultation of heart sounds.

- Assessment of hands for features of endocarditis and nailfold capillaries.
- Abdomen and testes for any tenderness/swelling.
- Joints for any evidence of arthritis.
- Routine fundoscopy and consider requesting slit lamp examination by ophthalmologist to look for uveitis/other intraocular pathology.
- Eyes, lips, palms, soles, perineum (peeling is often overlooked at this site), neck and trunk for features of Kawasaki disease: remember that clinical signs can present sequentially, may be subtle and can only last a few days.

Investigation and management

- Further investigations follow-up on clues found from the history, examination and initial test results. Table 2.9 includes the more common causes (focus being for a patient in the UK) and clues that should guide investigations, although this is not an exhaustive list.
- Foreign travel will raise the chances of different infections linked to the area visited.
- There are a few paediatric cohort studies published describing the ultimate diagnoses, but all are very dependent on local population and pathway of referral to the cohort.
- Management depends on the proven or strongly suspected diagnosis.

Consider consulting other specialties

- Infectious diseases
- Haematology/oncology
- Gastroenterology
- Endocrinology
- Interventional radiology
- Surgery.

Prognosis

- 5–15% remain undiagnosed even after extensive evaluation.
- No evidence to support prolonged hospitalization if patient stable and whose work-up is unrevealing.
- Further outpatient care:

Table 2.9 Causes and relevant investigations for PUO

Diagnosis	Suggestive features	Useful investigations
a) Localized bacterial infections		
Abscess, e.g. abdominal, pelvic	Localizing symptoms	Imaging e.g. USS, CT, MRI, white cell scan
Endocarditis	New murmur, haematuria, splinter haemorrhages, Janeway lesions, Roth's spots	Repeated blood cultures, transthoracic echocardiogram; consider oesophageal echocardiogram (seek expert advice)
Septic arthritis	Localizing symptoms and signs	Imaging e.g. US, MRI, joint aspiration
Osteomyelitis	Localizing symptoms	Plain x-ray (although insensitive), bone scan, MRI
Sinusitis/ mastoiditis	Localized pain/tenderness	CT with contrast
b) Other infections		
EBV, CMV	Lymphadenopathy	IgM against EBV/CMV, PCR of blood
Cat scratch disease	Lymphadenopathy. Contact with cats	Serology (*Bartonella*). Lymph node biopsy
Tuberculosis	Family contact history, travel, night sweats	CXR, Mantoux, Quantiferon TB test, specific culture, 16s ribosomal PCR of lesional tissue or fluid
HIV	Recurrent infections, maternal ill-health, sexually active or other risk factors	Blood HIV PCR
HHV6	Rash, febrile convulsion, aseptic meningitis	PCR of blood and CSF
Brucellosis	Farming community, hepatosplenomegaly	Serology (*Brucella*). Specific culture of urine + blood
Campylobacter, *Salmonella*, *Shigella*, or *Yersinia*	Diarrhoea	Stool microscopy and culture.
Hepatitis	Jaundice, abdominal pain, diarrhoea	Serology for HAV, HBV, HCV

Table 2.9 (*Contd.*)

Diagnosis	Suggestive features	Useful investigations
Leptospirosis	Farming/river contact, headache, myalgia then headache	Serology (Leptospira)
Malaria	Travel to endemic area in preceding months	Repeated blood films
Lyme disease	Rash, tick bite, aseptic meningitis	Serology (*Borrelia*)
c) Post-infectious		
Acute rheumatic fever	Recent pharyngitis, carditis, Ducket Jones criteria	Throat swab, ASOT/ anti-DNAase B, ECG, echocardiogram
Post streptococcal reactive arthritis	Recent pharyngitis, fleeting arthritis	Throat swab, ASOT/ anti-DNAase B
Other reactive arthritis	Arthritis, urethritis, conjunctivitis, recent infection	HLA B27 status, stool culture, urethral swab including *Chlamydia* culture/PCR and gonorrhoea microscopy/ culture
d) Malignancy		
Leukaemia	Anaemia, cytopenia, night pain	Blood film, bone marrow aspirate
Lymphoma	Lymphadenopathy, weight loss, night sweats	LDH, lymph node biopsy
Neuroblastoma	Mass, anaemia	Urine VMA and HVA: creatinine ratio, abdominal US
Wilm's tumour	Abdominal pain and mass, haematuria	Abdominal/renal US
e) Autoimmune/auto-inflammatory		
Systemic juvenile idiopathic arthritis	Typical rash with daily pyrexia, arthritis (may be later), lymphadenopathy, mild splenomegaly	Ferritin
Kawasaki disease	Irritable (with sterile CSF), eye and mouth changes, rash, lymphadenopathy, peeling skin	Echocardiogram. NB a normal result does not exclude Kawasaki disease.

(*continued*)

Table 2.9 (*Contd.*)

Diagnosis	Suggestive features	Useful investigations
Systemic lupus erythematosus	Rash, low mood and lethargy, Lymphopenia, cytopenia, proteinuria	ANA screen (and if positive: ENA Abs and dsDNA antibodies), ACL and lupus anticoagulant, C3 and C4, renal biopsy if significant nephritis
Juvenile dermatomyositis	Typical rashes, proximal weakness	CK, LDH, MRI thigh muscles—see 🕮 Juvenile dermatomyositis, p 266
Periodic fever syndromes (see 🕮 p 288)	Chronic episodic fever, well in between, oral ulceration and lymphadenopathy, otherwise thriving	Acute phase response when well and soon after onset, gene mutation analysis
CINCA	Neonatal onset, irritable, rash, arthritis	Gene mutation analysis. See 🕮 Cryopyrin associated periodic syndrome (CAPS), p 294
Sarcoidosis	Arthritis, rash, uveitis, chest disease (hilar lymphadenopathy ± interstitial lung disease)	Serum ACE, CXR, consider lesional tissue biopsy. See 🕮 Sarcoidosis, p 300
Vasculitis	Rash, renal concerns, arthritis, testicular/abdominal pain, many other potential multisystemic features	Skin biopsy, selective visceral digital subtraction arteriography, ANCA
Inflammatory bowel disease	Diarrhoea and/or nausea, weight loss	Upper and lower GI endoscopy, MRI bowel, labelled white cell scan
Thyrotoxicosis	Weight loss, tremor, sweating, tachycardia	Thyroid function tests (including T_3 if strongly suspect, as well as TSH and T_4), thyroid autoantibodies
f) Miscellaneous		
Factitious	Not recorded in hospital by others	Careful observation in hospital
Drug-induced fever	Suggestive history	Stop suspected drug(s)
Kikuchi disease	Lymphadenopathy progressing to necrotizing lymphadenitis (especially cervical), leukopenia, Asian origin especially; observed particularly in SLE	Lymph node biopsy
Castleman's disease	'Giant lymph node hypertrophy', unifocal or multicentric	HHV8 serology and/or PCR, lymph node excision biopsy. FDG PET-CT scan, serum cytokine analysis (esp. IL-6) if available

- Close follow-up procedures and systematic re-evaluation to ensure that no deterioration occurs, and to guide further outpatient investigation.

Further reading

Cogulu O, Koturoglu G, Kurugol Z, *et al*. Evaluation of 80 children with prolonged fever. *Pediatr Int* 2003; **45**:564–9.

Joshi N, Rajeshwari K, Dubey AP, *et al*. Clinical spectrum of fever of unknown origin among Indian children. *Ann Trop Paediatr* 2008; **28**:261–6.

Pasic S, Minic A, Djuric P, *et al*. Fever of unknown origin in 185 paediatric patients: a single-centre experience. *Acta Paediatr* 2006; **95**:463–6.

Back pain in children and adolescents

Recent epidemiological studies report back pain in children to be more common than previously thought, with a higher prevalence (15.7–28.8%) of non-specific lower back pain as the child matures. A detailed history and examination identifying red flag symptoms (Table 2.10) and signs (Table 2.11) should point towards appropriate investigation and diagnosis of pathological causes.

Table 2.10 'Red flag' symptoms in back pain

Examination	Red flag symptoms
Age of child	<4yr
Chronicity	>4 weeks, persistent and worsening
Site	Cervical spine
Exacerbating factors	Hyperextension
Diurnal variation	Worse at night, early morning stiffness
Systemic features	Pyrexia, weight loss, malaise
Neurological symptoms	Altered bladder and bowel function, headaches
Past medical or family history	Systemic disease, e.g. JIA, sickle cell, TB, (see Tuberculosis and mycobacterial disease, p 356), neurofibromatosis
Drug history	Pain unresponsive to analgesia,* chronic steroid use
Social activities	History of trauma or foreign travel, interference with function. Lifestyle and psychological factors should also be enquired about (e.g. bullying at school)

*Benign osteoid osteoma pain often responds well to NSAID therapy.

Table 2.11 'Red flag' signs in back pain

Examination	Red flag signs
Cardiovascular	Tachycardia
Respiratory	Reduced air entry, mediastinal shift
Gastrointestinal	Abdominal mass
Neurological	Altered power, tone, reflexes, sensation
Musculoskeletal	Altered normal spine curvature or gait. Scoliosis (especially if painful). Vertebral/intervertebral tenderness
Systemic	Pyrexia, lymphadenopathy
Dermatological	Rash, bruising, café au lait patches, infected skin, midline skin lesions

Back examination

(See 🕮 pREMS, p 23.)

- Look: observe posture and gait (evidence of kyphosis, loss of lumbar lordosis, scoliosis (and if present assess whether fixed or postural), pelvic tilt, shoulder asymmetry, leg-length discrepancy.
- Feel: palpate spine for point tenderness, muscle spasm. Palpate sacroiliac joints.
- Move: range of spinal movement (forward/lateral flexion, extension, rotation), and hyperextension on one leg ('stork test': for lumbar spondylosis—standing on one leg and bringing back into lumbar extension elicits pain ipsilateral to the pars interarticularis lesion).
  - Also examine hips, test straight leg raise with dorsiflexion of foot and assess hamstring length.
- Measure/other: leg-length discrepancy, neurological assessment.

Investigation

If no red flags, imaging unlikely to be helpful. If investigation clinically indicated, do not be reassured by a normal x-ray. MRI, CT, or bone scan may be needed.

Muscular pain

Common. Causes include poor posture, hypermobility, leg-length discrepancy, idiopathic scoliosis, asymmetrical load bearing (e.g. schoolbag on one shoulder). No need for imaging (refer scoliosis to scoliosis service). Treatment—advice, analgesia, physiotherapy.

Spondylosis

A bony defect in the pars articularis, analogous to a stress fracture.

- The commonest identifiable cause of low back pain in young athletes, and commonest in sports involving repetitive hyperextension and rotational spinal loading, e.g. gymnastics, weight lifting, cricket. Pain may radiate to buttocks. Usual sites L5 (85–95%), or L4.
- If bilateral may progress to ***spondylolisthesis***; the forward slip of one vertebra on the vertebra below—usually L5/S1. May compress nerve roots.
- One-legged hyperextension test (stork test—see 🕮 Chapter 1, p 26) may be positive. A lumbosacral step may be palpated.
- The defect may be seen on PA/lateral x-ray. If x-rays normal but clinical suspicion high, arrange localized MRI or CT (discuss with radiology).
- Management includes review by orthopaedic surgeon—rest, analgesia, physiotherapy. Indications for bracing and/or surgery include a slip of >50% vertebral body width, progressive changes, neurological deficit present.

Scheuermann's disease (juvenile kyphosis)

Often a coincidental finding on x-ray and considered a normal variant of unknown aetiology. May be associated with mild/moderate pain, onset around puberty.

- Kyphotic deformity of thoracic or thoracolumbar spine which does not disappear on lying supine or with hyperextension. Fixed kyphosis is 40° or more.
- X-ray criterion—>5° anterior wedging of at least 3 adjacent vertebral bodies. In addition there may be irregularity and flattening of vertebral

end plates, narrowed disc spaces, Schmorl's nodes (extrusion of disc substance through the vertebral end plate).
- If pain is severe, consider whether other pathology is present.
- Management—analgesia. Symptoms usually resolve with skeletal maturity.

Disc degeneration

This is present in a significant number (16–26%) of 10–19yr-olds.

May be asymptomatic but pain more likely if ***disc prolapse*** is present.
- May present with sciatica and/or have positive straight leg raise.
- MRI if suspect disc herniation.
- Management: rest, analgesia, NSAIDs, physiotherapy. Conservative management is less successful than in adults and surgery may be required (e.g. severe pain, progressive neurology).

Tumours

- Consider if painful scoliosis, persistent or night pain, progressive pain/disability.
- X-ray then MRI, CT or bone scan (discuss with radiology), ± bloods: FBC, CRP, LDH, urine: catecholamines, and abdominal US.

Osteoporosis

See 🕮 Metabolic bone diseases, p 330.

Idiopathic pain syndrome (see 🕮 Pain syndromes and the assessment of pain, p 87), and **infective causes** (see 🕮 p 64) are discussed elsewhere.

It is also important to remember the possibility of ***referred pain*** (e.g. from abdomen, chest, or renal causes).

Further reading

Houghton KM. Review for the generalist: evaluation of low back pain in children and adolescents. Pediatric *Rheumatology* 2010; **8**:28 (open access): 🖱 http://www.ped-rheum.com/content/pdf/1546-0096-8-28.pdf.

Scoliosis

Scoliosis is a three-dimensional deformity in which the spine deviates from the midline in the coronal plane by >10° and the affected vertebrae rotate maximally at the apex of the curve. The curve may be single or double (Fig. 2.11).

Causes

- Non-structural: postural/compensatory
- Transient: sciatic/hysterical/inflammatory/infection
- Structural:
  - Idiopathic (most common)
  - Congenital, e.g. hemivertebrae
  - Neuromuscular, e.g. muscular dystrophies, cerebral palsy
  - Neurofibromatosis-related
  - Connective tissue-related
  - Trauma
  - Tumour (intra- or extraspinal).

Idiopathic scoliosis

- 80% are idiopathic and classified according to age of onset:
  - Infantile <3yr
  - Juvenile 3–10yr (or onset puberty)
  - Adolescent >10yr (or after puberty).
- More common in adolescents than juveniles, more common in females:
  - Thoracic curves are usually to the right.

Symptoms

Idiopathic scoliosis is not associated with significant pain and may present with asymmetry of shoulders, trunk skin creases, or skirt hem, or be noticed by others. Often found incidentally. School screening programmes are not deemed cost-effective. A painful scoliosis or with neurological involvement suggest an underlying serious cause ('red flag' for urgent referral).

Examination (see 🕮 pREMS, p 23)

- 'Look'—observe standing posture. Is the head in the midline, is there shoulder asymmetry, are the iliac crests level?
  - Observe in forward flexion from behind and from the side—is there a single or double curve, is the curve to right or left, is a rib hump visible, are there skin changes (e.g. cafe au lait spots suggestive of neurofibromatosis)?
- 'Feel'—is there spinal tenderness?
- 'Move'—does the curve correct on lateral flexion, sitting, or is it fixed?
- 'Measure/other'—is there leg-length discrepancy? Is there neurological deficit?

Red flags (for urgent referral)

Pain, neurological signs (root or cord compression).

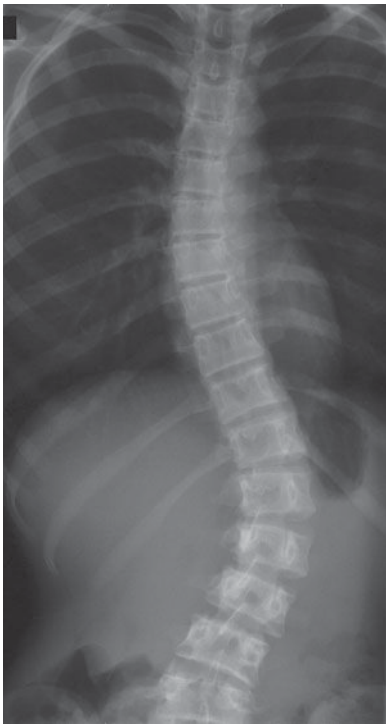

Fig. 2.11 X-ray of patient with idiopathic scoliosis. A right thoracic and left lumbar curve is seen.

Management

- If red flags, refer urgently to scoliosis service.
- If idiopathic scoliosis likely, refer to local scoliosis service for further assessment.
- Treatment options depend on severity and include physiotherapy, bracing, and surgical interventions.

Investigations

- Anteroposterior (AP) and lateral x-rays should be taken standing in a standardized way.
  - The Cobb angle is determined by identifying the vertebrae at the upper and lower end of the curve, with greatest tilt to concavity of curve and drawing a line along the upper and lower end plates accordingly.
  - The Cobb angle is the angle between these two lines (Fig. 2.12). Note: the Cobb angle correlates poorly with overall cosmetic appearance

which may be affected by number, size, and location of curves, associated chest wall deformity, muscle bulk, and fat distribution.
- MRI and isotope bone scan are required with a painful scoliosis—bone scan may detect osteoid osteomas which can be missed on MRI.
- MRI required with presence of red flags. It is reported that left-hand thoracic curves have a high incidence of neural axis abnormalities (e.g. Arnold Chiari malformation). Albeit a contentious observation, MRI is advised with left-hand thoracic curves.
- Pulmonary function tests are necessary in significant thoracic scoliosis; impact on cardiovascular function is low unless the curve is large with Cobb angle >100°.

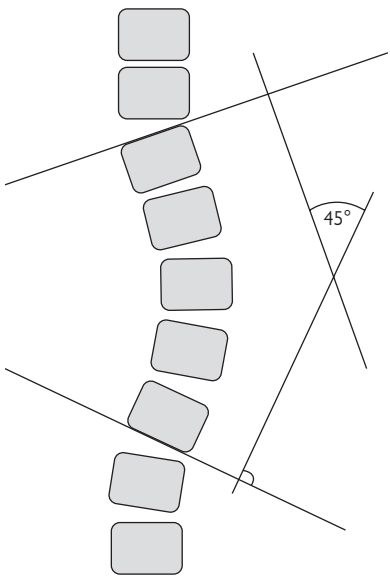

Fig. 2.12 Cobb angle.

Prognosis

Worse prognosis and greater likelihood of progression:
- Large curves, thoracic and double 1° curves.
- Earlier onset pre-skeletal maturation as scoliosis progresses through pubertal growth phases.
- In adolescent idiopathic scoliosis, the Riser grade (degree of fusion of the iliac apophysis reflecting skeletal age) can be used with the Cobb angle to give an estimate of the chance of progression in a population.
  - Riser stage 0–1: curves 20–29° have >65% risk of progression.
  - Riser grade 2–4: curves 20–29° have >20% risk of progression.

Hip pain and hip problems in children and adolescents

- Hip problems in children and adolescents can present with pain, limp (see 📖 p 80), deformity, inability to bear weight or as part of a systemic illness. Early diagnosis and appropriate treatment is paramount to avoid permanent damage.
- Children are optimally managed by an experienced MDT including orthopaedics, rheumatology, and infectious diseases as indicated, especially before invasive procedures are contemplated. Alleviation of pain should be given due importance from the start and throughout the investigation phase.
- The clinical assessment is integral to making a diagnosis and the differential diagnosis is broad but may be differentiated by age (see Tables 2.12–2.14 with more detail given in relevant chapters). ***Red flags*** (see 📖 p 8, p 64, p 66) for septic arthritis, osteomyelitis, malignancy and NAI are vital to consider and exclude. Investigations should be tailored to the most likely differential diagnoses based on the clinical assessment.
- Key features in the clinical assessment include:
  - History: onset and symptom duration, characteristics of pain, morning stiffness, functional impairment, presence of other joints affected, fever and associated systemic symptoms, coexistent medical conditions, and identification of precipitating factors including trauma. *Note that trauma is common in the young child and a common error to explain musculoskeletal presentations which can be due to other causes.*
  - Hip problems can present with subtle or vague symptoms, e.g. irritability, crying during nappy-change, or as delay in, or regression, of motor milestones in children. Hip pain can be localized to the groin or referred to the thigh or knee. Pain felt at the pelvic brim should not be confused with hip pain.
- Physical examination:
  - Presence of fever and systemic features of any concurrent illness. Examine all joints (the pGALS screen is useful—see 📖 pGALS, p 18), assess gait and check for limb shortening. Pain on passive movements, specifically internal rotation, suggest hip pathology—note that the position that allows for maximal intracapsular volume and resultant comfort in the presence of an effusion, is that of external rotation, flexion, and abduction.
  - Pathology elsewhere (e.g. abdomen, spine, sacroiliac joint, nerves) can mimic hip problems and requires diligent exclusion.
- Other differential diagnoses across all age groups:
  - JIA from late infancy: monoarthritis of hip is uncommon, but does occur.
  - Infection-related arthritis: reactive arthritis (*Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, and *Chlamydia* in adolescents); post-streptococcal arthritis; TB arthritis, gonococcal arthritis in adolescents—see 📖 p 64. Rarer bacteria: *Mycoplasma*, *Borrelia burgdorferi* (Lyme disease), *Brucella*.

- Congenital causes—epiphyseal dysplasia (see 📖 p 333), metabolic storage disorders (e.g. Gaucher's (see 📖 p 312).
- Malignancy—1° bone tumours, benign and malignant (see 📖 p 60)—referred pain from the spine or abdomen or pelvis (including retrocaecal appendicitis) may present with hip pain.
- Osteoarthritis—1° (rare in the absence of predisposing conditions such as skeletal dysplasia (see 📖 p 333) and 2° to pre-existing hip disease.
- Chronic idiopathic pain syndromes (see 📖 p 87) needs careful exclusion of organic pathology.

Further reading

Fabry G. Clinical practice: the hip from birth to adolescence. *Eur J Pediatr* 2010; **169**(2):143–8.
Houghton KM. Review for the generalist: evaluation of pediatric hip pain. *Pediatr Rheumatol Online J* 2009; **7**:10.

Table 2.12 Differential diagnosis of hip pathology by age: age group: 0–4 years

	Developmental dysplasia of hip	Transient synovitis	Septic arthritis/ osteomyelitis (see 📖 p 64)	Malignancy (see 📖 p 56)	Trauma
Demographics	♀>♂ 1–5 per 1000 (True dislocation)	♂>♀ 1–2 per 1000	Slightly more common in boys 5–10 per 100000	Generally more common in boys	Commonest cause in general—*beware not all causes of hip pain are trauma related*!
Patho-physiology	Disruption of normal relation between femoral head & acetabulum	Idiopathic self-limiting synovial inflammation	Haematogenous spread most often, direct extension less common. *Staph. aureus* most common pathogen overall. Consider Group B *Strep*. & Gram–ve bacilli in neonates. Others: TB, rarer bacteria	Bone marrow infiltration-leukaemia, metastatic tumours (neuroblastoma), 1° bone tumours and soft tissue tumours (such as rhabdomyosarcoma) are rare	Green-stick fractures common in toddlers Consider NAI
Predisposing factors & associations	Family history Breech Oligohydramnios Neuromuscular disease	Viral or bacterial illness Minor trauma	Immunosuppression Trauma Sickle-cell disease Interventional procedures in neonates especially preterms	Congenital: Down's, Bloom's, Fanconi's syndromes	Bone mineralization disorders (see 📖 p 330) Social history in NAI

Clinical features	Hip click/clunk Can present later in infancy, asymmetry of skin creases Shortening of limb	Pain +, limp ± Most common cause of hip pain in children excluding trauma	Fever, pain++, inability to bear weight, restriction of joint movement, other systemic signs	Severe/nocturnal pain, inability to weight-bear, bony tenderness ±, Systemic—fever, anaemia, weight loss	Pain, inability to weight bear, local tenderness, local bruising ±
Diagnosis	Clinical (neonatal screening)—Ortolani & Barlow test, MSUS (check abbreviation) ≤4–6 months of age X-ray—for late presentation MRI—for complications	Blood tests can be abnormal Radiology might show effusion (MSUS and MRI)	USS useful to show effusion, MRI for osteomyelitis/abscess Inflammatory markers are often high. Joint aspiration—gold standard A high index of suspicion is required for diagnosis (Kochers prediction rule; see 📖 p 66)	Radiology for site & extent—MRI/CT, bone scan may show 'hotspots' FBC/bone marrow to exclude leukaemia Urinary catecholamines-screening for neuroblastoma Bone biopsy—definitive histological diagnosis	History for mechanism of injury Imaging—x-ray usually suffices MRI for detailed evaluation & to exclude other causes
Treatment	Abduction brace Closed reduction Open surgical reduction Acetabuloplasty	Symptomatic NSAIDs	Arthroscopic/open drainage ± joint lavage Antibiotics—in general, IV followed by oral, although duration is not clearly defined	Modality dependent on pathology: chemotherapy, radiotherapy, surgical resection	Orthopaedic management Pain relief Management of NAI

(*continued*)

Table 2.12 (*Contd.*)

	Developmental dysplasia of hip	**Transient synovitis**	**Septic arthritis/ osteomyelitis (see 📖 p 64)**	**Malignancy (see 📖 p 56)**	**Trauma**
Course & complications	Good outcome if early identification & treatment Persistent dysplasia Avascular necrosis (2° to treatment)	Usually resolves within 2 weeks Recurrence risk of 15 %, usually within 6 months—unclear if associated with subsequent development of Perthes' disease	Increase in intra-articular pressure l compromised blood supply & avascular necrosis Joint destruction can occur without prompt or adequate treatment	Prognosis dependent on staging Poor prognosis in advanced malignant disease	Excellent prognosis with early treatment Prognosis for NAI is dependent on coexistent injuries and chronic impact

Table 2.13 Differential diagnosis of hip pathology by age: age group: 4–8 years

	Perthes' disease (Legg–Calve–Perthes)	Septic arthritis and osteomyelitis	Tumours/malignancy	Transient synovitis
Demographics	♂>♀ 5–15 per 100,000	See Table 2.12 and 🕮 Bone and joint infections, p 64	See Table 2.12 and 🕮 Bone tumours, p 60	Less common as age advances after 4–6yr
Patho-physiology	Idiopathic avascular necrosis of femoral epiphysis	Septic arthritis diminishes in frequency after 2yr of age—however should be excluded	Frequency of bone tumours increases with age	
Predisposing factors & associations	Epiphyseal dysplasia Hypothyroidism Delayed bone age Caucasians Coagulation abnormalities		Benign bone tumours: • Osteochondroma—most common • Osteioid osteoma—pain dramatically responsive to NSAIDs	
Clinical features	Pain ±, limp worsening with exercise Bilateral in 10–15%		Malignant bone tumours: • Osteosarcoma most common—association with previous irradiation • Ewing's sarcoma 2nd most common—commoner in white boys, diaphyseal in contrast to most 1° bone tumours which are metaphyseal	
Diagnosis	Clinical: restriction of internal rotation and abduction X-ray, MRI, bone scintigraphy			
Treatment	NSAIDs Restriction of activity/immobilization Surgery: osteotomy, augmentation plasty			
Course & complications	Treatment does not halt natural course Bad prognosis if older age at onset & greater extent of femoral head involvement Deformity of femoral head in severe cases Long term—early osteoarthritis			

Table 2.14 Differential diagnosis of hip pathology by age group: 8–16 years

	Slipped capital femoral epiphysis (SCFE)	Trauma	Tumours/malignancy	Infection	Avascular necrosis or osteonecrosis
Demographics	♂>♀ 1–3 per 100,000	♂>♀	Refer to Tables 2.12 and 2.13 Benign tumours can arise from bone, cartilage, fibrous tissue or soft tissues Benign tumours such as osteoid osteoma, and malignant tumours such as osteosarcoma and Ewing's sarcoma are more common in this age group As in all age groups, it is important to consider malignancy not arising primarily from the bone, e.g. leukaemia	Refer to Tables 2.12 and 2.13 Amongst other pathogens, also consider *Gonococcus* and *Chlamydia* in sexually active adolescents Gonococcal arthritis can lead to early joint destruction if not identified in time	♂=♀

Patho-physiology	Posterior & inferior displacement of epiphysis (2° to displacement of proximal femoral metaphysis) Classification: • Acute/chronic/ acute-on-chronic • Stable/unstable • Radiographic • Preslip, Grade I, II, III	Sports-related injuries: Ligamentous injuries Avulsion injuries—due to inherent weakness across open epiphysis Apophyseal injuries & apophysitis—chronic overuse & repetitive muscle contractions Stress fractures—chronic repetitive microtrauma Transient demineralization of hip Post-traumatic chondrolysis of hip		Circulatory compromise-can be 1° or 2° to causes listed below Bilateral occurrence in 50%, if not associated with trauma

(*continued*)

Table 2.14 (*Contd.*)

	Slipped capital femoral epiphysis (SCFE)	Trauma	Tumours/ malignancy	Infection	Avascular necrosis or osteonecrosis
Predisposing factors & associations	Overweight or obese (but can also occur in thin patients) Hypothyroidism Growth hormone deficiency Exposure to radiation Afro-Caribbeans	High-impact sports Chronic or repeated microtrauma/sustained overuse Inherent bone mineralization problems			Drugs—steroids, LMW heparin Haemoglobinopathies Coagulopathies Skeletal dysplasias Infections—HIV, *Meningococcus* Inflammatory bowel disease, trauma, malignancy, vasculitis/ JIA, orthopaedic (previous DH, SCFE, Perthe's)

Clinical features	Pain +, limp +, Inability to walk in unstable variety Presentation with knee pain or limp alone leads to delayed diagnosis Bilateral in 20–40%	Pain, restriction of movement, localized swelling/bruising ±, presence of hernia in 'sportsman's hernia' (a type of imminent direct hernia that can cause chronic groin pain in athletes) Sudden pain following intense physical activity typical of acute chondrolysis		Insidious onset of pain which typically occurs with standing or walking ↓ abduction and rotation on examination Limp is a late finding
Diagnosis	X-ray: • AP—'Klein's line' (a line drawn along the superior femoral neck should normally intersect a portion of the femoral head) • Frog lateral view MRI—useful in 'pre-slip' stage	Typical history X-ray MRI Hip arthroscopy for isolated labral tears, loose bodies		Low index of suspicion if associated risk factors MRI—most sensitive for early diagnosis

(*continued*)

Table 2.14 (*Contd.*)

	Slipped capital femoral epiphysis (SCFE)	Trauma	Tumours/ malignancy	Infection	Avascular necrosis or osteonecrosis
Treatment	Surgical: early *in situ* stabilization by screw fixation Unstable SCFE is an orthopaedic emergency	Orthopaedic management Pain relief			Medical: pain relief, bisphosphonates Surgical: core decompression and bone grafting
Course & complications	Bad prognosis if ↑ severity of slippage and delay in diagnosis Complications: • Avascular necrosis • Acute chondrolysis Long-term—early osteoarthritis	Consider pain syndromes if not getting better with conventional treatment after excluding important differentials			Femoral head collapse can occur if diagnosis is delayed, in which case total hip replacement might be needed Fractures can occur as a complication of surgery

Knee pain in children and adolescents

Pain in and around the knee joint is very common and often recovers spontaneously. More persistent knee pain may indicate a specific condition as described in the 'Causes' section.

Causes (Table 2.15)

Mechanical

- Anterior knee pain/patellofemoral pain:
  - Pain at the front of the knee, made worse by inactivity, stair climbing, or any activity involving bending the knee. Often aggravated by sport. Common at time of growth spurts.
  - Genu valgum, hypermobility, femoral torsion, and pronated feet contribute to anterior knee pain.
  - Management:
    - — Optimizing strength of pelvifemoral musculature.*
    - — Optimizing balance between quadriceps and hamstrings.
    - — Optimizing strength between individual components of quadriceps muscle bellies.
    - — Improving proprioception.
    - — *Note: non-participation in PE/sport does not influence rate of recovery* so participation is strongly encouraged where possible.
- Chondromalacia patellae:
  - This term is a misnomer and source of confusion. The presence of 'soft cartilage' is not correlated with patellar pain.
  - If anterior knee pain then see earlier in this list.
- Patella dislocation:
  - The patella commonly tilts and glides toward the lateral aspect of the knee—the patella may slip and stay there—'dislocation'—although slips which sublux and return to the anatomically correct position are more common.
  - Several anatomical conditions can precipitate recurrent dislocation—flat patella, patella alta, shallow femoral trochlea, femoral torsion, loose medial structures, general joint laxity.
  - Management: optimizing strength of pelvifemoral musculature, reduction of patella, and knee immobilized. For recurrent dislocation—arthroscopic lateral release of lateral retinaculum or stabilization of the patella.
- Osgood–Schlatter's disease:
  - Caused by repetitive microtrauma to the tibial tubercle apophysis, usually in jumping sports (overuse traction apophysitis).
  - Symptoms—often low-grade ache and inflammation around tibial tuberosity, associated with activity. Pain relieved by rest.
  - Signs—pain reproduced by resisted extension from 90° of flexion.
  - Imaging –x-ray usually normal. US/MRI may show fragmented apophysis.
  - Management—ice for pain, activity modification, i.e. encourage swimming and cycling and avoid jumping. Symptoms are self-limiting.

- Sinding–Larsen and Johansson syndrome:
  - Caused by repetitive microtrauma at the insertion of patellar tendon onto lower patella pole (overuse traction apophysitis). Often seen in conjunction with over pronated feet.
  - Symptoms—pain and tenderness precipitated by overstraining or trauma.
  - Signs—slightly swollen, warm tender bump. Pain worse on resisted extension.
  - Imaging—US/MRI may show fragmented lower pole of patella. Helpful to monitor disease course.
  - Management—initially ice, stretching, and strengthening exercises. Avoid running, jumping, squatting activities. Usually resolves in 3–6 months.
- Plica syndrome:
  - Result of remnant fetal tissue in the knee. When knee flexed plica is exposed to injury and becomes inflamed.
  - Can be confused with meniscal tears or patellar tendonitis.
  - Imaging—MRI often not helpful. Often seen on arthroscopic examination.
  - Management—NSAIDs, intra-articular cortisone, activity modification.
- Osteochondritis dissecans:
  - Focal area of detached or semi-detached subchondral bone with hyaline articular cartilage on top. Common cause of loose body within the knee. ♂:♀=3:1.
  - History of trauma in approx 40%.
  - Symptoms—initially pain, then locking and weakness.
  - Signs—may be normal.
  - Imaging—x-ray, MRI, or arthroscopy can be used to confirm diagnosis.
  - Management—referral to Orthopaedics. Fix bone fragments in place or remove if loose.
- Loose body:
  - Can be fibrinous (i.e. inflammation), cartilaginous (i.e. meniscal tear), or osteocartilaginous (i.e. osteochrondritis dissecans).
  - Presents with knee, pain, intermittent locking, the joint may 'give way' and signs of tenderness, soft tissue swelling, joint effusion may be present and extension may be limited.
  - Imaging—x-ray may demonstrate larger lesions. US/MRI and arthroscopy can confirm diagnosis.
  - Management—for small lesions NSAIDs may be helpful but in general loose bodies need to be removed by arthroscopy.
- Haemarthrosis:
  - In ~80% cases, this follows a twisting injury to the knee, i.e. anterior cruciate ligament rupture with pain and swelling (ofen large) <15 to 30min of injury with large tense knee effusion, often hamstring spasm and severe limitation of movement.
  - Imaging—x-ray, MRI, or arthroscopy to confirm underlying injury.
  - Management—aspiration to confirm. Referral to Orthopaedics.

- Fat pad impingement syndrome:
  - Traumatic and inflammatory changes in the infrapatellar fat pad.
  - Symptoms—pain, swelling, restricted movement, and symptoms may be chronic and infrapatellar. Pain is present when the flexed knee is extended suddenly.
  - Imaging—MRI, acute findings of ↑ fluid and chronic findings similar to scarring after arthroscopy. Arthroscopy doesn't visualize the fat pad well.
  - Management—NSAIDs if inflammation persistent, quadriceps strengthening or taping may be helpful.
- Iliotibial band* or tensor fascia lata (TFL) problems can present with knee pain or pain may be higher up thigh.

Inflammatory

- Septic arthritis or osteomyelits (see 🕮 p 64)
- Juvenile idiopathic arthritis (see 🕮 p 28 and p 129)
- Reactive arthritis (see 🕮 p 67)
- The presence of red flag symptoms (fever, chills, weight loss) indicate urgent referral.

Tumours

- Benign—osteochondromas can occur in femur or tibia resulting in knee pain. Often not painful and don't require surgery.
- Malignant—osteosarcoma (commonly around the knee) and Ewing's Sarcoma (involves long bones of leg or pelvis). Need urgent referral to paediatric orthopaedics/local bone tumour service (see 🕮 p 60).

*Optimizing hip abductors strength helps to support the knee whilst a tight iliotibial band can pull the patella laterally exacerbating maltracking along the femoral groove.

Further reading

Arthritis Research UK. *Topical Review — Anterior knee pain.* Available at: 🖱 http://www.arthritisresearchuk.org/files/6524_05032010143501.pdf.

Table 2.15 Summary of causes of mechanical knee pain

	Symptoms	Signs	Management	Orthopaedic referral
Patellofemoral pain	Pain Worse with activity	Genu valgum Hypermobility Tibial torsion Pronated forefeet	Physiotherapy Activity modification	No
Patella dislocation	Pain	Dislocated patella	Reduction of patella Mobilization	Yes if recurrent dislocation
Osgood–Schlatter	Pain on activity	Pain on resisted extension	Ice Activity modification	No
Sinding–Larsen–Johannson	Pain lower pole patella	Tender lower pole patella Worse on extension	Ice Physiotherapy Activity modification	No
Plica syndrome	Pain on flexion	May be tenderness	NSAID, IA steroids, activity modification	No
Osteochrondritis	Pain, Locking Weakness	May be normal	Analgesics	Yes
Loose body	Pain, Locking Giving way Swelling	May be normal Tenderness, effusion, ↓ extension	NSAIDs	Yes—arthroscopic removal of loose body
Haemarthrosis	Pain Swelling (soon after injury)	Large, tense effusion Hamstring spasm	Aspiration to confirm	Yes
Fat pad impingement	Pain, swelling ↓ movement	Pain when knee flexed suddenly	NSAIDS, Physiotherapy	No

Foot and ankle problems

Flexible flat feet

- Clinical—considered 'normal' in many children (see 🕮 Normal variants and chapters on podiatry, p 9):
  - By 8yr, few children have flat feet.
  - Absence of arch when standing flat, but arches apparent when stand on tip-toe or big toes passively dorsiflexed.
  - More common in hypermobile children—typically symptomless (present with parental anxiety).
- Management—reassurance and footwear advice, most do not benefit from insoles/physiotherapy input.

Red flag

Failure of arch to return on tip-toe standing implies rigid flat feet: consider tarsal coalition or arthritis at sub-talar joint (see 🕮 p 385).

Tarsal coalition

- Definition:
  - Failure of segmentation of tarsal bones, typically calcaneonavicular or talocalcaneal joints.
  - May be cartilaginous/fibrous (and therefore missed on x-ray).
- Clinical:
  - Painful feet, non-flexible flat feet (50% bilateral).
  - Typically presents in adolescents (♂>♀).
- Management—orthotics, NSAIDs, in extreme cases, surgery is required.

Pes cavus

- Clinical:
  - A normal variant (see 🕮 p 9).
  - 'High arches' and may associate with persistent tip-toe gait.
  - May be asymptomatic or present with pain (2° to metatarsal compression) or clumsy walking.
  - Consider neurological/neuromuscular abnormalities, e.g. spina bifida, Charcot–Marie–Tooth, Friedreich's ataxia, or metabolic storage diseases (see 🕮 p 312).
- Management:
  - Typically no treatment is needed.
  - May require insoles/orthoses and refer for surgery if pain is severe.

Metatarsus adductus

- Clinical:
  - A normal variant (see 🕮 p 9).
  - Causes in-toeing (medial deviation of foot); can be familial or positional.
- Management—tends to correct with wearing shoes, rarely needs treatment (such as serial casting, splints).

Rocker bottom feet

(= congential convex pes valgus = congenital vertical talus)

- Clinical:
  - Usually detected in newborn, talus dislocated, pointing downwards.
  - Associated with neurological problems but often idiopathic.
- Management—casting is little use if foot not flexible and surgery may be required.

Congenital talipes equinovarus

(=clubfoot)

- Clinical:
  - Usually detected in newborn, foot held pointing down (equino) and folded in (varus).
  - Structural abnormality (as opposed to positional talipes which resolved with physio).
- Management:
  - Casting (Ponseti method) is current treatment of choice.
  - May need surgery.

Intoeing

- Clinical:
  - Normal variant (see 🕮 p 9 Normal variants).
  - Usually a result of a rotational deformity of long bones rather than an abnormality in the foot (most often due to femoral anteversion (90%) or tibial torsion):
    - — Assess patella position with child standing feet pointing forwards—if patella pointing straight, then rotational deformity is distal, if pointing medially, rotational deformity is proximal).
    - — Assess thigh–foot angle (see 🕮 Clinical skills, p 1).

Achilles tendonitis

- Clinical:
  - Typically an overuse injury in sporty children.
  - Rare in those <14yr, pain with activity, especially jumping.
- Management:
  - Rest, ice, compress, elevate (RICE).
  - Modify activity/stretching exercises/physiotherapy/orthoses (gel heel cup).
  - NSAIDs.
  - ***Never*** inject steroids (this weakens the tendon, risking rupture).

Sever's disease (similar to apophysitis at other sites)

- Definition—apophysitis of os calcis at insertion of Achilles tendon.
- Clinical:
  - Typically occurs before skeleton matures, as a result of either rapid growth or excessive activity.
  - Usually children 7–14yr old and present with pain increasing with activity.
- Management: similar to Achilles tendonitis.

Plantar fasciitis

- Clinical:
  - Inflammation of plantar fascia, usually from repeat microtrauma.
  - Heel pain, worse with ↑ activity (or impact to ground).
- Differential diagnosis: includes JIA (enthesitis-related arthritis) see 🕮 JIA, p 129.
- Management—similar to Achilles tendonitis.

Osteochondroses (also see 🕮 Osteochondroses, p 343)

- Occur in growing skeleton, with disruption of blood supply due to recurrent insult.
- Kohlers's disease:
  - Osteochondrosis of navicular bone.
  - Typically 5–9yr-olds with midfoot pain, swelling, (can be bilateral).
  - X-ray: ↑ sclerosis of navicular bone.
  - Management—as for Achilles tendonitis.
- Freiberg's disease:
  - Osteonecrosis of 2nd or 3rd metatarsal head.
  - Typically adolescent girls, increasing forefoot pain and focal tenderness over head of affected head.
  - Management—RICE, modify activity/footwear, surgery in extremes.

Arthritis

- Can affect any joint in ankle/foot especially if swollen or restricted in range of movement.
- Need to consider septic/reactive/JIA (see 🕮 p 64):
  - Septic—febrile, unwell child, extreme reluctance to move joint, raised acute inflammatory markers (esp. CRP), other markers of sepsis—see 🕮 Infection, p 355.
  - Reactive—recent history URTI or GI upset (and sexually acquired infection in the adolescent)—see 🕮 Infection, p 64.
  - JIA: see 🕮 Chapter 3, p 129.

Joint hypermobility

Background

- The normal range of motion of joints is variable, with children possessing an inherently greater range than adults, and ♂>♀.
- The prevalence of hypermobility in children has been variously reported between 2.3% and 39% dependent on the age, ethnicity, and defining criteria used.
- The majority of these children are asymptomatic, and many use their hypermobility to advantage, e.g. ballet dancers who are hypermobile appear to be at less risk of injury, and musicians benefit from a wide hand span.
- Conversely, some children and young people suffer symptoms, presumed to be 2° to their hypermobility, and in this case the condition is called 'benign joint hypermobility syndrome' (BJHS).
- Various symptoms have been attributed to the BJHS including delayed motor milestones, constipation, urinary tract infection and dysfunction, impaired proprioception (↑ falls and developmental co-ordination disorder), and musculoskeletal pain although the relationship with these symptoms is controversial.
- Symptoms do not appear to be directly correlated with the number of joints involved.

Definition

- There are no validated scoring systems for hypermobility in children.
- The Beighton score and modified Brighton score are recognized in adults.
- However, 26.5% of healthy Dutch children (n=773) aged 4–9yr scored ≥4, and 5.3% aged 10–12yr. Thus Beighton scoring defines a quarter of all children <10yr of age as hypermobile. This scoring system is therefore not sufficient alone, to define those children with BJHS.
- There have been attempts at refining these scores (Bulbena score) but there is no scoring system validated for children.
- *Pragmatic definition of BJHS*—a child or young person with musculoskeletal pain and signs of hypermobility, with no other cause found for their symptoms.

9-point Beighton scoring system for joint hypermobility (≥4 points defines hypermobility)

Scoring 1 point each side

- Passive dorsiflexion of the 5th MCP joint to 90°.
- Apposition of thumb to volar forearm.
- Hyperextension of the elbow >10°.
- Hyperextension of the knee >10°.

Scoring 1 point

- Touch palms to floor with knees straight.

10-point Bulbena scoring system (≥3 in males and ≥4 in females defines hypermobility)

(% denotes incidence in 114 subjects with BJHS.)

Upper arm

- Passive apposition of thumb to flexor aspect of forearm at <21mm (92%).
- Palm of hand resting on table, passive dorsiflexion of the 5th finger ≥90° (93%).
- Hyperextension of the elbow ≥10° (75%).
- Excess shoulder lateral rotation: upper arm touching body, elbow flexed at 90, forearm externally rotates by >85° (84%).

Lower extremity, supine position

- Passive hip abduction >85 (78%).
- Patellar hypermobility—holding proximal tibia, excess passive lateral movement of the patella (89%).
- Excess range of passive dorsiflexion of the ankle and eversion of the foot (94%).
- Dorsal flexion of the 1st MTPJ ≥90° (61%).

Lower extremity prone position

- Knee flexion allows heel to contact buttock.
- Ecchymoses after minimal trauma (63%).

Epidemiology

- There is a greater range of joint mobility in Asians than sub-Saharan Africans, who are more mobile than Caucasians. Girls affected more commonly than boys.
- A significant proportion of new referrals to paediatric rheumatology clinics have musculoskeletal pain and hypermobility.

Pathophysiology

Unknown. Genes encoding collagens and collagen-modifying enzymes are considered to be good candidates. Adult studies suggest abnormality in collagen bundle structure on skin biopsy.

Clinical presentation

Symptoms

- The child has joint pain during or after activity. Typically they complain of pain in lower limbs after walking just short distances and this is commonly manifested when walking to and from school.
- Pain occurring in the evening after an active day, again typically in the lower limbs (see 🕮 Anterior knee pain, p 117).
- Occasional joint swelling, lasting a few days only.
- Handwriting difficulties.
- Joint dislocation/subluxation—less common.
- 'Clicking' and 'cracking' of joints.
- Frequent 'sprained ankles'.
- Back pain, anterior knee pain, and TMJ dysfunction may be associated.

Family history
Frequently 1st-degree relatives are also described as having lax joints or being 'double jointed'.

Past history
- There is some evidence that BJHS is linked with delayed motor development and the mean age of first walking may be later (15 months).
- Described as clumsy, poor coordination and some have a diagnosis of developmental coordination disorder.
- Constipation, urinary tract infections/dysfunction.
- Non-specific abdominal pain, headaches and generalized pain sometimes associated.

Examination
- Height and weight show normal growth.
- Normal examination of cardiovascular, respiratory, and abdominal systems. Neurological examination reveals normal muscle bulk, strength, and reflexes.
- Musculoskeletal examination shows ↑ range of joint movement. Pes planus with calcaneo valgus, i.e. a mobile flat foot (arch forms when child stands on tip-toe) and valgus heel position are common. Paradoxically tight hamstrings are often found (see 🕮 Anterior knee pain, p 117).
- Normal skin elasticity, absence of scarring, dentition, and palate. Bruising may be more common.

Differential diagnoses
BJHS is primarily a clinical diagnosis dependent on typical clinical history and physical signs. The following differentials should be considered and ruled out clinically or by investigation:
- Known heritable connective tissue disorder (see 🕮 Heritable connective tissue disorders, p 346), e.g.:
  - Ehlers–Danlos syndrome (other than type III—the hypermobility type)—look for skin hyperextensibility, bruising, tissue paper scarring.
  - Marfan syndrome—mafanoid habitus, cardiovascular or ocular involvement.
  - Osteogenesis imperfecta—blue sclerae, short stature, multiple fractures and hearing loss.
- Juvenile idiopathic arthritis (see 🕮 JIA, p 129).
- Pain syndromes: diffuse idiopathic pain syndrome; localized idiopathic pain syndrome; fibromyalgia (see 🕮 Pain syndromes, p 87).
- Malignancy: leukaemia; Ewing's sarcoma; osteosarcoma.
- Congenital disorders associated with hypermobility: Down syndrome; Williams' syndrome, Stickler's syndrome; autistic spectrum disorders; metabolic disorders such as homocystinuria.

Management
- In the majority of mild cases, all that is required is a diagnosis with explanation of the condition, reassurance that serious pathology has been excluded and written information (see 🕮 Patient information, p 127)

- The child and family need to know that there are no long-term consequences (the link with later osteoarthritis unproven).
- Escalation of analgesia is common, but universally unhelpful and should be avoided.
- Supportive footwear is often beneficial (e.g. trainers—fastened properly!). The evidence for orthotics is poor.
- More severe cases may benefit from physiotherapy, targeted or generalized and occupational therapy may help with handwriting and manual dexterity.
- If there are particular problems with generalized pain resulting in fatigue, reduced activities, and school absence, cognitive behavioural therapy with graded physical exercise and goal setting may benefit the child/young person.

Idiopathic nocturnal leg pain

Common, benign condition, otherwise known as 'growing pains' characterized by intermittent lower limb pain with symptom-free intervals of days, weeks or months. There is a reported association with hypermobility. See 🕮 Growing pains, p 92.

Patient information

- The Hypermobility Syndrome Association website for kids and teens: 🖰 http://teens.hypermobility.org/index.php.
- Arthritis Research UK patient information leaflet: 🖰 http://www.arthritisresearchuk.org/arthritis_information/arthritis_types__symptoms/joint_hypermobility.aspx http://www.arthritisresearchuk.org/files/6019_HYPER_05-3_01032010140241.pdf.

Further reading

Kemp S, Roberts I, Gamble C, *et al.* A randomised comparative trial of generalised vs targeted physiotherapy in the management of childhood hypermobility. *Rheumatology* 2010; **49**:315–25.

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Juvenile idiopathic arthritis

Genetics and JIA: HLA and non-HLA/MHC associations with subtypes of JIA

Association studies in JIA

The association study is the standard methodology used in the search for genetic risk factors for JIA. There are a number of issues regarding study design that the clinician must be aware of, to understand and put into context the genetic findings to date for JIA (Fig. 3.1).

Genetic risk factors identified to date for JIA

Human leucocyte association (HLA)

- The major histocompatibility complex (MHC) is the most consistently associated locus in JIA.
- Multiple HLA class I and class II associations exist with JIA, with each ILAR subtype having a specific pattern of HLA associations, although it should be noted that there are also overlapping associations, particularly between oligoarthritis and RF−ve polyarthritis.

Non-HLA/MHC loci

- The candidate gene approach has been the main strategy used in the search for JIA susceptibility loci to date.
- Some association studies performed in the past for JIA have suffered from inadequate sample sizes.
- There are now 10 regions of the genome that show association with JIA in more than one dataset, these are highlighted in Table 3.1.
- There has been only one genome wide association study (GWAS) for JIA published to date. This GWAS identified the HLA region as being associated with JIA and association of the *VTCN1* (*B7-Homolog 4* [*B7-H4*]) gene with JIA was identified and subsequently validated in an independent dataset.
- Larger well-powered GWAS will be required to detect additional loci with modest effect sizes. The International Childhood Arthritis Genetics (INCHARGE) consortium has now been established and this will enable the collection of large sample sizes for all JIA ILAR subtypes, which will be used for GWAS and validation.

Subgroup-specific associations

There is an issue with association analysis by JIA subtype in that, for many JIA case cohorts, it results in small sample sizes that often are not sufficiently powered to detect the modest effects conferred by these complex disease genes. A few potential subtype specific effects are emerging:

- A number of SNPs in the *IL1 ligand* cluster and *IL1 receptor* cluster show replicated association with sJIA.
- A SNP in the *IL6* promoter shows association with sJIA.
- A SNP in the endoplasmic reticulum aminopeptidase 1 (*ERAP1*) gene, formerly known as *ARTS1*, which shows robust association with AS has been shown to be associated with the enthesitis-related arthritis subtype of JIA.
- A SNP in the *IL23* receptor gene shows association with the psoriatic arthritis subtype of JIA.

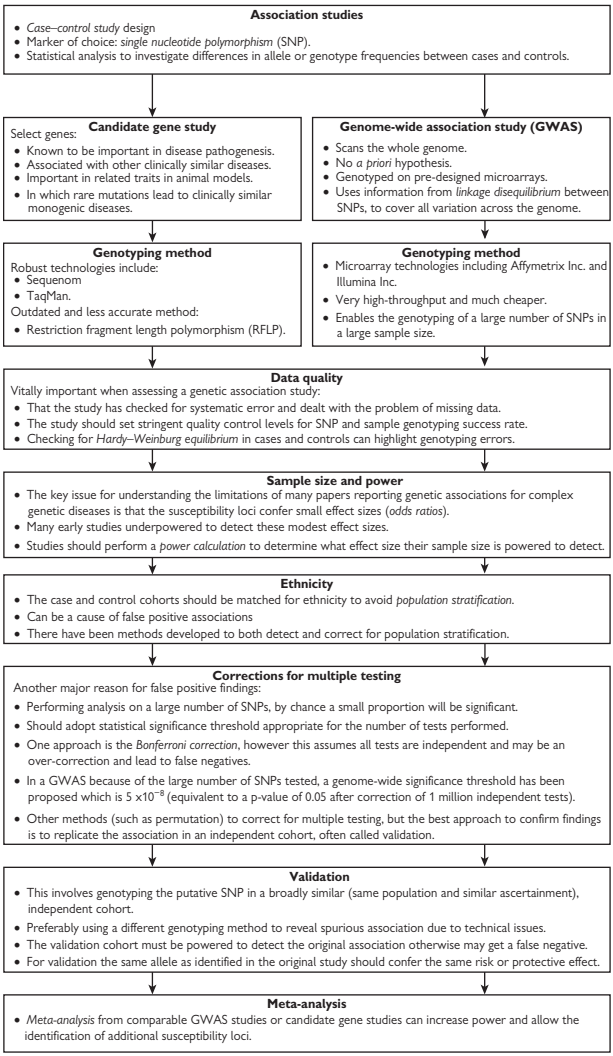

Fig. 3.1 Association studies.

What happens once a genetic effect has been identified?

Resequencing/fine-mapping

- This is the stage that many of the studies are currently at, and the next step is a challenging one.
- In most cases it is unlikely that the candidate gene study or GWAS will identify the actual *causal variant*, but they detect single nucleotide polymorphisms (SNPs) which happen to be correlated with the causal variant.
- In most situations it will be important to screen the whole region for all genetic variation, by resequencing and then fine-mapping the association by genotyping them in cases and controls.

Functional analysis

- Once all the statistical analysis has been performed and the most likely causal variants have been identified then the functional role of the implicated variants will be investigated.
- This will highlight the molecular and pathological mechanisms that are involved in the development of the disease.

What can these genetic findings tell the clinician about JIA?

- It will inform us of the important pathways involved in JIA disease pathogenesis. We are already seeing strong evidence to suggest a vital role for the IL-2 pathway in JIA and other autoimmune diseases. Once we know more about the biology of JIA, we may identify novel therapeutic targets.
- Eventually it may help us predict disease risk. We are not at this stage yet as it is important to remember that for many of the loci identified to date the actual causative genetic variant has not yet been clearly defined.
- Genetic susceptibility factors may be important in determining not only susceptibility to JIA but also to a child's disease outcome. Prospective, long-term outcome studies, such as the CAPS (Childhood Arthritis Prospective Study), will be vital in exploring this hypothesis.

Conclusions

We have made some progress in the search for genetic risk factors for JIA, but the next few years look set to bring huge advances in the genetic knowledge for JIA, with the publication of well-powered GWAS in JIA as a whole and by subtype.

Table 3.1 Non-MHC loci associated with JIA and validated in independent cohorts

Gene	SNP	Study population	Subtypes tested	Association
PTPN22	rs2476601	UK	All	Y
	rs2476601	Norway	All	Y
	rs2476601	Finland	O and RF-P	N not in total dataset
	rs2476601	US	O, EO, and RF-P	Y
IL2RA	rs2104286	UK	All	Y
	rs2104286	US	O, EO, and RF-P	Y
	rs2104286	US	All	N
IL2	rs6822844	Dutch	O, EO, RF-P, and SO	Y
	rs6822844	UK	All	Y
	rs17388568	US	O, EO, and RF-P	Y
STAT4	rs7574865	UK	All	Y
	rs7574865	US	All	Y
	rs7574865	US	O, EO, and RF-P	Y
TRAF1/C5	rs10818488	Dutch	O, EO, RF-P, RF+P and SO	N not in total dataset. Association in the O subset
	rs3761847	US	All	Y
	rs2900180	UK	All	Y
	rs3761847	US	All	N
	rs3761847 rs2900180	US	O, EO, and RF-P	N
TNFAIP3	rs6920220 rs13207033*	UK	All	Y
	rs6920220 rs10499194	US	All	Y
	rs6920220 rs13207033 rs10499194	US	O, EO, and RF-P	N

O=Oligoarticular; EO= Extended oligoarticular; RF-P=Rheumatoid factor polyarticular; RF+P=Rheumatiod factor positive polyarticular; SO=Systemic onset

(*continued*)

Table 3.1 (*Contd.*)

Gene	SNP	Study population	Subtypes tested	Association
CCR5	CCR5Δ32	US	O, EO, RF-P, RF+P and SO	Y
	CCR5Δ32	Norway	All	N
	CCR5Δ32	UK	All	Y
C12orf30/ SH2B3 /ATXN2	rs17696736	US	All	Y
	rs653178	UK	All	Y
	rs17696736	US	O, EO, and RF-P	Y
SLC11A1 (NRAMP1)	D2S1471	Latvia	O, EO, RF-P and RF+P	Y
	D2S1471	Finland	O, EO, RF-P and RF+P	Y
PTPN2	rs7234029	US	O, EO, and RF-P	Y
	rs7234029	UK	All	Y

O=Oligoarticular; EO= Extended oligoarticular; RF-P=Rheumatoid factor polyarticular; RF+P=Rheumatiod factor positive polyarticular; SO=Systemic onset

Definitions often used in Clinical Genetics

Allele
Alternative form of a genetic locus; a single allele for each locus is inherited from each parent.

Association study
Investigation of correlation between a genetic variant and disease/trait.

Bonferroni correction
The simplest correction of individual p-values for multiple testing, the formula is $p_{corrected} = 1 - (1 - p_{uncorrected})^n$.

Candidate gene
A gene for which there is evidence for a possible role in the disease or trait that is under investigation.

Case–control design
An association study design which compares group of individuals (cases) that are selected for the phenotype of interest with a group not ascertained for the phenotype (controls).

Causal variant
The actual disease causing variant. This may be a non-synonymous coding SNP which has a significant effect on the protein, or it can affect expression of the gene, causing upregulation or downregulation of the protein.

Genome wide association study (GWAS)
Association study performed for a dense array of SNPs, which capture a substantial proportion of common variation in the genome, genotyped in disease cases and ethnically matched controls.

Genotype
The combination of each allele inherited from each parent forms a person's genotype for a SNP.

Haplotype
A combination of alleles at a region (locus) on a chromosome that are transmitted together.

Hardy–Weinberg equilibrium (HWE)
A theoretical relationship between genotype and allele frequencies, for a SNP, that is found in a stable population. In the context of genetic association studies, deviations from HWE can be used to highlight genotyping errors.

Linkage analysis
Mapping of genes, by typing genetic variants, in families to identify regions that are associated with a disease or trait within a pedigree more often than expected by chance.

Linkage disequilibrium
Combinations of alleles or genetic markers which occur together more or less frequently in a population than would be expected from a random formation of haplotypes from alleles based on their frequencies.

Meta-analysis
A method of combining results across genetic studies. It can involve the combination of p-values or, more commonly, effect sizes. It can lead to increased statistical power, give more precise estimates of effect size, and also allows assessment of consistency and heterogeneity of association across different study populations.

Minor allele frequency (MAF)
The frequency of a SNP's less frequent allele in a given population.

Odds ratio (OR)
A measurement of association that is commonly used in case–control studies. It is defined as the odds of exposure to the susceptible genetic variant in cases compared with the odds of exposure in controls. If the odds ratio is >1, then the genetic variant is associated with disease.

Population stratification
This is caused by systematic differences in allele frequencies between subpopulations in a population possibly due to different ancestry; if these subgroups also have a difference in prevalence of the disease or trait studied that it can lead to false positive associations.

Power calculation
Assessment of how many samples must be collected and analysed in order to achieve sufficient power to detect the hypothesized effect. After conducting a study, power analysis can also shed light on negative results by indicating whether the study was underpowered, or what the smallest detectable effect size would be given the actual sample size.

Single nucleotide polymorphism (SNP)
DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered.

Further reading

Angeles-Han S, Prahalad S. The genetics of juvenile idiopathic arthritis: what is new in 2010? *Curr Rheumatol Rep* 2010;**12**(2):87–93.

Immunology and aetiology of JIA

Pathogenesis

- JIA is an autoimmune disorder; the immune system fails to distinguish between self and non-self and attacks synovium (membrane lining of the joint), leading to arthritis. The synovium becomes thickened, highly vascular, and infiltrated with T cells, macrophages, dendritic cells, B cells, and NK cells, and secretes an exudate (synovial fluid).
- Persistence of inflammation: cells are recruited into the joint by attaching to upregulated adhesion molecules on inflamed endothelium (inner layer of blood vessels). Resident fibroblasts (synoviocytes), and recruited immune cells, secrete high levels of chemokines, which attract further inflammatory cells, angiogenic factors (e.g. VEGF) lead to highly vascular proliferation of synovium.
- T cells are ↑ in synovium and synovial fluid and secrete several potent cytokines (see Table 3.2), leading to cartilage and bony damage. T cells secreting IL-17 (Th17 cells) are heavily implicated in chronic uveitis, extended oligoarthritis, psoriatic- and enthesitis-related arthritis. Remission in JIA is linked with high levels of synovial regulatory T cells (specialized T cells which counter inflammation).
- B cells are ↓ in synovial fluid, but circulating B cells secrete cytokines and activate T cells. Specialized B cells, plasma cells, secrete auto-antibodies (RF, anti-cyclic citrullinated protein [CCP], and ANA) associated with specific disease subtypes but are not thought to be directly pathogenic.
- sJIA shares features with other auto-inflammatory disorders (see 🕮 p 288); high levels of IL-1β and IL-6 cause systemic features and growth retardation. Macrophage activation syndrome (MAS, see 🕮 p 305) in sJIA is associated with a defect in NK cell function which prevents NK cells from killing activated lymphocytes and macrophages (see also 🕮 Genetics and JIA, p 130).

Genetics

- JIA is linked with several genetic polymorphisms (variations in the genetic code), but each only contributes a small risk of developing the disease.
- Genes linked with JIA include:
  - HLA system of immune recognition, expressed on almost all cells: *HLA-B27* is strongly associated with enthesitis related arthritis (ERA), A*02 with oligoarthritis and DRB1*11, DQB1 with RF –ve polyarthritis, *DR4* with RF+ve polyarthritis (as in adult RA).
  - Cytokine/chemokine-related genes: *IL-10* with oligoarthritis, *IL-6* with sJIA, and *IL-23* receptor with psoriatic arthritis and the chemokine *CCL5* and its receptor *CCR5*, and *TNF*α across all JIA subtypes.
  - Immune associated genes: *PTPN22*, *TRAF1*, *STAT4*, *CD25* are important in the control of T cell activation, mutations of *MUNC13-4*, and perforin in sJIA may be important in the development of MAS.

Environment

- *Infection:* there is no clear infectious trigger for JIA. DNA from several bacteria and viruses including parvovirus B19 have been detected in JIA serum and joints but are of uncertain significance.
- *Family conditions:* high parental income and being an only child are associated with JIA which relates to the hygiene hypothesis: lack of early childhood infection increases the risks of autoimmunity. Fetal exposure to smoking may increase the risk of JIA in girls.

Table 3.2 Summary of cytokines and inflammatory mediators important in JIA

Cytokine/mediator	Cell	Pathology
TNFα	Monocytes, T, B cells, PMN, mast cells, fibroblasts	Activates monocytes and neutrophils Damages cartilage ↑ endothelial cell adhesion molecules Inhibits regulatory T cells
IL-1β	Monocytes, B cells, fibroblasts	Activates osteoclasts (bone damage) Fibroblast cytokine, chemokine release ↑ endothelial cell adhesion molecules
IL-17	T cells (Th17), mast cells	Chemokine release (recruit PMN) Cartilage damage Activates osteoclasts Synergizes with TNFα and IL-1β
IL-6	Monocytes, fibroblasts, B cells	B cell activation Inhibits regulatory T cells Growth retardation Acute phase response and anaemia
IFNγ	T cells (Th1, CD8, NK cells)	Activates monocytes ↑ endothelial cell adhesion molecules May assist recruitment of Th17 cells
MRP8/14 (inflammatory mediator important in sJIA)	Monocytes, PMN	Activates monocytes, Promotes pathological CD8+ T cells Secretion of IL-1β ↑ endothelial cell adhesion molecules

Classification of JIA

- The Classification Taskforce of the Pediatric Standing Committee of the ILAR proposed consensus criteria for the classification of childhood arthritis under the umbrella term Juvenile Idiopathic Arthritis (JIA).
- The aim of this classification system was to attempt to address the differences in nomenclature and criteria between Europe and North America, enabling research on cause, epidemiology, therapeutic trials and outcome studies. A comparison of 3 criteria sets is given in Table 3.3.
- Many paediatric rheumatologists have embraced the ILAR classification. There are 7 different subtypes based on features present in the first 6 months of the illness as noted in Table 3.4. It was last updated in 2001.
- It is acknowledged that there are restrictions intrinsic to any classification system based on clinical criteria and there remains the need for further validation, modification, and consensus as new information on pathogenesis and genetics becomes available.

Table 3.3 Comparison of classification systems

	ILAR	EULAR	ACR
Name	Juvenile idiopathic arthritis	Juvenile chronic arthritis	Juvenile rheumatoid arthritis
Age of onset	<16yr	<16yr	<16yr
Duration	6 weeks	3 months	6 weeks
Subtypes of arthritis	1. Systemic 2. Oligoarticular: • Persistent • Extended 3. Poly; RF–ve 4. Poly; RF+ve 5. Enthesitis related 6. Psoriatic 7. Other	1. Systemic 2. Pauciarticular 3. Polyarticular (excludes RF+ve disease: known as juvenile rheumatoid arthritis)	1. Systemic 2. Pauciarticular 3. Polyarticular 4. (excludes spondyloarthopathies and psoriatic arthritis)

Further reading

Petty RE, Southwood TR, Baum J, *et al.* Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban. *J Rheumatol* 1998; **25**:1991–4.

Petty RE, Southwood TR, Manners P, *et al.* International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; **31**:390–2.

Table 3.4 Summary of ILAR classification of JIA

Subtype	Systemic onset	Oligoarthritis	Polyarthritis RF –ve	Polyarthritis RF +ve	Psoriatic arthritis	Enthesitis related arthritis	Other
Arthritis	In 1 or more joints with or preceded by daily (quotidian) fever for at least 3 days, accompanied by ≥1 of: • Evanescent erythematous rash • Generalized lymphadenopathy • Hepatomegaly and/or splenomegaly • Serositis	In 1–4 joints during first 6 months of disease Subcategories: • Persistent—affecting no more than 4 joints throughout course • Extended—affecting a total of >4 joints after the first 6 months of disease	In 5 or more joints during the first 6 months of disease RF test negative	In 5 or more joints during the first 6 months of disease RF test positive	Arthritis and psoriasis, or arthritis and at least 2 of • Dactylitis • Nail pitting or onycholysis • Psoriasis in 1st-degree relative	Arthritis and enthesitis or arthritis with at least 2 of the following • Presence or history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain • Presence of HLA B27 antigen • Onset in ♂ >6yr • Acute anterior uveitis • Ankylosing spondylitis, enthesitis-related arthritis • Sacroiliitis with inflammatory bowel disease • Reiter syndrome • Acute uveitis in 1st-degree relative	Undifferentiated with no category or 2 or more categories
Exclusions	A,B,C,D	A,B,C,D,E	A,B,C,D,E	A,B,C,E	B,C,D,E	A,D,E	

A: psoriasis or history of psoriasis in patient or 1st-degree relative, B: arthritis in HLAB27-positive male after 6th birthday, C: ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome or acute uveitis, or history of 1 of these in 1st-degree relative. D: presence of IgM RF on at least 2 occasions at least 3 months apart, E: the presence of systemic JIA.

JIA subtypes and their clinical presentations

- JIA is the commonest form of chronic inflammatory joint disease in children and adolescents and is defined as persistent joint swelling (of >6 weeks' duration) presenting before 16yr of age in the absence of infection or any defined cause.
  - 95% of children with JIA have a disease that is clinically and immunogenetically distinct from RA in adults.
  - Newly presenting JIA is one of the commonest physically disabling conditions of childhood, with a prevalence of approximately 1 in 1000 children, (i.e. the same as diabetes or epilepsy) and amounting to over 12,000 affected children in the UK.
  - JIA is a heterogeneous group of conditions and clinical presentations vary with both the disease subtype (Table 3.5).There are at least 7 different subtypes of JIA, the classification is essentially clinical and based on the number of joints affected in the first 6 months, the presence or absence of RF, HLA B27 tissue type, systemic features (such as fever or rash), and other extra-articular features (such as psoriasis or enthesitis).
- JIA is essentially clinical and one of exclusion with a wide differential diagnosis (see 📖 Clinical skills p 1):
  - Classically a joint affected by arthritis is swollen and painful with some restriction of movement. In the younger child, however, a history of pain is often absent. Parents may describe a child who refuses to stand or has a limp first thing in the morning but runs about normally later in the day. In the youngest children, JIA may present as delay in walking. Examination may be limited by lack of cooperation and findings may be subtle. Fortunately in the young child, joint involvement is usually asymmetrical and subtle loss of range of movement may be detected in comparison with the normal side.
  - Infection and malignancy are not uncommon and require careful consideration.
  - Consider septic arthritis in an unwell child with a single hot, swollen, painful joint (see 📖 p 64).
  - Consider malignancy in child with severe joint pain, especially at night (see 📖 p 56).
  - Consider haematological malignancy in a child presenting with suspected systemic onset JIA but with low white count and/or platelets and/or low ferritin (see 📖 p 56).
  - Acute rheumatic fever and Lyme disease are both increasingly seen in the UK and should be remembered in the differential diagnosis (see 📖 p 363 and p 368 respectively).

Table 3.5 Clinical features of JIA subtypes

	Population affected	Specific features of history	Characteristic clinical findings	Helpful investigations	Clinical course
Systemic onset	♀=♂ Peak at 4–7yr ~10% JIA	**Fever pattern**: 2 weeks of fever with daily (quotidian) spikes for at least 3 days; temperature falls to baseline or below in between. Fever spikes tend to be in the evenings but can occur at other times **Rash**: intermittent; most noticed when febrile or in bath/shower **Other systemic features:** general malaise; anorexia	**Arthritis:** may not be present for several weeks/months **Extra-articular:** *Systemically unwell:* (but may look surprisingly well between fever spikes) *Rash:* salmon pink, intermittent, macular rash (occasionally urticarial), rarely on the face, most evident during fever spikes. Koebner phenomenon may be observed *Other* lymphadenopathy, hepatosplenomegaly, pericardial rub, other evidence serositis	Full blood count and blood film—typical features: • Low haemoglobin • Raised platelets • Leucocytosis and neutrophilia • Serum ferritin elevated (if very marked, consider macrophage activation syndrome—see 📖 p 305) • High ESR, high CRP • Low albumin • Raised ALT/AST (transaminases) and abnormal clotting may indicated MAS* • Extensive investigations to rule out infection and malignancy frequently necessary • Bone marrow and urine catecholamines to exclude malignancy	Variable: • Monocyclic • Intermittent/recurrent • Persistent (50%) systemic and polyarticular phases

Oligo-articular onset	♀>>♂ Peak 2–4yr ~50% JIA	Swollen joint/s Limp or abnormal gait	**Arthritis** • 1–4 joints. Knee most common but also ankles/wrists • Up to 50% present with single joint • With late presentation may have limb length discrepancy or contracture **Extra-articular:** risk of uveitis	• ANA: positive in 50–70% • Normal inflammatory markers do *not* exclude JIA • Eye screening for uveitis • Imaging (x-ray/MRI):to exclude other pathology • Exclude TB in mono-articular presentation	**Persistent:** • 1–4 joints throughout course of disease • Up to 50% remission **Extended:** evolves to polyarticular course disease (>4 joints) after 6 months
Polyarticular onset RF+ve	♀>>♂ Usually 10yr+ ~5% JIA	Joint swelling, pain and loss of function, frequently affecting small joints of the hands	**Arthritis:** symmetrical joint involvement; small and large joints **Extra-articular:** • If acute often associated malaise, weight loss • Occasionally rheumatoid nodules • Uveitis very rare	RF+ve (antibodies to anti-CCP used as alternative in some centres) ESR/CRP raised	Clinically equivalent to adult RA May be aggressive with early erosive changes.

(*continued*)

Table 3.5 (*Contd.*)

	Population affected	Specific features of history	Characteristic clinical findings	Helpful investigations	Clinical course
Polyarticular onset RF–ve	♀>♂ Peaks at 2–4yr and 7–12yr	Varies from: **Acute**: history of joint pain, swelling and systemic upset to **Low grade:** an insidious onset, often presenting late with stiffness and/or joint deformity	**Arthritis** • 5 or more joints • Large and small joints • Usually symmetrical involvement • Risk of uveitis **Extra-articular** • Poor growth if late presentation • May have uveitis: ↑ risk if ANA is positive	RF−ve ANA+ve or −ve Normal inflammatory markers do not exclude JIA	Variable
Psoriatic	♀>♂ Peak 9–11yr	Psoriasis in child or 1st-degree relative	**Arthritis** • Large or small joints; any number • Dactylitis (diffuse swelling of a finger or toe; joint and surrounding tissues) **Extra-articular** • Psoriasis ± nail pitting/dystrophy • Uveitis not uncommon		Variable Oligo- or polyarticular course

Enthesitis related	♂>♀ >6yr	Joint swelling and or stiffness, usually lower limbs	**Arthritis:** • Lower limb, large joint involvement • Hips common • Sacroiliitis in minority (but may not be clinically evident until late adolescence/early adulthood) **Extra-articular:** enthesitis (inflammation of insertion of tendons into bone) characteristic	HLA B27 positive (30–50% depending on ethnic background) Imaging to exclude alternative pathology, e.g. SUFE MRI to determine sacroiliac joint involvement	Variable May evolve insidiously through teenage years to include spinal involvement (highest in those who are HLA B27+ve)
Other		Variable	Joint pain and swelling confirming inflammatory arthritis but excluded from other category by classification		

Prognostic indicators in JIA

It remains difficult to predict the prognosis for a child with JIA. Expert clinical consensus supports the view that current management of JIA, with its emphasis on rapid and effective disease control early in the disease course, is improving outcome; disability should now be preventable in the majority.

An ideal outcome for a child or young person with JIA is one where there is lifelong disease remission with no long-term functional or psychological effects. Suboptimal outcomes may result from:
- Poorly controlled joint disease with resultant joint damage.
- Visual loss from JIA-associated uveitis.
- Psychosocial morbidity.

The existing literature on the long-term outcomes generally shows poor functional outcome for many young people with JIA. However, these studies reflect historical treatment regimens rather than current best practice. Evidence predicting outcomes from current therapeutic approaches is limited to anecdote and awaits validation from ongoing long-term outcome studies, e.g. the Childhood Arthritis Prospective Study (CAPS, UK) and Research in Arthritis in Canadian Children Emphasizing Outcomes Study (ReACCH-Out, Canada).

In predicting the prognosis for a child with JIA, 2 main factors require to be taken into consideration:
- Heterogeneity in the disease and its response to treatment.
- Variability in access to optimal clinical care.

Disease heterogeneity

Indicators of poor outcome related to the disease itself are summarized in Table 3.6 and can be divided into:
- Risk factors for continuing active disease.
- Risk factors for long-term damage.

Access to care

For any child with JIA, regardless of the disease subtype and features, there is increasing consensus that access to appropriate care is an important determinant of outcome. The British Society of Paediatric and Adolescent Rheumatology (BSPAR) Standards of Care for children and young people with JIA (see 🕮 BSPAR, p 409) emphasize the importance of:
- Prompt diagnosis and referral to specialist care*
- Early aggressive treatment to control inflammation
- Support from a paediatric rheumatology MDT.

Success in achieving a good outcome mandates that the management must remain patient-centred, maximizing both physical and psychosocial well being. Optimal disease control may require challenging drug regimens and the support of a MDT is essential.

* Defined as: all children in whom JIA is suspected should be seen by a specialist paediatric rheumatology MDT within 10 weeks from onset of symptoms and 4 weeks from date of referral in order to facilitate early diagnosis, eye screening, and commence appropriate treatment.

Adverse prognostic factors for any child with JIA therefore include:

- Delay in diagnosis.
- Delay in referral to specialist team.
- Late disease control.
- Continued disease activity.

Paediatric rheumatology is a rapidly changing specialty. In the near future improvements in our ability to predict prognosis for a child with JIA will undoubtedly result from further advances in our understanding of:

- Genetic and molecular mechanisms involved in the immunological and inflammatory processes.
- Genetic predictors of response to drugs.
- Detection of subclinical disease with imaging.
- Availability of new targeted therapeutic approaches.

Table 3.6 JIA subtypes and risk factors for poor disease outcomes

	Risk factors for:	
	Continuing active disease	**Long-term damage**
Subtype of JIA	Psoriatic	*Polyarticular onset:* both onset and disease course (e.g. extended oligoarticular disease) *sJIA*: ongoing active systemic features at 6 months defined as fever, need for corticosteroids, and thrombocytosis
Sex		♂ in sJIA
Age	Young age in oligoarticular and RF−ve polyarticular	
Blood markers	RF+ve ANA+ve (↑ risk of uveitis) Persistently raised platelet count in sJIA	RF+ve Normal inflammatory markers with late diagnosis
Clinical features	Subcutaneous nodules	Symmetrical joint disease Hip involvement Rapid & early involvement of small joints of hand and feet Early radiographic changes Presentation with uveitis as 1st symptom; or visual loss at 1st eye screen

Further reading

CAPS: http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/outcomestudies/caps.

ReACCH-Out: http://www.icaare.ca/index.php?option=com_content&task=view&id=28&Itemid=46.

Uveitis screening in JIA: the approach to screening and guidelines

Rationale for screening

- JIA is associated with a significant risk of developing asymptomatic chronic anterior uveitis (CAU).
- JIA CAU is the leading cause of visual loss from childhood uveitis, and is associated with a high level of eye complications.
- Early regular eye-screening is a key component in the care of JIA patients because it aims to reduce the incidence of visual impairment by early detection and intervention.

Justification for a screening programme

- Provision of expensive screening is justified because it fulfils many, but not all, of the criteria for an effective screening programme, principally:
  - Slit lamp examination is a safe, effective screening test identifying CAU earlier in the disease course than children can themselves identify the subtle eye symptoms.
  - The incidence of CAU is high, affecting 10% of all JIA patients; the highest-risk subgroup of JIA, extended oligoarthritis, has an incidence of 35–57%.
  - 40% of CAU is present at the first eye screen.
  - The duration of persistent inflammation in the eye is a key poor prognostic factor which can be reduced by screening.
- The outcome of JIA CAU remains poor despite screening, indicated by the following:
  - Bilateral disease in 67–85%; significant eye complications in >40% of cases—cataract, glaucoma, macular oedema, hypotony.
- Early treatment is a key aim to improve outcomes. There is increasingly effective treatment for CAU available.

Population requiring screening

- Screening should equally be offered to children with JIA (all subgroups), whether they have few or many affected joints, and despite some variation in risk.
  - Evidence of significant risk to warrant screening exists for persistent and extended oligoarthritis, RF−ve polyarthritis, psoriatic arthritis, and also undifferentiated arthritis
- Performing the first screen as early as possible is a key aim and in reality eye screening is often performed before the diagnosis of JIA is absolutely clear (e.g. in cases which are ultimately are diagnosed as reactive arthritis). Screening should be performed before the subgroup of JIA is confirmed as the classification evolves over time.
- Uveitis is more common in the following:
  - Girls, younger age patients.
  - JIA patients who are ANA+ve (albeit of patients with uveitis, 50% are ANA−ve)—therefore children with JIA and who are ANA−ve also need eye screening).
  - Severe uveitis is associated with younger age and male sex.

- Enthesitis-related arthritis (ERA) is usually associated with acute anterior uveitis (and often patients carry HLA B27) which presents promptly with a painful red eye. However, reports of asymptomatic CAU in ERA, leads to its inclusion in some screening programmes.

Exclusions to screening

Two subgroups of JIA are not associated with a high level of CAU, and are not offered screening in all programmes. A single eye screen at presentation of JIA is recommended, particularly where the diagnosis is unclear.

- RF+ve polyarticular JIA (RF+JIA) is not associated with CAU, and as disease onset is usually in later adolescence may not be considered for screening in some programmes.
- A small number of case reports exist of CAU in sJIA. Other conditions that could mimic sJIA, such as CINCA (amongst many others), do develop CAU, which raises a question about the diagnosis in these older case reports. *As a rule of thumb developing CAU in sJIA should lead to the question: 'Is this really sJIA?'.*

Structure of the screening programme

The core principles of the screening programmes are listed in Table 3.7.

Variations in screening programmes between countries often relate to the lack of a clear evidence base to address these statements. Important points to consider are the following:

- Those providing eye screening should be appropriately trained, skilled at examining young children, and should audit the robustness of their screening programme.
- Most uveitis develops early in the disease course:
  - The first eye screen is critical, and should be made immediately after the diagnosis of JIA, or before certain diagnosis if JIA is likely.
  - Screening in the first and early years should be adhered to robustly.
  - Robust mechanisms to identify non-adherence to the screening programme are important.
- Immediate access to advice and assessment should be offered should eye symptoms develop between screening visits or after discharge from the screening programme.
- A revised screening schedule should be offered if the risk of uveitis increases, such as discontinuation of maintenance drugs (e.g. patients on biologics who stop taking methotrexate—*anecdotally there are reports of de novo uveitis or flares occurring with etanercept use*—see 📖 p 434).
- Children with JIA who are too young or otherwise unable (e.g. learning difficulties) to recognize subtle changes in their vision associated with the development of CAU must be offered eye screening.
  - Rapid access to an examination under anaesthetic (EUA) should be available for all children unable to comply with screening examinations. The children least likely to comply are at the highest risk for undetected disease, i.e. the youngest or those with learning disability.
- Once considered high enough risk to merit inclusion in the screening programme, the screening interval offered should *not* be related to the risk of developing uveitis, but to the natural history of uveitis should it develop.
  - The screening intervals should be short enough so that should uveitis develop, no irreversible damage occurs between screening visits.

  - There is a poor evidence base for determining the screening interval.
- Eye screening continues until the child is old enough to detect the symptoms of uveitis and is usually 12yr of age as a minimum.
  - Whilst the risk of developing uveitis falls with time from the date of last active arthritis, date of diagnosis, and with increasing age, children discharged from screening are still at risk of uveitis, and are discharged because they are considered old enough to identify subtle changes in their vision. In children with learning difficulties screening may be required for longer until the risk is low.

Details of the screening assessment

- Screening involves slit lamp examination of anterior, intermediate, and posterior chambers of the eye:
  - A slit lamp examination by a skilled operator is required, i.e. ophthalmologist (or optometrist) skilled and experienced at examining children's eyes.
  - Examination by ophthalmoscope alone is *not* able to detect the presence of uveitis.
- Anterior uveitis is by far the commonest presentation, but the other chambers are also affected.
- Macular involvement, whilst rare, is associated with a poor prognosis and is particularly important to detect.
- Some screening programmes also check visual acuity, and proceed to intraocular pressure measurements as indicated.

Table 3.7 Comparison of screening programmes between different countries

Core principle	Current UK guidance*	Current USA guidance	German variation on USA guidance
Rapid first eye screen	Within 6 weeks of referral to eye clinic	Within 1 month of diagnosis of arthritis	None given
Minimizing delay of symptom onset of JIA to diagnosis of JIA	Seen within 10 weeks of onset of symptoms and 4 weeks of the referral	Not discussed	
Screening intervals	2-monthly for the first 6 months, then 3–4-monthly	3–12-monthly depending on risk category. No discussion of psoriatic arthritis at all	3–12-monthly depending on risk category. Recognizes psoriatic as important risk factor in addition to oligoarthritis and RF−ve JIA
Access to examination under anaesthetic as appropriate	'Urgent' if deemed high risk—no timescale given	Not discussed	
Access if symptomatic	Within 1 week	Urgent access, no time interval given	Not discussed

Table 3.7 (*Contd.*)

Core principle	Current UK guidance*	Current USA guidance	German variation on USA guidance
Altered screening with altered risk	Return to 1st- year screening intervals on discontinuation of methotrexate	Complex algorithm dependent on age, ANA status, and disease duration	
Adherence to screening	Priority to rebook (no time given)	Not discussed	
Ages included, and duration of screening	Complex detail, summarized as until 12th birthday	Continue with 12-monthly screening throughout adolescence	Continue with 12-monthly screening throughout adolescence
Exclusions from screening	RF+ve JIA and sJIA offered baseline screen only	Uses 1986 classification, and screens only sJIA, oligoarthritis, and polyarthritis	None, RF positive JIA, ERA and sJIA offered 12-monthly screening

Note: current screening programmes are not fully evidence-based because of lack of adequate study in large enough numbers of patients. There is little or no evidence to support different screening regimens between subgroups of JIA, nor to determine the best screening interval. This lack of evidence leads to some debate about the validity of the use of the term screening, suggest surveillance as a better term, and also discussion about the validity of guidelines which are not fully evidence-based. Nonetheless screening is performed in many countries with consensus that it is effective and worthwhile.

* Current UK guidance is based on the following:

- The Royal College of Ophthalmologists 2006 guidelines for screening for uveitis in juvenile idiopathic arthritis. Produced jointly by BSPAR and the RCPOphth (2006) available at http://www.rcophth.ac.uk/docs/publications.
- BSPAR Standards of Care 2010. BSPAR Standards of Care for JIA. http://www.bspar.org.uk/downloads/clinical_guidelines/Standards_of_Care.pdf.

Further reading

Cassidy J, Kivlin L, Lindsley C, *et al.* Ophthalmological examination in children with juvenile rheumatoid arthritis *Pediatrics* 2006: **117**:1843–5.

Heiligenhaus A, Niewerth M, Ganser G, *et al.*, and the German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines *Rheumatology* 2007; **46**:1015–19.

Surgery in the young adult with JIA: practical issues

Introduction

- Surgery has an important but diminishing part in the overall management of JIA.
- The literature reports that young adults in their 20s have limited physical function and continued disease activity although these studies are retrospective and predate the effects of newer treatments such as biologic drugs in combination with methotrexate. Better treatment has also meant that growth has been completed with epiphyseal closure and bone density has reached the adult peak.
- Since the advent of these drugs, many centres have noted the reduction in need for certain types of surgery such as synovectomy and soft tissue release (tenotomies and capsulotomies) and delay in others such as joint replacement.
- Surgery for joint failure in most centres has been delayed into young adulthood rather than in adolescence when maturation is incomplete.
- There is currently a cohort of young adult patients who have received biologic drugs in their later years after a period of sustained disease activity and who present new problems for those providing services for people with arthritis.
  - It is important that the surgeon has skill in this age group and JIA.
  - Combined management with a rheumatologist and surgeon is important but may have to be in a dedicated setting.

Orthopaedic surgery in the young adult

- There is now experience in young people in arthroplasty of the hip, knee, ankle, shoulder, elbow, and wrist. Cervical surgery and arthrodesis of various joints may be considered.
  - The highest requirement for surgery is in polyarticular course JIA, especially if RF+ve and systemic onset disease, as well as RF−ve disease and extended oligoarticular arthritis, particularly if disease has been active for many years.
  - The best results are obtained in controlled disease with joints in a good position. If >1 joint needs surgery, the proximal one should be first and lower limbs should precede upper limbs.
  - Intra-articular steroid may reduce activity and fixed flexion deformity although should not be used within 3 months of surgery. Soft tissue release to obtain a good position is equally rarely necessary. Hydrotherapy may be needed to maintain muscle strength.
  - There is still a place for synovectomy if disease remains uncontrolled despite drug treatment.
- Many orthopaedic surgeons are reluctant to operate on young people. Hip and knee arthroplasty are now the commonest operations with achievement of good 10-yr survival in specialist centres. The key symptoms requiring surgery are:
  - Pain despite control of the other joints with active therapy.
  - Reducing exercise tolerance (walking distance in the legs or pain on movement in the arms.

- Night pain or pain at rest.
- Increasing disability and instability (locking or giving way of lower limb joints).
- *The threshold should be considerably above the level of immobility where the person has to regularly use a wheel chair.*

Precautions with surgery in adults with JIA

- Cervical spine: x-rays should be performed prior to surgery; any doubt should be followed with MRI. Poster anterior and lateral views in flexion and extension views should be obtained to assess for:
  - Atlanto-axial subluxation (can be at any level).
  - Cervical spondylolisthesis (slip of one vertebra on another).
  - Cervical fusion with limited range of movement or movement at one level.
- Temporomandibular joint disease: micrognathia and abnormal/restricted jaw opening may cause intubation difficulty.
  - Occasionally there may have been previous intubation difficulty due to a small larynx or cricoarytenoid arthritis.
- Medications:
  - *Methotrexate* should not be stopped prior to surgery. Infection rates after replacement surgery are less if the drug is continued. *It is better to be immunosuppressed and have controlled disease then have no immunosuppression and uncontrolled disease.*
  - *Biologics*—the current advice is to stop anti TNF therapy in the peri-operative period—the half-life of etanercept is 100h, adalimumab 15–19 days, and infliximab 8–9.5 days.
  - A practical rule is to omit the biologic drug for 14 days before and 14 days after surgery for etanercept and adalimumab, and 4 weeks for infliximab (if surgery is timed correctly within the 8-week interval between infusions no dosage will be missed).
  - There is a balance between successful wound healing and reduction of infection by stopping anti-TNF therapy versus perioperative risk of disease flare.
  - There is some evidence that anti-TNF therapy has a higher incidence of infection and deep vein thrombosis in patients with RA undergoing surgery but the numbers studied were small.
- Other considerations:
  - Small stature—patients should be assessed against standard growth charts and consideration given to a need for greater anaesthetic care for small airways. Special surgical prostheses may be required (small standard prosthesis or a custom-made prosthesis).
  - Osteoporosis—bone densitometry is recommended prior to surgery with higher risk in those patients with long disease duration or previous high steroid requirement.
  - Down's syndrome—higher risk of atlanto-axial subluxation and also an ↑ sensitivity to marrow suppression from immunosuppressant and other drugs.
  - Corticosteroid usage—steroid dosage may need to be adjusted over the perioperative period depending on the length and dosage of steroid use in the preceding months and years.

- Preoperative assessment—blood counts and routine chemistry should be performed prior to surgery particularly if the patient is on disease-modifying therapy. In particular, patients with systemic disease may need cardiac assessment with ECG and echocardiogram. Thrombosis risk should be assessed.
- Amyloidosis—it is important not to dehydrate young people with amyloid undergoing surgery. An IV line will be needed prior to surgery to maintain hydration.

Perioperative care

- Anaesthetists should be experienced in treating young people with JIA. They should be aware of potential intubation difficulties and the need for nasal intubation using a fibreoptic laryngoscope.
- Pressure-reducing measures may be required to avoid skin ischaemia in vulnerable patients.
- Early mobilization is important and hydrotherapy should be considered.
- Preoperative physiotherapy assessments should alert the need for temporary or permanent aids and adaptations.
- Written antibiotic advice needs to be given for future surgical and dental procedures.

Advice concerning pregnancy

- Young women who have had arthroplasty are often unaware of issues related to pregnancy. All young people should be under consultant care. The physician and obstetrician will need to assess:
  - Pelvic size.
  - Stability of prosthesis.
  - Neck issues as outlined on 📖 p 153.
  - Drug therapy in pregnancy and risk of postpartum disease flares.
  - Physical issues around breastfeeding and child care.
  - Timing of reintroduction of drug therapy in relation to delivery and breastfeeding.
- Even if the mother has not had an arthroplasty, long labours should be avoided and the mother should be aware of the potential need for assisted delivery and Caesarean section.

Further reading

Ding T, Ledingham J, Luqmani R, *et al.* BSR and BHPR rheumatoid arthritis guidelines on the safety on anti-TNF therapies. London: BSR, 2010. Available at: 🖱 http://www.rheumatology.org.uk/includes/documents/cm_docs/2010/d/draft_anti_tnf_safety_guideline_april_2010.pdf.

Hall MA Surgical interventions. In Szer IS, Kimura Y, Malleson PN, *et al.* (eds) *Arthritis in Children and Adults*. Oxford: Oxford University Press, 2006; 403–14.

Treatment approaches in JIA

- JIA is a complex and chronic condition and is therefore optimally managed by an experienced MDT as part of a managed clinical network as outlined in the BSPAR Standards of Care (see 📖 p 409).
- The MDT is integral to the management with the patient and family at the centre (Fig. 3.2), with input from specialist consultant, specialist nurse, paediatric physiotherapist, and paediatric occupational therapist (with interests in musculoskeletal conditions if possible).
- Access to ophthalmology for monitoring and treatment of JIA-associated eye disease is vital, with other services such as orthopaedic surgeons, radiology, social work and psychology services able to be accessed readily as required; these disciplines all have to interlink efficiently to achieve the best possible outcome. See 📖 p 377 and related chapters for more information on MDT members and their specific roles.
- The general treatment approach is to achieve early diagnosis and rapid control of the inflammatory process, whilst minimizing adverse effects of treatment and supporting general physical and mental health (Fig. 3.3).
- Early and adequate treatment aims to prevent long-term joint damage and the need for joint replacement therapy.
- Each member of the team contributes to the holistic management of the patient and family, with medical treatment forming only one strand of the overall picture.
- Education and information form one of the most important features of management throughout the duration of disease and should be undertaken by all members of the team, although the nurse specialist often takes an ongoing role in this area.
- Physiotherapy and occupational therapy have important roles in maintaining maximum function—the aim of treatment is as near to functional normality as possible. It is important to maintain muscle strength despite inflammatory processes within joints and these disciplines aim to achieve this by teaching specific exercises, pain management, and joint protection techniques as necessary.
- A healthy balanced diet with particular emphasis on calcium and vitamin D intake for bone health are recommended in JIA but there is no evidence for dietary modification affecting the inflammatory process in this disease.

Specific medical management in subtypes of JIA

- Table 3.8 illustrates some of the similarities and differences in the specific management of the different subtypes but should only be regarded as a guide to management.
- There is a lack of good evidence for many aspects of JIA management, therefore variability in practice between specialists exists.
- Particular management controversies remain around joint injection; dose, timing, number, and duration of treatment whilst in remission; and the use of specific disease-modifying drugs in particular disease types.
- In future, the possibility of genetic and phenotypic subtyping may determine prognosis and more predictable response to particular drugs.

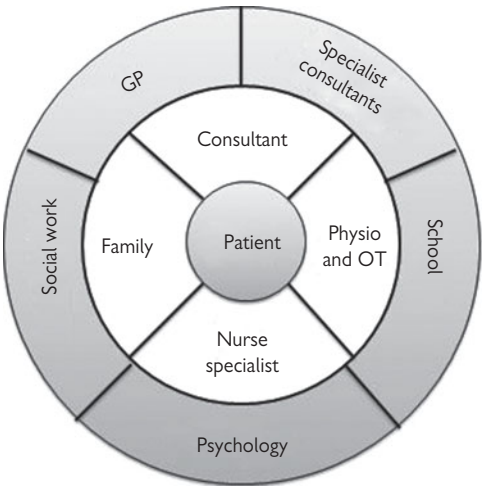

Fig. 3.2 Patient-centred MDT management of JIA.

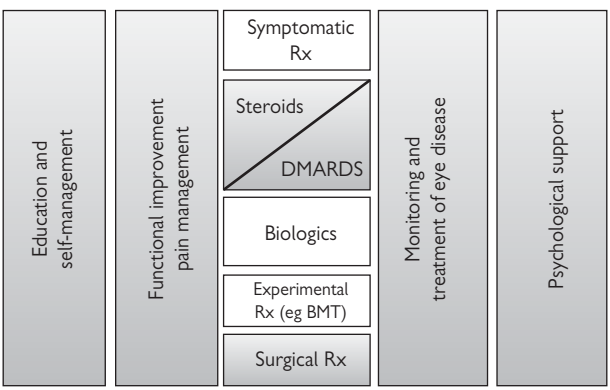

Fig. 3.3 General treatment approach in JIA.

Rx=Treatment; DMARDS=Disease Modifying Anti-Rheumatic Drugs; BMT=Bone marrow transplant.

Table 3.8 Specific management of subtypes of JIA

	Systemic onset JIA	Oligoarthritis	Polyarthritis	Established polyarthritis/ oligoarthritis	Enthesitis related arthritis
		Psoriatic arthritis			
Early/mild disease	Medium-dose corticosteroids	Intra-articular steroids NSAIDs	MTX Steroids (intra-articular or systemic)		NSAID IVMP/ high-dose corticosteroids followed by 2–4 weeks of low dose
Established/ severe disease	Pulsed IV methyl prednisolone (IVMP)*. Methotrexate (MTX) (usually given by subcutaneous (SC) route) Consider ciclosporin, and biologics (e.g. anakinra or tecilizumab) pending local and national guidelines/availability	See next column		MTX (ensure maximum dose, SC route) May need to add etanercept. ± corticosteroids + joint injections	Disease >2–4 months' duration Sulphasalazine (may work better than other DMARDS) MTX/anti-TNF
Remission	Wean prednisolone slowly Reduce other treatment with extreme caution—high risk of relapse	Ongoing monitoring	Wean off Steroid first DMARD continues longer then consider reduction or discontinuation	Continue treatment for several months Wean and discontinue steroids first Wait 1 year before weaning off DMARDs—off MTX last	Continue sulfasalazine 6 months–1yr

(*continued*)

Table 3.8 (*Contd.*)

	Systemic onset JIA	Oligoarthritis	Polyarthritis	Established polyarthritis/ oligoarthritis	Enthesitis related arthritis
		Psoriatic arthritis			
Relapse	Repeat high-dose corticosteroids Consider other biologic agents	If previous IACS effect >4 months repeat injection If lasted <4 months add NSAID, repeat IAC consider DMARD	Reintroduce all drugs on which remission was achieved.	Reintroduce all drugs that induced remission Often requires step up in treatment to reinduce remission	Generally episodic course Short courses of NSAID and sulphasalazine sufficient to obtain remission in recurrences
Persistent disease	IL-6 and IL-1ra directed treatments Tocilizumab (anti-IL-6) and canakinumab (anti-IL-1B)		IAC targeted joints	Consider alternate biologic agents In severe cases consider bone marrow transplant (see 🕮 p 405)	

* If macrophage activation syndrome develops (see 🕮 p 305).

MTX, methotrexate; IAC, intra-articular corticosteroid; DMARD, disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug.

Treatment pathways in JIA

Note these are *suggested* treatment pathways and where possible based on current national (BSPAR) guidance for biologics and methotrexate use (see 🕮 other chapters for details, p 415). These treatment pathways have not been validated in clinical practice but illustrate the different management approaches for the spectrum of JIA subtypes (Figs. 3.4–3.8).

Please note that reference to referral for consideration of autologous stem cell transplantation is after failure to response to at least 2 different biologic agents—this differs from the BSPAR (2006) guidance from autologous stem cell transplantation (see 🕮 AHSCT, p 405) with the ↑ experience and range of biologic agents now available.

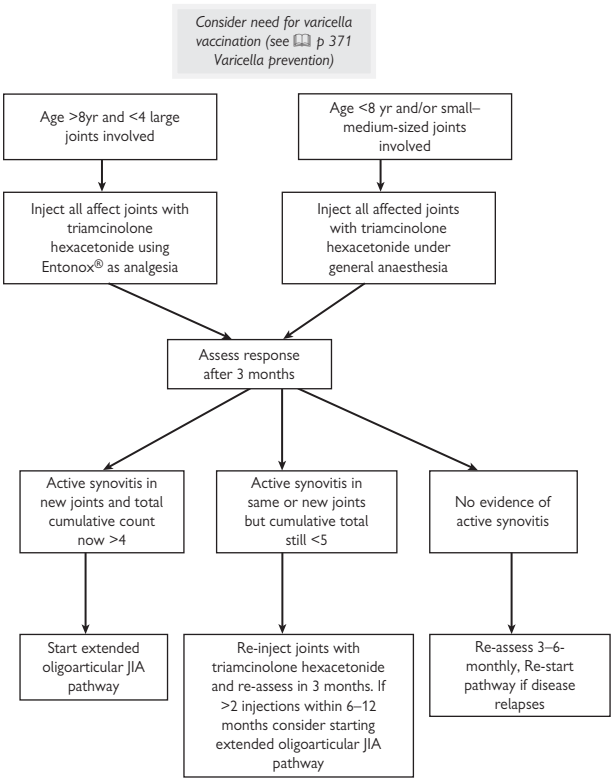

Fig. 3.4 Suggested treatment pathway for oligoarticular JIA.

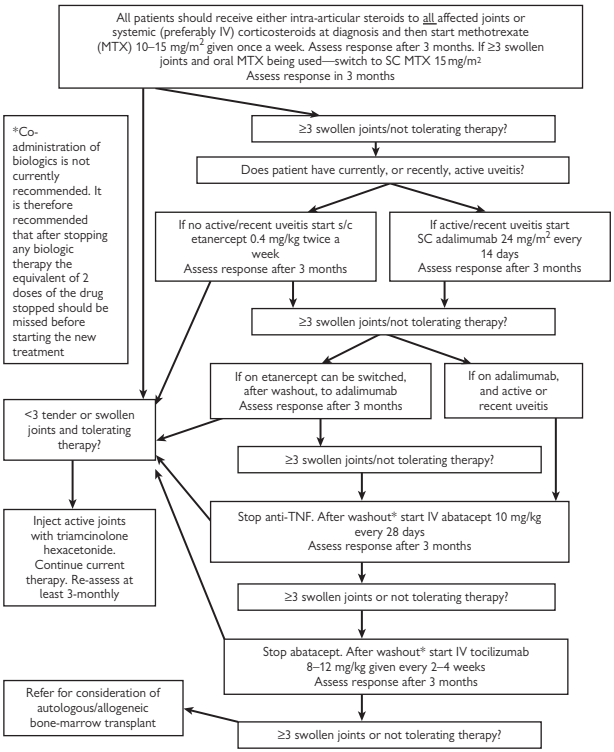

Fig. 3.5 Suggested treatment pathways in children with extended oligoarticular JIA, polyarticular (RF−ve) JIA, psoriatic JIA, and enthesitis-related arthritis, affecting a cumulative total of >4 non-axial joints.

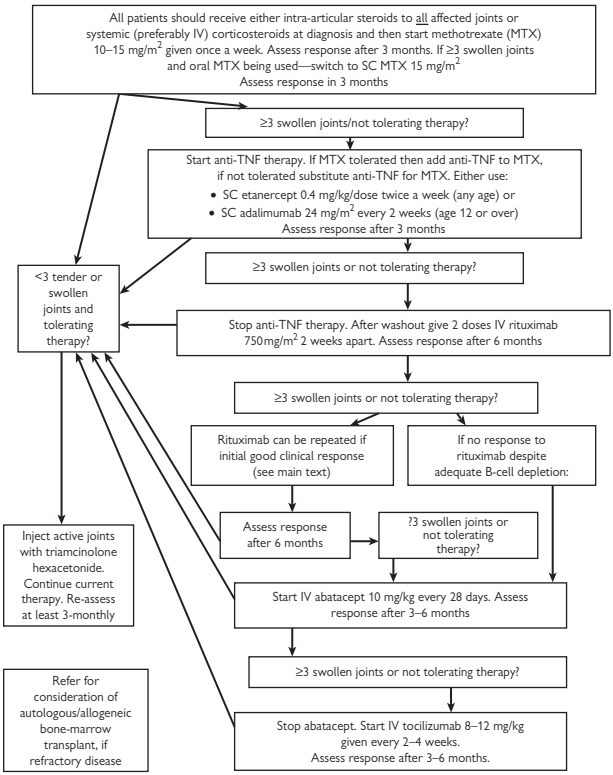

Fig. 3.6 Suggested treatment pathways in children with polyarticular (RF+ve) JIA.

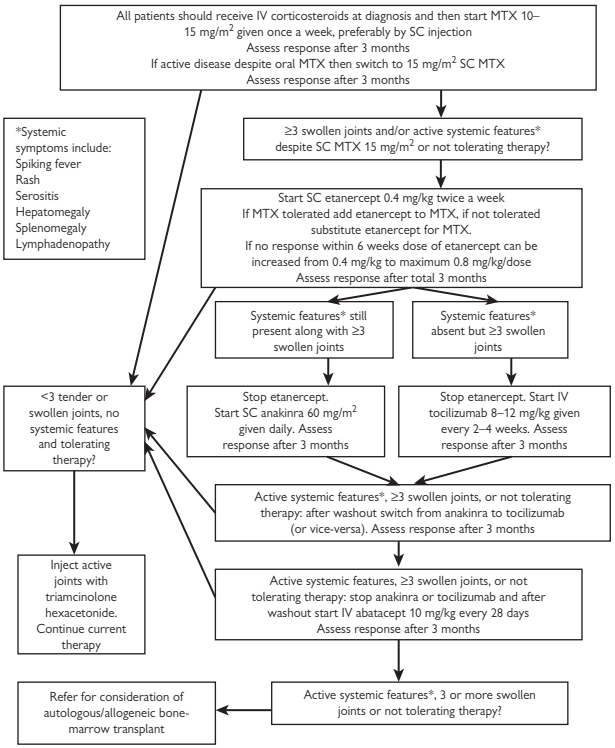

Fig. 3.7 Suggested treatment pathway in children with systemic-onset JIA.

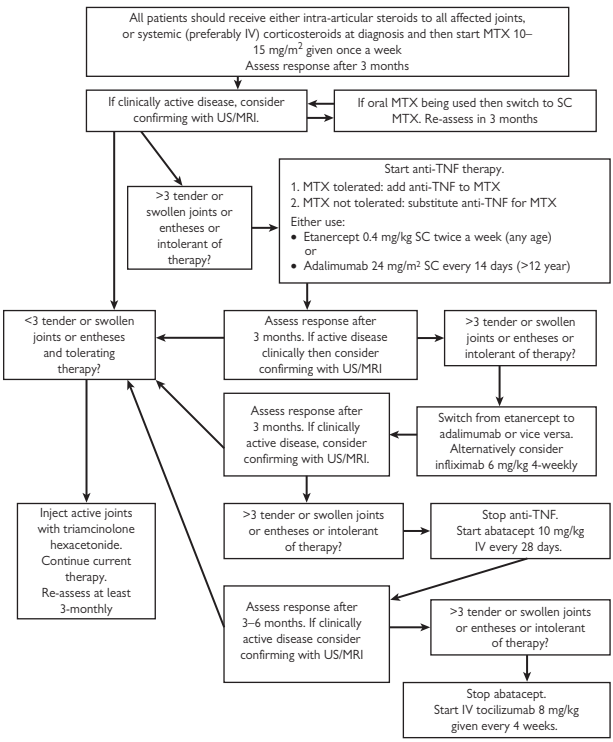

Fig. 3.8 Suggested treatment pathways in children with enthesitis-related arthritis affecting the entheses, sacro-iliac, or other axial joints.

Disease activity scores in rheumatoid arthritis and JIA

Composite indices of disease activity are more precise tools than their individual components with higher sensitivity to change; the Disease Activity Score (DAS) was developed in an attempt to improve upon the arbitrary classification of adult RA into high or low disease activity. The DAS28 is commonly used in adult practice and involves scoring of 28 joints (PIPs, MCPs, wrists, elbows, shoulders, and knees) for swelling and tenderness, in combination with ESR and general health assessment (visual analogue scale, VAS).

Key points of the DAS 28 are:

- The score is derived from:
  DAS28 = 0.56 x square root (tender count 28) + 0.28 x square root (swollen count 28) + 0.70 x log(to base 10)(ESR) + 0.014 x VAS
  - Many desktop and Internet-based calculators available.
  - The DAS28 score (0 to 10) indicates current disease activity; >5.1 defines 'high' disease activity; <3.2 defines 'low' disease activity.
  - Remission is defined as DAS28 score <2.6 (comparable to the ACR remission criteria)—EULAR response criteria are based on change in DAS28 score.
- Frequent assessment by DAS is now considered best practice in optimizing RA control for the best long-term outcome, particularly when using 'tight' control and combination therapies. Health professionals are trained to rapidly and consistently score the DAS28 using standard examination with low inter-and intra-observer variation.
- Serial measurements of the DAS28 are strong predictors of physical disability, radiological progression, and are a sensitive discriminator between patients (high/low disease activity) and treatments (active/placebo-treated patient groups).
- The clinical utility of the DAS28 led to its central position in determining the suitability of adult RA patients for receiving anti-TNF therapy
  - A score >5.1 on 2 occasions, 1 month part, is considered to be the minimal disease activity to receive anti-TNF therapy.
  - To continue therapy >3 months, the score must have fallen by >1.2 or be <3.2.

Disease Activity Score in JIA (see 🕮 Outcome measures, p 41)

There is no currently accepted paediatric analogue of the DAS28 for assessing disease activity in JIA. The proposed Juvenile Arthritis Disease Activity Score (JADAS) includes the following:

- Physicians' global assessment of disease activity (VAS).
- Parents' global assessments of disease activity (VAS).
- Active joint count assessed by 1 of a) JADAS-10 (any involved joint to a maximum of 10); or b) JADAS-27 (27 joints); or c) JADAS-71 (all 71 joints).
- ESR normalized to a 1–10 scale.

Evidence to date reports that JADAS is a valid instrument for the assessment of disease activity in JIA and it can predict disease outcome (radiographic progression at 3yr). Potential confounders exist, e.g. ESR may be normal in children with active oligoarticular JIA, it may not be sensitive to change with low joint counts and there is to date no evidence of utility in the various subsets of JIA.

Further reading

Consolaro A, Ruperto N, Bazso A, *et al.* Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis and Rheum* 2009; **61**(5):658–66.

DAS website: http://www.das-score.nl.

Neogi T, Felson DT. Composite versus individual measures of disease activity in rheumatoid arthritis. *J Rheumatol* 2008; **35**(2):185–7.

Rheumatology Research website: http://www.reuma-nijmegen.nl/.

Chapter 4

Systemic diseases

The classification of paediatric vasculitis

Background to classification criteria

- Classification criteria 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), and
  - 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 described, and validated on >1300 cases worldwide (Table 4.1).
- These criteria do not include Kawasaki disease (see 🕮 Kawasaki disease, p 183); 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 2 entities, although the pathogenesis and treatment for these 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 as follows.
- It should be noted, however, that most vasculitides exhibit a significant degree of 'polyangiitis overlap': e.g. Wegener's granulomatosis can affect the aorta and its major branches, and small vessel vasculitis can occur in polyarteritis nodosa.

1. Predominantly large-vessel vasculitis
- Takayasu arteritis.

2. Predominantly medium-sized vessel vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease.

3. Predominantly small-vessel vasculitis
- Granulomatous:
  - Wegener's granulomatosis
  - Churg–Strauss syndrome
- Non-granulomatous:
  - Microscopic polyangiitis
  - Henoch–Schönlein purpura
  - Isolated cutaneous leucocytoclastic vasculitis
  - Hypocomplementemic urticarial vasculitis.

4. Other vasculitides
- Behçet's disease
- Vasculitis 2° to infection (including hepatitis B-associated PAN), malignancies and drugs, including hypersensitivity vasculitis
- Vasculitis associated with other connective tissue diseases
- Isolated vasculitis of the CNS (childhood 1° angiitis of the central nervous system: cPACNS)
- Cogan's syndrome
- Unclassified.

Table 4.1 Classification criteria for specific vasculitic syndromes[1]

Vasculitis	Classification criteria	Sensitivity[2]	Specificity*
HSP	Purpura, predominantly lower limb ***or*** diffuse* (mandatory) ***plus*** 1 out of 4 of: • Abdo 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 criteria:** • 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 BP discrepancy • Bruits • Hypertension • Acute phase response	100%	99%

[1]Adapted from Ozen S, Pistorio A, Iusan SM, *et al*. Paediatric Rheumatology International Trials Organisation (PRINTO). 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* 2010; **69**:798–806.

[2]Based on 1347 children with miscellaneous vasculitides. Ruperto N, Ozen S, Pistorio A, *et al*.; for the Paediatric Rheumatology International Trials Organisation (PRINTO). EULAR/PRINTO/PRES criteria for Henoch–Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: Overall methodology and clinical characterisation. *Ann Rheum Dis* 2010; **69**:790–7.

The epidemiology of paediatric vasculitis

- Childhood vasculitis is rare and the incidence and prevalence are not accurately described.
- Henoch–Schönlein purpura (HSP) and Kawasaki disease (KD) are the 2 commonest childhood vasculitides and as such those with the most epidemiological information.
  - There is undoubtedly some ethnic variation for these diseases (see individual section).
- In paediatric populations other systemic vasculitides including polyarteritis nodosa (PAN), Wegener's granulomatosis (and other ANCA-associated vasculitides), Behçet's disease, and Takayasu arteritis are rare and epidemiology difficult to assess.
  - Some ethnic variation has been noted: Takayasu's being more common in Asians than North Americans and Europeans.

Henoch–Schönlein purpura

The estimated annual incidence in the West Midlands, UK has been reported as 20.4 per 100,000 and was highest in the 4–7yr age group. This is comparable to reported figures from the Czech Republic of 10.2 per 100,000 and Taiwan of 12.9 per 100,000.

Kawasaki disease

- KD has the highest incidence and prevalence in Asian populations, particularly Japan.
- Nationwide surveys conducted in Japan show the incidence of KD in children aged 0–4yr continues to rise with the average annual incidence in 2007 being 184.6 per 100,000.
- This compares to an estimated annual incidence rate of 5.5–8.1 per 100,000 (0–5yr) in the UK and an estimated annual incidence rate of 1.6 per 100,000 (0–5yr) in the Czech Republic.
- There are limitations to these studies as they were all done by survey or questionnaire reporting.

Further reading

Dolezalova P, Telekesova P, Nemcova D, *et al.* Incidence of vasculitis in children in the Czech Republic: 2-year prospective epidemiology survey. *J Rheumatol* 2004; **31**:2295–9.

Gardner-Medwin JMM, Dolezalova P, Cummins C, *et al.* Incidence of Henoch-Scholein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002; **360**:1197–202.

Yang YH, Hung CF, Hsu CR, *et al.* A nationwide survey on epidemiological characteristics of childhood Henoch-Scholein purpura in Tiawan. *Rheumatology* 2005; **44**:618–22.

The investigation of primary systemic vasculitis

Background

Clinical features that suggest a vasculitic syndrome:

- Pyrexia of unknown origin
- Palpable purpura, urticaria, dermal necrosis
- Mononeuritis multiplex
- Unexplained arthritis, myositis, serositis
- Unexplained pulmonary, cardiovascular, or renal disease
- ***Plus*** 1 or more of:
  - Leucocytosis, eosinophilia
  - Hypocomplementaemia, cryoglobulinaemia
  - Circulating immune complexes
  - Raised ESR or CRP, thrombocytosis.

Level 1 investigations—to be performed in all

- Haematology and acute phase reactants:
  - FBC, ESR, CRP, clotting, prothrombotic screen (if patchy ischaemia of digits or skin), blood film
- Basic biochemistry:
  - Renal and liver function, CPK, thyroid function, LDH, amylase/lipase, urine dip and UA:UC (spot urine albumin:creatinine ratio)
- Infectious disease screen:
  - Blood cultures
  - Urine MC&S
  - ASOT and anti-DNase b
  - *Mycoplasma pneumonia*e serology
- Immunological tests:
  - ANA, dsDNA Abs, ENAs, ANCA, RF,
  - Anti-GBM antibodies
  - TTG antibodies (coeliac disease screen)
  - Immunoglobulins: IgG, IgA, IgM, and IgE
  - Anticardiolipin antibodies, lupus anticoagulant
  - C3/C4, MBL (memose binding lectin, if available), CH100 or alternative functional complement assay if available
  - VZV antibody status (prior to starting immunosuppressive therapy)
  - Serum ACE
- Radiological: CXR, abdominal and renal USS
- Other: ECG, echocardiography, digital clinical photography of lesions.

Level 2 investigations—to be considered on an individual basis

- Infection screen:
  - Mantoux 1:1000, and/or quantiferon
  - PCR for CMV, EBV, enterovirus, adenovirus, VZV, HBV, HCV
  - Serology for HIV, Rickettsiae, *Borrelia burgdorferi*
  - Viral serology for: hepatitis B & C, parvovirus B19.

- Imaging:
  - Radiograph of bones and joints.
  - Selective contrast visceral angiography.
  - DMSA scan.
  - MRI/MRA of brain (for suspected cerebral vasculitis).
  - 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).
  - PET-CT: for differential of malignancy or Castleman's disease.
  - DEXA scan.
  - V/Q scan.
  - USS Doppler of peripheral arteries.
  - Thermography and nail fold capillaroscopy.
- 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).
- Biochemistry, immunology and immunogenetics:
  - Serum amyloid A.
  - Formal GFR.
  - Organ specific autoantibodies.
  - IgD.
  - β2 Glycoprotein 1 antibodies.
  - Urinary catecholamines (consider plasma catecholamines as well), and urine VMA, HVA (for phaeochromocytoma, or neuroblastoma).
  - 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.
  - Mitochondrial DNA mutations.
  - DNA analysis for periodic fever syndromes that can mimic vasculitis: MEFV (familial Mediterranean fever, TNFRSF1A (TNFα receptor associated periodic fever syndrome, TRAPS), MVK (hyper IgD syndrome, HIDS), NLRP3 (cryopyrin associated periodic syndrome, CAPS), and NOD2 (Crohn's/Blau's/juvenile sarcoid mutations).
  - Nitroblue tertrazolium test if granulomatous inflammation found on biopsy.
- Nerve conduction studies (PAN, WG, Behçet's [before starting thalidomide]).
- Ophthalmology screen.
- Ambulatory 24h BP/4-limb BP.

The standard treatment of childhood vasculitis

Guidelines for the use and monitoring of cytotoxic drugs in non-malignant disease are shown in Table 4.2. Standard vasculitis therapy (*excluding* crescentic glomerulonephritis) is described in Fig. 4.1. Prior to using this approach, remember 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. 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.

Other points of note

- Although the use of oral cyclophosphamide is highlighted in Table 4.3, 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 biologic therapy in systemic vasculitis of the young

- Whilst the therapeutic approach and drugs used as suggested in Figs. 4.1 and 4.2 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 have led to the increasing use of biologic therapy such as rituximab, anti-TNF alpha, or other biologic therapy.
- Evidence to support the use of rituximab as a 1° 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).
- 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. 4.1.
- Evidence for the use of anti-TNFα or other biologic agents such as anakinra remains anecdotal for children and adults with vasculitis.
- Whilst there is not enough evidence to recommend specific biologic therapy for specific vasculitic syndromes, a general approach favoured by the author is given in Table 4.3

Table 4.2 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 once a day PO 2–3 months; 0.5–1.0g/m^2 IV monthly with mesna to prevent cystitis (see 📖 p 427 Chapter 9 for mesna dose and IV CYC administration protocol)	0.5–2.5mg/kg once a day PO for 1yr or more	(600 mg/m^2 twice a day)	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 (↓ 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
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 neutropenia <1.5 × 10^9/L, platelets <150 × 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 neutropenia <1.5 × 10^9/L, platelets <150 × 10^9/L, and check TPMT enzyme-patients deficient in TPMT require reduced doses (or may not tolerate) azathioprine because of ↑ marrow toxicity	Fortnightly FBC for 2 months, then monthly for 2/12. 3-monthly when stable. Baseline monthly renal and liver function until stable Discontinue temporarily and/or reduce dose if neutropenia <1.5 × 10^9/L, platelets <150 × 10^9/L, or significant GI side effects	Weekly measurement of BP; baseline then monthly renal and liver function; maintain 12h 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 >3× upper limit of normal, neutropenia <1.5× 10^9/L, new or worsening cough, severe nausea, vomiting, or diarrhoea, platelets <150 × 10^9/L or falling rapidly

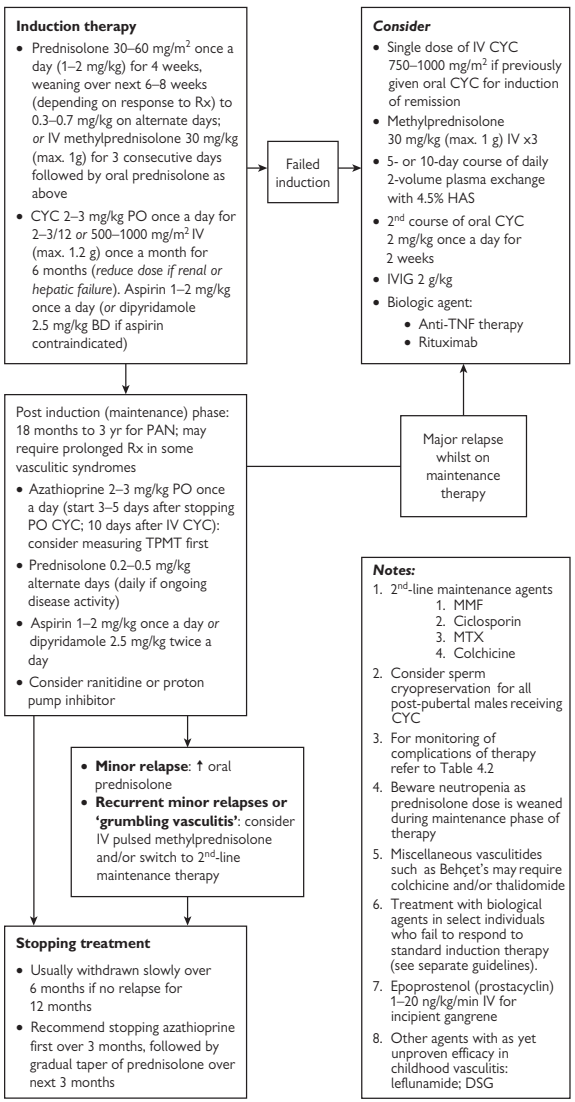

Fig. 4.1 Standard vasculitis therapy (*excluding* crescentic glomerulonephritis).

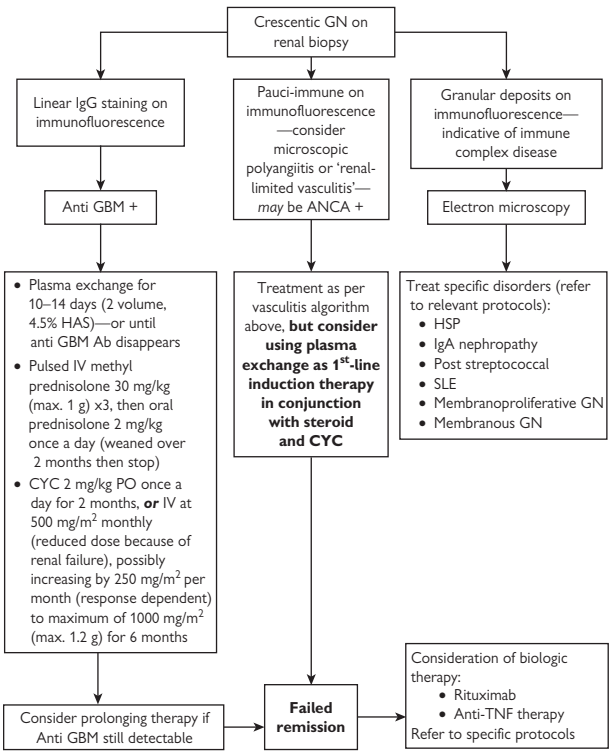

Fig. 4.2 Guidelines for treatment of crescentic glomerulonephritis (note early diagnosis and starting therapy is of major importance).

Table 4.3 Recommendations for indication and choice of biologic therapy for primary systemic vasculitis of the young based on published experience[1]

Vasculitis type	Indication for biologic agent	Proposed first choice of biologic 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; [*]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 biologic for PAN.

[1]Adapted from Eleftheriou D, Melo M, Marks SD, *et al.* Biologic therapy in primary systemic vasculitis of the young. *Rheumatology* 2009; **48**:978–86.

Further reading

Eleftheriou D, Melo M, Marks SD, et al. Biologic therapy in primary systemic vasculitis of the young. *Rheumatology* 2009; **48**:978–86.

Henoch–Schönlein purpura

Introduction

- Henoch-Schönlein purpura (HSP), the commonest systemic vasculitis in childhood is predominantly a small-vessel, non-granulomatous leucocytoclastic vasculitis of unknown aetiology.
  - Reported by Heberden (1801), Willan (1808), Schönlein (1832), and Henoch (1874).
  - Also called anaphylactoid purpura (1948).
- Classification criteria are palpable purpura in a predominantly lower limb distribution with at least 1 of 4 of:
  - Diffuse abdominal pain.
  - Any biopsy showing IgA deposition (mandatory criterion if rash is atypical).
  - Arthritis and/or arthralgia.
  - Haematuria and/or proteinuria.
- Variable and often relapsing course without specific laboratory findings with 1/3 of children having symptoms up to a fortnight, another 1/3 up to 1 month and recurrence of symptoms within 4 months of resolution in 1/3.
- Henoch–Schönlein nephritis (HSN) accounts for 1.6–3% of all childhood cases of end-stage renal failure (ESRF) in the UK.

Epidemiology

- Commoner in Caucasian and Asian populations and boys:
  - ♂:♀ ratio of 1.5–2:1.
  - 50% present before the age of 5yr, 75% present before the age of 10yr.
- Incidence of 10–20.4 (mean of 13.5) per 100,000 children.
  - 22.1 per 100,000 children under 14yr of age.
  - 70.3 per 100,000 children aged 4–7yr.
- Almost 20× rarer in adults.
  - 0.8 cases per 100,000 adults.
  - More severe in adults.
- Seasonal variation (commoner in winter) with infectious triggers.
  - Associations with bacteria (e.g. Group A beta-haemolytic streptococci) and viruses (hepatitis, CMV, HSV, human parvovirus B19, coxsackie, and adenovirus), and some cases after vaccination described.

Immunopathology

- Type III hypersensitivity reaction with immune complex.
  - IgA deposition: galactose deficient IgA may contribute to this.
  - Alternate pathway complement activation.
  - Associated C2 deficiency.
- Vasculitis of small blood vessels with diffuse angiitis.
  - Perivascular exudate of leucocytes.
- Polygenic inheritance with renal involvement associated with HLA-B35, IL-1β (–511) T allele, and IL-8 allele A.

Systemic involvement

Dermatological

- All patients have purpura but skin involvement may not be present at time of initial presentation.
- Generally symmetrical purpura involving lower limbs and buttocks but can spread to upper limbs (rarely abdomen, chest or face).
- Urticaria and angio-oedema can occur.

Gastrointestinal

- Commonly occurs (68% of patients).
- Abdominal pain precedes rash by 1–14 days in 43% of patients.
- Presents with intermittent colicky abdominal pain, vomiting with or without haematemesis or melaena (faecal occult blood may be positive) as a result of haemorrhage into gut wall.
- Involvement may result in intussusception, appendicitis, cholecystitis, pancreatitis, GI haemorrhage, ulceration, infarction, or perforation.

Rheumatological

60% of patients will have joint involvement with arthritis and/or arthralgia usually affecting the knees and ankles resulting in pain, swelling and ↓ range of movement.

Renal

- 25–60% of patients will have renal involvement with HSN:
  - 76% will develop within 4 weeks of disease onset.
  - 97% will develop within 3 months of disease onset.
- Most cases are usually asymptomatic which necessitates screening up to 6 months after last recrudescence of rash or HSP symptoms with <10% having significant involvement requiring referral for consideration of renal biopsy (Fig. 4.3).
  - Microscopic haematuria without proteinuria is benign.
  - 82% have normal renal function after 23yr.
  - Good prognosis with isolated haematuria and mild proteinuria with mild histological changes as less than 5% will develop chronic kidney disease (CKD) within 10–25yr.
  - Improved renal prognosis in children <7yr.
- Severe disease indicated by increasing proteinuria, development of nephrotic syndrome and/or renal failure.
  - 20% of patients with acute mixed nephritic and nephrotic syndrome progress to ESRF.
  - 44–50% develop hypertension or CKD.
  - Histological pattern is identical to IgA nephropathy and includes focal segmental proliferative glomerulonephritis and rapidly progressive crescentic glomerulonephritis (Table 4.4).

Other

Patients may present with orchitis, severe pulmonary haemorrhage, and/or cerebral vasculitis (which may respond to immunosuppression combined with plasmapheresis).

Treatment

- Symptomatic treatment with rest and analgesia.
- No role of antibiotics unless suspected or proven infection.
- Prophylactic corticosteroid therapy at commencement of HSP does not prevent renal or GI involvement.
- However, corticosteroids do seem to be effective in treating these complications and severe facial and/or scrotal haemorrhagic oedema.
- Patients with severe renal involvement may require other immunosuppressive agents, antiproteinuric and antihypertensive agents.

Table 4.4 ISKDC classification of Henoch–Schönlein nephritis

ISKDC grade	Pathoanatomical findings
I	Minimal alterations
II	Mesangial proliferation
III A	Focal proliferation or sclerosis with <50% crescents
III B	Diffuse proliferation or sclerosis with <50% crescents
IV A	Focal proliferation or sclerosis with 50–75% crescents
IV B	Diffuse proliferation or sclerosis with 50–75% crescents
V A	Focal proliferation or sclerosis with >75% crescents
V B	Diffuse proliferation or sclerosis with >75% crescents
VI	Membranoproliferative glomerulonephritis

ISKDC=International Study of Kidney Diseases in Children.

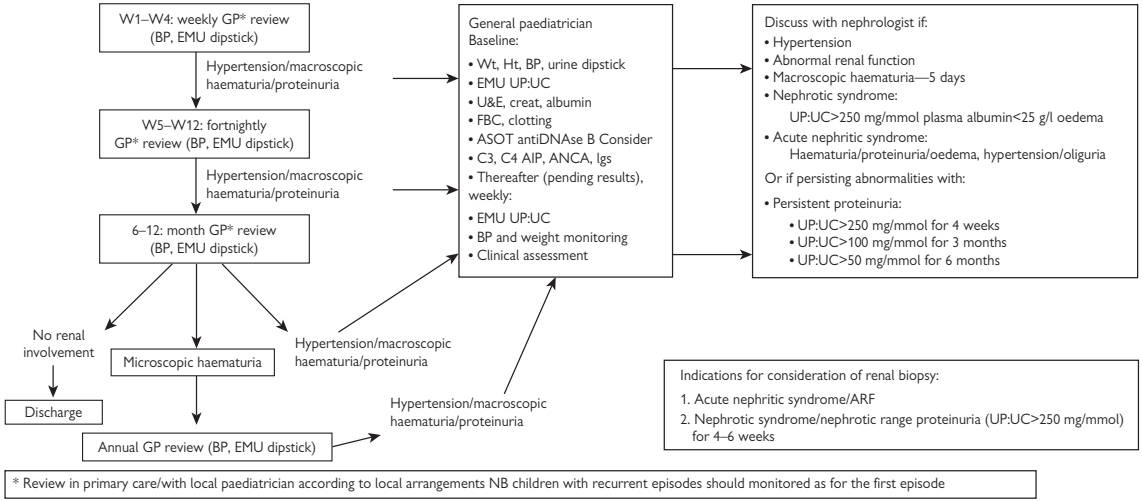

Fig. 4.3 Clinical pathway for investigation and referral for renal biopsy in HSN: Reproduced with permission from Tizard EJ, Hamilton-Ayres MJJ. Henoch–Schönlein purpura. *Arch Dis Child Educ Pract Ed* 2008; **93**:1–8.AIP, auto-immune profile; ANCA, anti-neutrophil cytoplasmic Abs; ARF, acute renal failure; ASOT, anti-streptolysin O titre; BP, blood pressure; C3,C4, complement C3 and C4; EMU, early morning urine; GP, general practitioner; Ht, height; U&E, urea and electrolytes; Wt, weight; UP:UC, urine protein:creatinine ratio.

Kawasaki disease

Kawasaki disease (KD) is a self-limiting vasculitic syndrome that predominantly affects medium- and small-sized arteries. It is the 2nd commonest vasculitic illness of childhood (the commonest being HSP) and it 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. However, 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 world-wide distribution with a ♂ preponderance, an ethnic bias towards Asian and in particular Japanese or Chinese children, some seasonality, and occasional epidemics.
- The incidence of KD is rising world-wide, including the UK. The current reported incidence in the UK is 8.1/100,000 children aged <5yr. This may reflect a truly rising incidence or ↑ 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), and
- Acute non-purulent cervical lymphadenopathy.

- For the diagnosis of KD to be established 5 of the 6 clinical features should be present.
- Patients with <5 or 6 principal features can be diagnosed with KD when coronary aneurysm or dilatation is recognized by two-dimensional (2D) 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 patients between specific epitopes of mycobacterial and human heat shock proteins.
- An important point worthy of emphasis 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 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 JIA
- Infantile PAN
- SLE
- Adenovirus, enterovirus. Epstein–Barr virus, CMV, parvovirus, influenza virus infection
- *Mycoplasma pneumoniae* infection
- Measles
- Leptospirosis
- Rickettsiae infection
- Adverse drug reaction
- Mercury toxicity (acrodynia)
- Lymphoma—particularly for 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 beta-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, Epstein–Barr virus, cytomegalovirus.
- Urine MC&S.

- Dip test of urine for blood and protein.
- Consider serology for rickettsiae and leptospirosis if history suggestive.
- Consider CXR.
- ECG.
- 2D echocardiography to identify coronary artery involvement acutely and monitoring changes long term.
- Coronary arteriography has an important role for delineating detailed anatomical injury, particularly for children with giant coronary artery aneurysms (>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 (Fig. 4.4)

The treatment of KD 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 4 divided doses.
- The dose of aspirin can be reduced to 2–5mg/kg/day when the fever settles (disease defervescence). Aspirin at antiplatelet doses is continued for a minimum of 6 weeks.
- If the symptoms persist within 48h or there is disease recrudescence within 2 weeks a 2nd 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 2nd dose of IVIg, consider IV pulsed methylprednisolone at 15–30mg/kg daily for 3 days to be followed by oral prednisolone 2mg/kg/day once a day 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-TNFα 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 1° target of KD therapy, TNFα 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 weeks and 6 weeks from initiation of treatment (refer to paediatric cardiology).
- If the repeat echocardiogram shows no coronary artery abnormalities (CAAs) at 6 weeks, aspirin can be discontinued and lifelong follow-up at least every 2yr should be considered.

- 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 ↓ 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 ↑ 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.

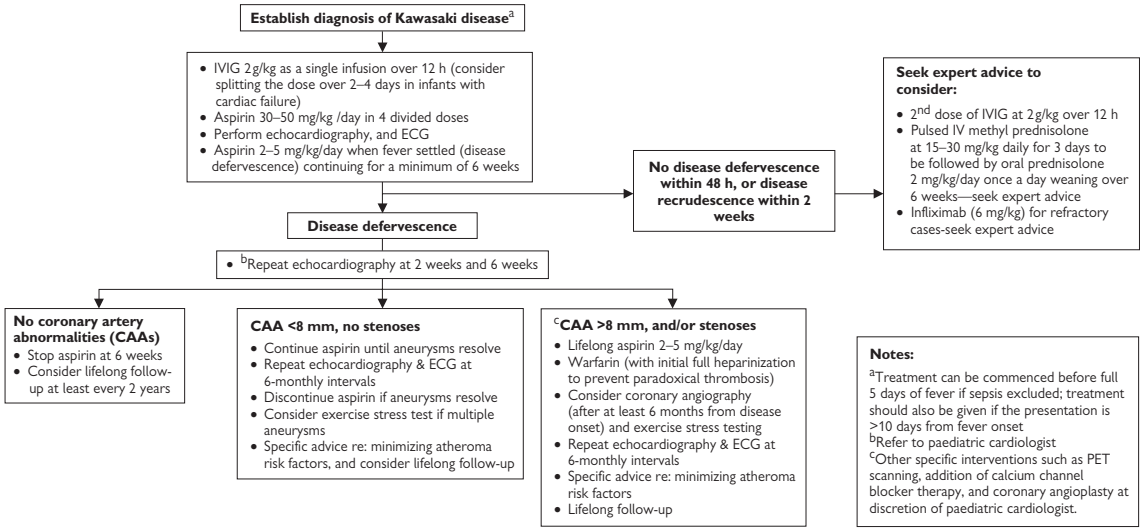

Fig. 4.4 Guideline for the management of Kawasaki disease.

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides

Background

- The ANCA-associated vasculitides (AAV) are:
  - Wegener's granulomatosis (WG)
  - Microscopic polyangiitis (MPA)
  - Churg–Strauss syndrome (CSS) and
  - Renal limited vasculitis (previously referred to as idiopathic crescentic glomerulonephritis).
- Although rare, the AAV do occur in childhood.

Definitions of AAV

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 a separate section on classification.

- ***WG:*** granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-size 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 ANCA (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 WG

From a clinical perspective WG may be broadly considered as having 2 forms:

- Predominantly granulomatous form with mainly localized disease, and
- Florid, acute small vessel vasculitic form characterized by severe pulmonary haemorrhage and/or rapidly progressive vasculitis or other severe vasculitic manifestation.

These 2 broad presentations may coexist or present sequentially in individual patients.

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 (Fig. 4.5).
  - 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 (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.
  - Significant 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) (Fig. 4.5).
- 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 (also see 📖 Vasculitis investigation, p 172)

- WG is commonly associated with a cytoplasmic staining pattern of ANCA by IIF, and ELISA reveals specificity against PR3 (PR3-ANCA).
- MPA and renal limited AAV are typically associated with pANCA 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:
  - 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 urinary spot protein creatinine ratio.
  - Raised serum creatinine and other associated laboratory features of renal failure.
- Chest radiography 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

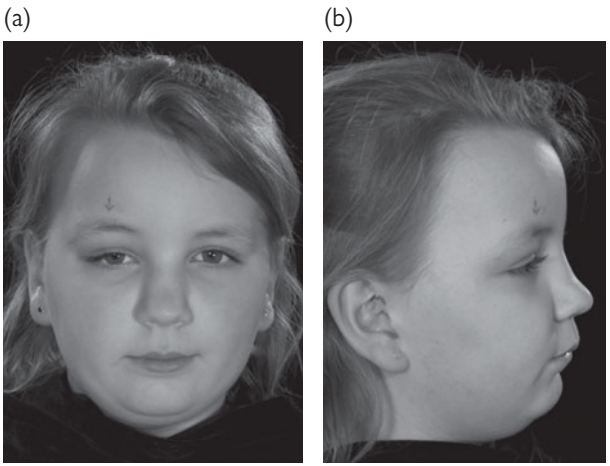

Fig. 4.5 Right orbital and characteristic saddle nose deformity in Wegener's granulomatosis.

Treatment of AAV

(See 🕮 BSPAR guidelines for treatments used in paediatric rheumatology, p 415.)

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:

- The 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 rapidly progressive glomerulonephritis—'pulmonary-renal syndrome') to induce remission; followed by low-dose corticosteroids and azathioprine to maintain remission.
- Antiplatelet doses of aspirin can also be considered empirically on the basis of the ↑ risk of thrombosis associated with the disease process.
- MTX 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-TNF 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 AAV

- The AAV still carry considerable disease-related morbidity and mortality, particularly due to progressive renal failure or aggressive respiratory involvement, and therapy-related complications, such as sepsis.
- The mortality for WG from one recent paediatric series was 12% over a 17yr period of study inclusion. The largest paediatric series of patients with WG reported 40% of cases with chronic renal impairment at 33 months of follow-up despite therapy.
- Mortality in paediatric patients with MPA during follow-up has been reported to be 0–14%.
- For CSS in children, the most recent series quotes a related mortality of 18%

Further reading

Brogan P, Eleftheriou D, Dillon M. Small vessel vasculitis. *Pediatr Nephrol* 2010; **25**:1025–35.

Polyarteritis nodosa (PAN)

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 USA, has 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 7–11yr, often with a ♂ 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 rest of section and 📖 Vasculitis classification, p 168.

Aetiology

- Unknown: possible interaction between infection and aberrant host response.
- There may be genetic factors that 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 familial Mediterranean fever 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 PAN

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.

- 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 erythema multiforma. 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 (nailbed 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.
  - Panreatitis.
- ***Neurological 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 1° vasculitides: HSP, WG, MPA, KD. See 🕮 relevant chapters, HSP p 179, WG p 188, MPA p 188, KD p 183.
- Autoimmune or autoinflammatory diseases:
  - JIA—particularly the systemic form.
  - 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/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 leucocytosis, thrombocytosis, ↑ ESR and CRP.
- Platelets are hyperaggregable.
- 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 (Fig. 4.6).
- 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. 4.7).
  - Treatment with prior corticosteroids will alter the arteriography and can result in false negatives.
  - Non-invasive arteriography such as CT or MR angiography (CTA/MRA) are *not* as sensitive as catheter arteriography for the detection of medium-sized vessel vasculitis such as PAN (discussed later in this list).
  - Consider formal cerebral arteriography if clinical and MRI features suggest cerebral vasculitis (see 🕮 Cerebral vasculitis, p 209).
- 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 ↓ isotope uptake on Tc-99m dimercaptosuccinic acid (DMSA) scanning of the kidneys.
- Magnetic resonance angiography (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—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.

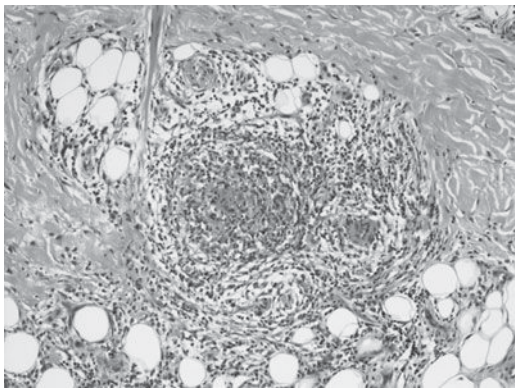

Fig. 4.6 (See also Colour plate 1.) PAN—skin biopsy.

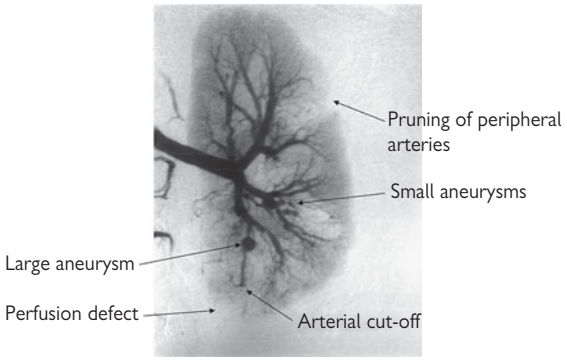

Fig. 4.7 PAN—renal arteriogram.

Treatment

(See 🕮 The standard treatment of childhood vasculitis, p 174, for specific drug doses and protocols, and 🕮 BSPAR guidelines for treatments used in paediatric rheumatology, p 415.)

- 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 (see 🕮 Cutaneous PAN, p 198), 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 favourable 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 MTX, MMF, and ciclosporin.
  - Some advocate alternate day low-dose prednisolone in the maintenance phase with the intention of limiting steroid toxicity such as growth impairment although data to support this approach are limited.
- Adjunctive plasma exchange can be used in life-threatening situations (see 🕮 Vasculitis treatment, p 174).
- Biologic 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 multicentre 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. Medium-size-vessel vasculitis. *Pediatr Nephrol* 2010; **25**(9):1641–52.

Ozen S, Anton J, Arisoy N, *et al.* Juvenile polyarteritis: results of a multicenter survey of 110 children. *J Pediatr* 2004; **145**:517–22.

Cutaneous polyarteritis nodosa (cPAN)

Background and clinical features

- cPAN is a form of vasculitis affecting small- and medium-sized vessels limited to the skin.
- It is characterized by the presence of fever; subcutaneous nodular, painful, non-purpuric lesions with or without livedo reticularis occurring predominantly in the lower extremities; with no systemic involvement (except for myalgia, arthralgia, and non-erosive arthritis).
- In a recent international survey of childhood vasculitis, approximately 1/3 of children identified as having PAN were categorized as cPAN.
- The clinical course is characterized by periodic exacerbations and remissions that may persist for many years.
- Skin biopsy shows features identical to systemic PAN.
- ANCA are usually negative and the condition is often associated with serological or microbiological evidence of streptococcal infection.
- There is debate as to whether the condition should be classed as a separate entity or as a part of the spectrum of PAN since a proportion of cases appear to evolve into full-blown PAN.

Treatment of cPAN

- NSAIDs may suffice.
- Some require moderate doses of oral steroids.
- When streptococcal infection is implicated, penicillin may be effective.
  - Some recommend continuing prophylactic penicillin throughout childhood, as relapses are common and occur in up to 25% of cases in association with further streptococcal infections.
- When there is a lack of response to the above, or concerns about possible steroid toxicity, other agents may be considered:
  - IVIg has been successfully used.
  - Alternatives with anecdotal success for cPAN therapy include colchicine, hydroxychloroquine, azathioprine, MTX, dapsone (beware haemolytic anaemia as a relatively common and severe side effect of this agent), cyclophosphamide, and pentoxifylline.

Outcome of cPAN

- A minority of patients experience a persistence of cutaneous lesions through childhood.
- Overall it is uncommon for the condition to progress to PAN.
- However, it is mandatory for such patients to remain under surveillance to detect any evidence of developing systemic disease that would be an indication for intensification of treatment as per that of PAN.

Further reading

Dillon MJ, Eleftheriou D, Brogan PA. Medium-size-vessel vasculitis. *Pediatr Nephrol* 2010; **25**(9):1641–52.

Ozen S, Anton J, Arisoy N, *et al*. Juvenile polyarteritis: results of a multicenter survey of 110 children. *J Pediatr* 2004; **145**:517–22.

Takayasu arteritis

Background

- Takayasu arteritis (TA) is an idiopathic, chronic inflammation of the large vessels, affecting the aorta and its major branches.
- The disease is named after Mikito Takayasu, a Japanese ophthalmologist, who first described an association between retinal peri-papillary arterio-venous anastomoses and absent radial pulses.
- Other names include 'pulseless disease', aortic arch syndrome, or idiopathic aortoarteritis.
- Classification criteria are provided in the 📖 Vasculitis classification, p 168.

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 ♀ predominance. In children however gender ratios vary amongst different studies. A recent study from Southeast Asia and Africa report a ♀:♂ ratio of 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 3rd 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 RA, ulcerative colitis, and other auto-immune 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 TNFα.
  - 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 2° 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 2° 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 haemorrhage
  - Micro aneurysms of the peripheral retina
  - Optic atrophy.

Renal involvement

- Renal hypertension 2° to renal artery stenosis with 2° glomerular damage.
- Chronic renal failure.
- 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: Kawasaki disease; polyarteritis nodosa; Wegener's granulomatosis is also recognized cause of aortitis.
- Infections:
  - Bacterial endocarditis
  - Septicaemia without true endocarditis
  - TB
  - Syphilis
  - HIV
  - Borelliosis (Lyme disease)
  - Brucellosis (very rare).
- Other autoimmune or autoinflammatory diseases: SLE; rheumatic fever; sarcoidosis; Blau's syndrome.
- Non-inflammatory large vessel vasculopathy of congenital cause. ***Treatment with immunosuppression will be ineffective and could be harmful:***
  - 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 (also see 📖 Vasculitis investigation, p 172)

- Normochromic normocytic anaemia, leucocytosis, 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.
- Poyclonal hyperglobulinaemia.

Further tests required to exclude other causes mimicking TA or for disease monitoring

- Regular 4-limb BP measurement (preferably with a manual sphygnomanometer).
- In cases of significant peripheral artery stenosis, central BP measurements may be required.
- Renal function tests, urinalysis.
- Auto-immune 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 a CXR are simple 1st-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, MR lacks sensitivity in evaluation of the distal aortic branches, and may overestimate the degree of arterial stenosis, especially in small children.
  - Cardiac MRI is increasingly employed to look for valvular involvement and/or myocarditis.
- Angiographic findings form the basis of one classification for TA (Takayasu Conference, 1994):
  - 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 the above types.
  - Type V. Includes patients with involvement of the coronary arteries.
- Doppler USS:
  - 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 ↑ wall thickness.

- ***^{18}F-FDG-PET co-registered with CTA*** can be a powerful technique combining information relating to the metabolic activity of the arterial wall (***^{18}F-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.

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 (also see 📖 Vasculitis treatment, p 174)

- 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 MTX or cyclophosphamide for induction of remission. Maintenance agents include MTX, azathioprine, or more recently MMF. There are case reports of benefit with the use of infliximab.

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. *Seek specialist advice from a paediatric nephrologist.*
- Revascularization procedures may be required.

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 centres 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 10–30%:
  - 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. Large vessel vasculitis. *Paed Nephrol* 2010 **25**:1037–48.

Behçet's disease

Behçet's disease (BD) is a multisystem disease with a classic triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis, which may also affect the skin, joints, GI tract, and CNS. Both small- and large-vessel vasculitis occurs, and in some patients there is a propensity to arterial and venous thromboses. Many now regard BD within the spectrum of autoinflammatory diseases.

Pathophysiology

- Unknown.
- BD has geographical variability, being more commonly found in the Mediterranean, Middle East, and Japan than in the USA and the UK.
- Likely auto inflammatory condition with possible environmental triggers in genetically susceptible individuals.
- HLA-B51 is significantly associated with BD.
- Recent studies also implicate the familial Mediterranean fever gene (*MEFV*) as an additional genetic susceptibility factor in some patients.
- Other genetic associations including *MICA* and *TNF* genes are thought to be the result of linkage disequilibrium with the *HLA-B 51* gene, and are thus not causally associated.
- ***Pathergy:*** the skin hyper-reactivity response or pathergy test is not pathognomic of BD but may be an important diagnostic indicator. Early or pathergy-induced cutaneous lesions in BD show a neutrophilic vascular reaction. This may be vascular or perivascular with a diffuse dermal neutrophilic infiltrate. Longstanding lesions may show a lymphocytic vasculitis. A typical pathergy test protocol is described later in this section.

Diagnostic criteria

The presence of recurrent oral aphthae (>3 times in one year), plus 2 of the following in the absence of other systemic diseases:

- Recurrent genital aphthae
- Eye lesions (uveitis or retinal vasculitis)
- Skin lesions
- Positive pathergy test.

Clinical features

Almost any organ can be involved due to the vasculitis affecting both arteries and veins of all sizes:

- Oral ulcers—painful, occur singly or in crops, affect lips, gingivae, buccal mucosa and tongue, last 1–2 weeks.
- Genital ulcers—affect scrotum in ♂, vulva in ♀, may result in scarring.
- Cutaneous lesions may be erythema nodosum-like, papulopustular, vesicular, abscesses, erythema multiforme-like eruptions, folliculitis, thrombophlebitis. Less commonly are pyoderma gangrenosum-type lesions, palpable purpura, purulent bullae, bullous necrotizing vasculitis and Sweet syndrome-like lesions.
- Ocular—iridocyclitis affecting the anterior segment or chorioretinitis, optic papillitis, retinal thrombophlebitis, arteritis.
- Arthralgia and arthritis usually affecting knees and ankles.

- GI—nausea, vomiting, diarrhoea, weight loss. May mimic inflammatory bowel disease. Ulcers may occur anywhere but usually affect ileum and caecum.
- Neurological—headaches, paralysis, hyperparaesthesia, dementia, behavioural disorders, psychiatric problems, cerebellar signs, peripheral nerve palsies. Underlying pathology includes meningoencephalitis, cerebral venous thrombosis and 'benign intracranial hypertension', parenchymal inflammatory brain disease without obvious vasculitis ('neuro-Behçet's'), and true arterial vasculitis.
- Cardiovascular—myocarditis, pericarditis.
- Vascular—arterial or venous occlusions, varices, aneurysms.
  - Pulmonary arterial aneurysms are of particular concern in adults with BD, and can present with haemoptysis mimicking pulmonary embolism, but anticoagulation can be fatal in this situation so beware this diagnostic pitfall.
- Respiratory—pulmonary infiltrates may be associated with pulmonary haemorrhage.
- Nephro-urological—haematuria and proteinuria (which may cause nephrotic syndrome), urethritis, orchitis, and epididymitis.
- Haematological—thrombocytopenia, neutropenia.
- Systemic—malaise, anorexia, weight loss.

Investigations

- FBC, CRP, ESR, routine clinical chemistry, thrombophilia screen (to exclude other causes of thrombosis), urinalysis.
- IgG, A, and M to exclude common variable immunodeficiency or other cause of low immunoglobulins (can present with oral ulcers).
- ANA, ds-DNA antibodies, RF, C3 and C4, ANCA, anticardiolipin antibodies, and antiphospholipid antibody are negative or normal but should be performed to exclude other autoimmune disease.
- Consider IgD and genetic testing for hyper IgD syndrome in atypical cases of suspected BD.
- Skin pathergy test—A 20-gauge needle is inserted obliquely 5mm into the skin of the anterior forearm. The presence of erythema, papules, erythematous papules, or pustules at 24–48h indicate a positive test result.
- MRI of the brain including MR arteriography and venography should be considered early for those with headaches to exclude neuro-BD or cerebral venous thrombosis.

Treatment

Evidence in children is limited. EULAR recommendations for treatment in adults are based on limited evidence and were not designed with children in mind, but provide a framework for the management of children. See Table 4.5.

General principles of treatment of BD in the young.

- Tailored to the individual and reflecting organ involvement and severity.
- Least toxic therapies should be tried first.
- Oral ulcers should be treated with topical agents before considering systemic drugs.
- Anti-TNFα agents (etanercept, infliximab, and adalimumab) are increasingly used before thalidomide in children.

- Thalidomide is still used on a named-patient basis for children and adolescents with BD, typically for severe and resistant oral and/or genital ulceration, although it may also benefit other systemic symptoms of BD. Peripheral neuropathy and teratogenicity limit its use.
  - Suggested dosing regimen: 0.5–1mg/kg (maximum 100mg) orally once a week at nighttime (to avoid daytime drowsiness). ↑ dose by adding another daily dose every week until symptoms controlled or until dose of 1mg/kg daily (whichever achieved first).
  - Exclude pregnancy, and check peripheral nerve conduction studies prior to starting thereafter repeating nerve conduction 3–6-monthly (or after every 10g of total accumulative dose). Stop immediately if symptoms of neuropathy (e.g. numbness, tingling) develop.
  - Remember that teratogenic risk also applies to mothers/female carers who handle the drug- full precautions always must be advised.
  - The L isomer lenalidomide may be less toxic but have greater (or comparable) efficacy, but experience in paediatric BD is limited.

Prognosis—variable

- Eye disease can result in long-term visual impairment.
- Course may be worse in children than adults.
- ♂ tend to be more severely affected.
- Reported mortality of 3%, usually due to vascular complications.

Patient and parental support, including information sheets for children and adults can be found at: http://www.behcets.org.uk.

Table 4.5 EULAR 2008 recommendations for the treatment of Behçet's disease*

Recommendation	Category of evidence
1. Eye involvement: any patient with BD and inflammatory eye disease affecting the posterior segment should be on a treatment regimen that includes azathioprine and systemic corticosteroids	**Ib**
2. Refractory eye involvement: if the patient has severe eye disease defined as >2 lines of drop in visual acuity on a 10/10 scale and/or retinal disease it is recommended that either ciclosporin or infliximab be used in combination with azathioprine and corticosteroids; alternatively interferon-α with or without corticosteroids could be used instead	**Ib/IIb**
3. Major vessel disease: there is no firm evidence to guide the management of major vessel disease in BD. For the management of acute deep vein thrombosis immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide, or ciclosporin are recommended. For the management of pulmonary and peripheral arterial aneurysms, cyclophosphamide and corticosteroids are recommended	**III**

(*continued*)

Table 4.5 (*Contd.*)

Recommendation	Category of evidence
4. Anticoagulation: there are no controlled data on, or evidence of benefit from uncontrolled experience with anticoagulants, antiplatelet,or anti-fibrinolytic agents and management of deep vein thrombosis or for the use of anticoagulation for the arterial lesions of BD	**IV**
5. Gastrointestinal involvement: there is no evidence-based treatment that can be recommended for the management of GI involvement of BD. Agents such as sulfasalazine, corticosteroids, azathioprine, TNFα antagonists and thalidomide should be tried first before surgery, except in emergencies	**III**
6. Joint involvement: in most patients with BD, arthritis can be managed with colchicine	**Ib**
7. Neurological involvement: there are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement agents to be tried may include corticosteroids, interferon-α, azathioprine, cyclophosphamide, MTX, and TNFα antagonists. For dural sinus thrombosis corticosteroids are recommended	**III**
8. Ciclosporin neurotoxicity: ciclosporin should not be used in BD patients with CNS involvement unless necessary for intra ocular inflammation	**III**
9. Mucocutaneous involvement: the decision to treat skin and mucosal involvement will depend on the perceived severity by the doctor and patient. Mucocutaneous involvement should be treated according to the dominant or codominant lesions present.	**Ib**
Topical measures (i.e. topical corticosteroids) should be the 1st-line treatment for isolated oral and genital ulcers	
Acne like lesions are usually of cosmetic concern only. Thus, topical measures as used in acne vulgaris are sufficient	
Colchicine should be preferred when the dominant lesion is erythema nodosum	
Leg ulcers in BD might have different causes. Treatment should be planned accordingly	
Azathioprine, IFNα and TNFα antagonists may be considered in resistant cases	

CNS, central nervous system; IFN, interferon; TNF, tumour necrosis factor.

Categories of evidence: Ia: meta-analysis of randomized controlled trials; Ib: randomized controlled trial; IIa: controlled study without randomization; IIb: quasi-experimental study; III: non-experimental descriptive studies such as comparative, correlation and case-control studies; IV: expert committee reports or opinion or clinical experience of respected authorities or both.

*Adapted from: Hatemi G, Silman A, Bang D, *et al.* EULAR recommendations for the management of Behcet disease. *Ann Rheum Dis* 2008; **67**:1656–62.

Central nervous system vasculitis in children

Background

- Central nervous system (CNS) vasculitis in children is an increasingly recognized inflammatory brain disease that continues to pose great diagnostic and therapeutic challenges. CNS vasculitis may occur as a 1° disease that is isolated to the CNS (primary angiitis of the CNS, PACNS) or as a 2° manifestation of an underlying systemic condition.
- The most common systemic inflammatory diseases and infections that may cause 2° CNS vasculitis are summarized in Box 4.1.

Diagnostic criteria

Diagnostic criteria for PACNS in adults were proposed by Calabrese *et al.* in 1992 and they include the following:

- An acquired neurological deficit.
- Angiographic and/or histopathological features of angiitis within the CNS, and
- No evidence of systemic condition associated with these findings.

Although a paediatric case definition of PACNS in children (cPACNS) has not been proposed, most reported cases fit the Calabrese *et al.* criteria.

cPACNS is broadly subdivided into two forms of the disease:

- Large–medium-vessel vasculitis (further divided into progressive and non-progressive, according to angiographic evidence of disease progression 3 months after diagnosis).
- Small-vessel vasculitis.

Epidemiology

The true incidence of cPACNS is difficult to establish as the condition is rare and there is lack of consensus on diagnostic criteria.

Clinical features

The clinical presentation of cPACNS is heterogeneous, with some children presenting with a rapidly progressive neurological deficit, whereas others have a slowly evolving disease course over weeks or months. Most common presenting features (in isolation or in various combinations) include the following:

- Acute severe headache.
- Focal neurological deficit.
- Gross motor deficit, hemiparesis.
- Cranial nerve involvement and optic neuritis.
- Concentration and cognitive deficits, behaviour, and personality changes.
- New onset of seizures.
- Acute loss of consciousness and symptoms of ↑ intracranial pressure caused by either intracerebral or subarachnoid haemorrhage, or a CNS mass lesion.
- Movement abnormalities.
- Constitutional symptoms (fever, fatigue, weight loss) are uncommon but can present in a minority of patients with small vessel vasculitis.

Box 4.1 Secondary central nervous system vasculitis in children

Inflammatory disorders
- Systemic lupus erythematosus
- Behçet's disease
- Sjögren's syndrome
- Juvenile dermatomyositis
- Scleroderma
- Inflammatory bowel disease.

Systemic vasculitides
- Polyarteritis nodosa
- Kawasaki disease
- Henoch–Schönlein purpura
- ANCA-associated vasculitides: Wegener's granulomatosis; microscopic polyangiitis; Churg–Strauss syndrome.

Infectious/post-infectious
- Bacterial:
  - *Streptococcus pneumoniae*
  - *Salmonella* spp.
  - *Mycoplasma pneumonia*
  - *Mycobacterium tuberculosis*
  - *Treponema pallidum*
- Viral:
  - Hepatitis C virus
  - Cytomegalovirus
  - Epstein–Barr virus
  - HIV
  - Parvovirus B19
  - Varicella zoster virus
  - Enterovirus
  - Spirochete
  - *Borrelia burgdorferi.*
- Fungal:
  - *Candida albicans*
  - *Aspergillus.*

Other
- Malignancy
- Graft-versus-host disease.

Differential diagnosis

CNS vasculitis can be mimicked in both its clinical presentation and radiological manifestations by a number of inflammatory and non-inflammatory disorders, summarized in Box 4.2.

Investigations

The aim of the diagnostic work-up in patients with suspected cPACNS is to exclude causes of 2° CNS vasculitis or other neuro-inflammatory conditions that can present in the same way. In general there are no consistent or reliable laboratory abnormalities in children with cPACNS, and normal inflammatory markers by no means exclude an active vasculitic process in the CNS. The following investigations should be considered:

Laboratory investigations

- FBC and blood film, haemoglobin electrophoresis/sickle cell screen if patient is black or of Mediterranean ethnicity.
- ESR and CRP.
- ANA/dsDNA, ENA.
- ANCA.
- C3 and C4 levels.
- IgG, IgA, IgM.
- Clotting screen.
- Full thrombophilia screen including:
  - Lupus anticoagulant and anticardiolipin antibodies
  - Protein C
  - Protein S
  - Antithrombin
  - APC resistance ratio
  - Factor V Leiden
  - Methylenetetrahydrofolate reductase (MTHFR) and prothrombin G20210A gene mutations
  - Von Willebrand antigen levels may be elevated
  - CSF studies to establish cell count, protein levels, and exclude infection. CSF opening pressure should also be measured; CSF oligoclonal bands (simultaneous serum testing for total IgG required)
  - Plasma amino-acids and plasma homocysteine
  - Plasma lactate and ammonia
  - Alpha galactosidase A (to exclude Fabry's disease)
  - Serology for mycoplasma, *Borrelia burgdorferi*, VZV.
- ***Ophthalmology assessment*** to look for retinal vasculitis, infection, or other inflammatory disease.
- Echocardiogram and ECG.
- ***Imaging studies:***
  - MRI brain/spine and MRA.
  - MRI in cPACNS reveals areas of acute ischemia in a vascular distribution when large–medium vessels are affected. In cases of small-vessel disease, the lesions may be multifocal and not necessarily conform to a specific vascular distribution.
  - The parenchymal lesions may involve both grey and white matter, and meningeal enhancement has also been described.

  - Diffusion weighted imaging (DWI) identifies areas of ischaemia in large-vessel disease.
  - MRA provides an assessment of the vasculature and may reveal beading, tortuosity, stenosis, and occlusion of the vessels.
  - Conventional catheter arteriography (CA) continues to be the radiological gold-standard for identifying cerebrovascular changes in patients with suspected CNS vasculitis and is more sensitive than MRA at detecting distal lesions that affect small calibre vessels, and for lesions in the posterior part of the brain.
- Brain biopsy for confirmation of vasculitis should be considered in difficult cases, but is rarely performed in children due to the invasiveness of the procedure. It should however be strongly considered in cases of high clinical suspicion but with negative arteriography findings or in cases of poor response to therapy.
  - Biopsy findings characteristically reveal segmental, non-granulomatous, intramural infiltration of arteries, arterioles, capillaries, or venules.
  - Non-lesional biopsy may be considered when lesions identified on imaging are not easily accessible.

Treatment

There are no randomized control trials (RCTs) to guide therapy.

- Current therapeutic recommendations are based on those for systemic vasculitis (see 🕮 Vasculitis therapy, p 174) and include:
  - 6 months' induction therapy with IV cyclophosphamide: 500–1000mg/m^2 (max 1.2g) every 3–4 weeks (usually 7 doses); corticosteroids and antiplatelet doses of aspirin, followed by
  - 1–2yr maintenance therapy with azathioprine (1.5–3mg/kg/day), low dose daily or alternate day corticosteroid, and continuation of aspirin.
  - MMF has also been reported to be effective in some cases to maintain remission.
- Full anticoagulation may need to be considered on an individual patient basis.
- Treatment of large-vessel non-progressive disease remains controversial. There may be a role for steroids and aspirin without cytotoxic immunosuppression.

Outcome

- A recent study of 62 children with cPACNS suggested a poorer prognosis for patients presenting with: 1) a neurocognitive dysfunction, 2) multifocal parenchymal lesions on MRI, or 3) evidence of distal stenoses on arteriography.
- Further long-term follow-up studies are necessary to accurately define the prognosis of this condition in children.

Box 4.2 Mimics of CNS vasculitis in children

- Arterial dissection
- Thromboembolic disease (congenital heart disease, inherited thrombophilia)
- Antiphospholipid syndrome
- Sickle cell disease
- Moyamoya disease (cerebral arteriopathy characterized by progressive steno-occlusive changes at the terminal portions of the bilateral internal carotid arteries with arterial collateral vessels at the base of the brain)
- Fibromuscular dysplasia
- Fabry's disease
- Sneddon's syndrome (morphologically fixed livedo reticularis and cerebrovascular accidents)
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
- Susac's syndrome (acute encephalopathy, branch retinal artery occlusions and sensorineural hearing loss)
- Amyloid angiopathy
- Neurofibromatosis type I
- Hyperhomocysteinaemia
- Drug-exposure (cocaine, amphetamine, methylphenidate)
- Metabolic diseases:
  - Mitochondrial diseases
  - Leucodystrophies
  - Mucopolysaccharidoses
- Multiple sclerosis
- Acute disseminated encephalomyelitis (ADEM)
- Devic's disease/neuromyelitis optica (CNS demyelinating condition affecting predominantly the spinal cord and optic nerves characterized by the presence of aquaporin-4 water channel IgG antibodies)
- Vitamin B12 deficiency
- Rasmussen syndrome (neurological disorder characterized intractable focal seizures, progressive hemiplegia and increasing cognitive impairement)
- Sarcoidosis
- Coeliac disease
- 1° and 2° haemophagocytic lymphohistiocytosis (HLH)
- Progressive multifocal leukoencephalopathy (JC virus)
- Lymphoma
- Glioma
- Migraine/vasospasm
- Post radiation therapy for CNS tumour.

Further reading

Elbers J, Benseler SM. Central nervous system vasculitis in children. *Curr Opin Rheumatol* 2008; **20**:47–54.

Other vasculitides

Background

The EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides include a category of "other vasculitides" for vasculitides where an aetiological process was defined, or in which no other classification category was appropriate (see 🕮 p 168). These include:

- Behçet's disease
- Vasculitis 2° to infection (including hepatitis B-associated PAN), malignancies, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue diseases
- Cogan's syndrome
- cPACNS
- Unclassified vasculitides.

Isolated cutaneous leucocytoclastic vasculitis, and hypocomplementic urticarial vasculitis are also described in this chapter. Behçet's disease and cPACNS are described in their respective chapters.

Vasculitis secondary to infection, malignancies, and drugs, including hypersensitivity vasculitis

Vasculitis secondary to infection

- Many viruses (HIV, parvovirus B19, cytomegalovirus, varicella-zoster virus, and human T-cell lymphotropic virus- HTLV1) can be responsible for systemic vasculitis, the most frequent being hepatitis B virus-related polyarteritis nodosa (HBV-PAN), even though its incidence has ↓ over the past few decades.
- Mixed cryoglobulinemia has been shown to be associated with hepatitis C virus (HCV) infection in adults, but has not been reported in children.
- Some bacteria, fungi, or parasites can also cause vasculitis, mainly by direct invasion of blood vessels or septic embolization.
- Effective antimicrobial drugs are mandatory to treat bacterial, parasitic or fungal infections, while the combination of antiviral agents (vidarabine, interferon-α) and plasma exchange has been proven to be effective against HBV-PAN.

Vasculitis secondary to drugs, including hypersensitivity vasculitis

- Therapeutic agents from virtually every pharmacological class have been implicated in the development of drug-induced vasculitis.
- Typically presents with cutaneous vasculitis alone (palpable purpura, macules, plaques, bullae and ulcers), low grade fever, arthralgia, and microcopic haematuria.
- More rarely can present with life-threatening systemic involvement, which may result in a severe and sometimes fatal illness.
- Withdrawal of the offending agent alone is often sufficient to induce prompt resolution of clinical manifestations.
- Steroids may be used for systemic involvement and azathioprine or other immunosuppressants may be appropriate for refractory disease.

Vasculitis secondary to malignancy

- In some patients, vasculitis occurs during the course of or prior to malignancies, most often haematological rather than solid tumours. Evidence of autoantibodies, immune complexes, and complement consumption is typically absent.
- Vasculitis may also occasionally be a complication of chemotherapy, radiation therapy, and bone marrow transplantation.

Vasculitis associated with connective tissue diseases

- Vasculitis 2° to connective tissue disorders in children most commonly arises in the context of pre-existing SLE, 1° Sjögren's syndrome (SS), systemic sclerosis, relapsing polychondritis, 1° antiphospholipid syndrome, juvenile dermatomyositis, or mixed connective tissue (see 📖 specific chapters on each of these entities, SLE p 223, Sjogren's syndrome p 277, systemic sclerosis p 260, antiphospholipid syndrome p 279, mixed connective tissue or overlap syndromes p 275).
- The vasculitis may involve vessels of any size, but small-vessel involvement is predominant.
- Patterns of involvement vary with the associated underlying disorder, and range from isolated cutaneous involvement to life-threatening internal organ involvement.
- When vasculitis occurs in the setting of a pre-existing connective tissue disorder, it often correlates with disease severity and portends a poorer prognosis. Prompt recognition and treatment of vasculitis can dramatically improve the outcome for these patients.

Isolated cutaneous leucocytoclastic vasculitis

- This refers to cutaneous leucocytoclastic vasculitis without systemic vasculitis or glomerulonephritis.
- Histologically leucocytoclastic vasculitis appears as a neutrophil infiltration in and around small vessels, with neutrophil fragmentation (often referred to as 'nuclear dust' or leucocytoclasis), fibrin deposition, and endothelial cell necrosis.
- Treatment may require corticosteroids, colchicine, hydroxychloroquine, azathioprine, MTX or rarely dapsone (beware severe haemolytic anaemia and/or methaemoglobinaemia with dapsone).

Hypocomplementaemic urticarial vasculitis syndrome

- Hypocomplementaemic urticarial vasculitis syndrome (HUVS) is an uncommon immune complex–mediated entity characterized by urticaria with persistent acquired hypocomplementaemia.
- The disease is extremely rare in the paediatric population.
- In patients with HUVS, systemic findings include leucocytoclastic vasculitis, angio-oedema, laryngeal oedema, pulmonary involvement (interstitial lung disease, haemoptysis, pleural effusions), arthritis, arthralgia, glomerulonephritis, and uveitis.
- Laboratory findings include low levels of C1q, C2, C3, and C4. The binding of C1q antibodies to immune complexes is thought to be important in the pathogenesis of renal disease in HUVS.
- Treatment is individualized and is based on disease severity and will typically include corticosteroids and other immunosuppressive agents such as azathioprine or cyclophosphamide.

- Patients may have significant morbidity and mortality, most commonly caused by chronic obstructive pulmonary disease and acute laryngeal oedema.

Cogan's syndrome

- Cogan syndrome is a rare syndrome of:
  - Interstitial keratitis.
  - Vestibuloauditory symptoms (hearing loss and balance problems).
  - Occasionally aortitis.
- The cause is unknown, although autoantibodies and small-vessel vasculitis have been implicated.
- Typical Cogan's is characterized by:
  - Ocular involvement: primarily interstitial keratitis and occasionally conjunctivitis, uveitis, or subconjuctival haemorrhage.
  - Audiovestibular involvement giving a clinical picture similar to Ménière's disease accompanied with progressive hearing loss of hearing, usually ending in deafness within 1–3 months.
  - Other symptoms include fever, loss of weight, cardiac involvement (aortic insufficiency reported to up to 15% of patients), myalgia, arthralgia, mucocutaneous manifestations, GI and neurological involvement.
- The differential diagnosis is:
  - Vogt–Koyanagi–Harada syndrome (audiovestibular involvement with uveitis, vitiligo, alopecia).
  - Susac syndrome (retinocochleocerebral vasculopathy, presenting with acute or subacute encephalopathy, branch retinal artery occlusions and sensorineural hearing loss as a result of small infarcts in the brain, retina and cochlea).
  - Other vasculitides.
  - Relapsing polychondritis.
  - SLE or Sjögren's may cause similar symptoms.
- During attacks patients may have raised inflammatory markers. Detection of antibodies against corneal or inner ear antigens has been studied in small case series.
- Treatment includes corticosteroid therapy, while other immunosuppressants such as MTX, cyclophosphamide have been used with variable efficacy. Cochlear implantation may ultimately be necessary for hearing loss, and physiotherapy is required for the vestibular symptoms.
- The course of the disease is variable, with some patients experiencing episodes of ocular and audiovestibular symptoms at variable intervals with complete remission in between. In the longer term ~90% of patients suffer severe hearing loss while long-term ocular sequelae are rare. Systemic involvement is associated with the worst prognosis and can develop years after the initial onset of symptoms justifying prolonged close monitoring.

Further reading

Jara LJ, Navarro, C, Medina, G, *et al*, Hypocomplementemic urticarial vasculitis syndrome *Curr Rheumatol Rep* 2009, **11**:410–15.

Ozen S. The 'other' vasculitis syndromes and kidney involvement. *Pediatr Nephrol* 2010; **25**(9):1633–9.

Grasland A, Pouchot J, Hachulla E, *et al*, Typical and atypical Cogan's s syndrome: 32 cases and review of the literature, *Rheumatology* 2004; **43**:1007–15.

Vasculitis mimics: non-inflammatory vasculopathies

Background

There are numerous non-inflammatory vasculopathies that may mimic the clinical, laboratory, radiological, and/or pathological features of the 1° vasculitides. Some will have associated musculoskeletal manifestations and will be referred to the paediatric rheumatologist. Awareness of these mimics is essential to avoid the use of unnecessary and potentially harmful immunosuppression and to direct management to the correct underlying cause of disease. The commonest of these vasculitis mimics are discussed in this section. Mimics of CNS vasculitis are covered in 📖 p 213.

Fibromuscular dysplasia (FMD)

- FMD is a non-inflammatory vasculopathy leading to stenoses of small- and medium-sized arteries, sometimes with poststenotic dilatation resembling aneurysms. It is a major differential diagnosis for Takayasu disease.
- FMD has been detected in almost every vascular bed although the most commonly affected are renal arteries (60–75%) followed by the cervico-cranial arteries (25–30%), non-renal visceral arteries (5%), and arteries in the extremities (5%). Intracranial arterial poststenotic dilatations have been reported in 7% of adult patients, but rarely in children.
- Patients can remain asymptomatic or present with signs of vascular insufficiency such as hypertension, stroke, abdominal pain, or claudication.
- The pathological classification for FMD is based on the arterial layer involved. Medial fibroplasia accounts for 80–90% of all cases and is characterized by a 'string of beads' appearance on angiography due to alternating areas of stenosis and aneurysmal dilatation involving the mid-to-distal portions of the vessel.
- It can be difficult to differentiate diffuse intimal FMD from large-vessel vasculitis, since their angiographic appearance can be similar. Histological examination may be required in these cases.
- Imaging investigations to be considered include:
  - Renal ultrasonography and Doppler studies.
  - CTA and MRA have been increasingly used for non-invasive imaging of the vascular tree.
  - However, selective catheter arteriography continues to be the radiological gold standard for delineating the extent of vascular involvement.
  - Cerebral perfusion scans or other measures to exclude cerebral arterial insufficiency should be carried out before angioplasty or surgical correction of renal artery stenosis to relieve hypertension, since a drop in BP can precipitate stroke in this situation.
- The management of hypertension associated with renal artery FMD involves antihypertensive therapy and revascularization with percutaneous angioplasty or other revascularization procedures for patients with significant renal artery stenosis, severe hypertension with

inadequate response, or intolerance of antihypertensive medication. Management of dissecting carotid artery due to FMD includes antiplatelet therapy and percutaneous angioplasty or surgical repair for patients with signs of cerebral vascular insufficiency.

Vasculopathies involving the TGFβ-signalling pathway

Marfan syndrome

- Incidence of Marfan syndrome is reported to be 1 in 10,000.
- Marfan syndrome results from mutations in the fibrillin-1 (*FBN1*) gene on chromosome 15, which encodes the glycoprotein fibrillin. Recent studies have suggested that abnormalities in the transforming growth factor-beta (TGFβ)-signalling pathway may represent a final common pathway for the development of the Marfan phenotype.
- Affected patients are usually taller and thinner than their family members. Their limbs are disproportionately long compared with the trunk (dolichostenomelia). Arachnodactyly, pectus excavatum, or carinatum are common features (Fig. 4.8).
- Ocular findings include ectopia lentis, flat cornea, cataract, glaucoma, retinal detachment.
- Cardiovascular involvement is the most serious complication associated with Marfan syndrome and comprises aortic root dilatation, aortic dissection involving the ascending aorta, and mitral valve prolapse.
- Patients can also present with spontaneous pneumothorax, stretch marks (striae atrophicae in the lower back), recurrent or incisional hernia, and dural ectasia.

Management: seek expert cardiological advice

The paediatric rheumatologist should be aware that evidence now suggests that the vasculopathy of Marfan syndrome is associated with dysregulation of TGFβ, and that this can be blocked using angiotensin II receptor 1 blockade (AT1 antagonists) such as losartan. Animal and human data have demonstrated that this can significantly slow the progression of aortic root dilatation and prolong life. Thus early referral to a paediatric cardiologist is essential. Other management of the vasculopathy under expert paediatric cardiology supervision may include:

- General measures: moderate restriction of physical activity, endocarditis prophylaxis, echocardiography at annual intervals.
- Beta-blocker therapy (propanolol 2–4mg/kg/day in divided doses) should be considered at any age if the aorta is dilated, but prophylactic treatment may be more effective in those with an aortic diameter of <4cm.
- ACE inhibitors (enalapril 0.08mg/kg/day—up to 5mg) reduce central arterial pressure and conduit arterial stiffness and may be useful.
- Prophylactic aortic root surgery should be considered when the aortic diameter at the sinus of Valsalva is >5cm.

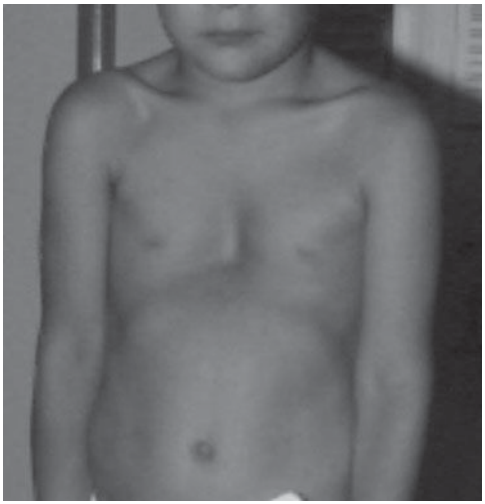

Fig. 4.8 Pectus excavatum of moderate severity.

Loeys–Dietz syndrome

- Loeys–Dietz syndrome is considered an autosomal dominant disorder associated with mutations in either of the TGFβ receptors (TGFβ R1/TGFβ R2).
- 2 subtypes of Loeys–Dietz syndrome have been identified:
  - Loeys–Dietz syndrome type I patients have both craniofacial and vascular disorders. The most characteristic craniofacial findings are hypertelorism and broad or bifid uvula or cleft palate, 2 of the 3 components of the clinical triad that also includes arterial aneurysms and tortuosity.
  - Loeys–Dietz syndrome type II patients may have a bifid uvula but do not have a cleft palate, craniosynostosis, or hypertelorism.
- Additional manifestations include blue sclera, malar hypoplasia, exotropia, and retrognathia. Cervical spine instability, pectus deformity, arachnodactyly, craniosynostosis, scoliosis, and joint laxity are some of the many musculoskeletal manifestations. Patients may also have congenital cardiac anomalies (bicuspid aortic valve).
- Due to the high risk of death from aortic aneurysm rupture, patients should be followed closely to monitor aneurysm formation, which can then be corrected with vascular surgery.
- The role of TGFβ antagonism is currently being explored in this condition too.

Ehler–Danlos syndrome (vasculopathic EDS) type IV

- EDS type IV is an autosomal dominant disorder that results from mutations in the type III pro-collagen gene (*COL3A1*).
- Although joint and skin laxity is not common, patients often have easy bruising, thin skin with visible veins, or characteristic facial features (loss of subcutaneous fat and collagen, referred to as acrogeria).
- Arterial complications may include aortic or other arterial aneurysm, dissection, and carotico-cavernous sinus fistulae. Patients can present acutely with life-threatening rupture of the intestines, the gravid uterus, or other viscera.
- There is currently no preventative treatment for this condition but close follow-up to monitor aneurysm formation is recommended.

Grange syndrome

- Grange syndrome is an hereditary disorder that is associated with a variable combination of multiple arterial stenoses and aneurysms, brachydactyly, and syndactyly of the hands and feet, bone fragility consistent with a mild form of osteogenesis imperfecta, learning disability, and cardiac defects (PDA, VSD, bicuspid aortic valve).
- No underlying genetic defect has yet been determined.

Susac's syndrome

- Susac's syndrome is a microangiopathy of unclear aetiology that is more frequently reported in young adult ♀.
- Susac's syndrome is characterized by the typical clinical triad of acute or subacute encephalopathy, branch retinal artery occlusions, and sensorineural hearing loss that results from small infarcts in the brain, retina, and cochlea.
- Typical findings on brain MRI are multiple small white-matter hyperintensities; grey-matter involvement may also be seen. CSF analysis usually reveals a lymphocytic pleocytosis and elevated protein levels. Histological evidence of microangiopathic infarct is seen, without evidence of vasculitis or thrombosis.

Degos disease (DD)

- DD, also known as malignant atrophic papulosis, is characterized by thrombo-occlusive vasculopathy affecting the skin and various internal organs.
- DD has been described in 2 forms: the limited benign cutaneous and the lethal multiorgan systemic variant.
- In the skin, DD initially manifests with erythematous, pink or red papules that leave scars with pathognomonic, central, porcelain white atrophic centres.
- In the systemic form, GI involvement has been reported in the majority of patients and may manifest as abdominal pain, GI bleeding or bowel perforation. Central and peripheral nervous system, heart, lung, eye, pancreas, adrenal gland, and kidney involvement have been described.
- There has been no proven effective treatment for DD. Antiplatelet agents including aspirin and dipyridamole have been reported to reduce the formation of new skin lesions but there is no evidence in their role to prevent systemic complications. Immunosuppressants, anticoagulants,

and plasma exchange have been shown to be ineffective. Since corticosteroids may worsen other forms of occlusive vasculopathy, they should be used with caution in DD. Prompt surgical intervention is often needed for bowel infarction, perforation, or intracranial haemorrhage.
- The systemic form has a poorer prognosis and is usually fatal within the first 2yr after diagnosis because of major organ involvement.

Livedoid vasculopathy (LV)

- LV is an occlusive vasculopathy characterized by thrombosis and ulceration of the lower extremities.
- While the aetiology of LV remains unclear, it likely has a prothrombotic pathogenesis. Factor V Leiden mutation, heterozygous protein C deficiency, and hyperhomocysteinaemia have been associated with LV. In addition, plasminogen activator inhibitor (PAI)–1 promoter 4G/4G genotype has also been linked to the disease.
- Skin biopsies reveal segmental hyalinizing vascular involvement of thickened dermal blood vessels, endothelial proliferation, and focal thrombosis without nuclear dust. No true vasculitis is evident.
- The initial clinical findings are typically painful purpuric macules or papules on the ankles and the adjacent dorsum of the feet. Patients may have a history of livedo reticularis on their lower legs. The initial lesions, which often appear in clusters or groups, eventually ulcerate over a period of months and years and form irregular patterns of superficial ulcers. When the ulcers finally heal, they leave behind atrophic porcelain-white scars, which are referred to as 'atrophie blanche'.
- Small- and medium-sized vasculitides, such as isolated cutaneous leucocytoclastic vasculitis and PAN occasionally present with ulceration resulting in ivory-white, stellate scarring on the lower limbs and may be difficult to differentiate from LV.
- A number of therapies have been employed with variable effect:
  - Corticosteroids in combination with pentoxifyllin have been used in cases of widespread LV. Pentoxifyllin is believed to enhance the blood flow in the capillaries, making red blood cells more flexible and thereby reducing viscosity effectively. ***However, anecdotally some report that corticosteroids can worsen the occlusive vasculopathy associated with LV.***
  - As thrombogenic mechanisms may be involved in the disease pathogenesis, anticoagulant therapy (low-molecular-weight heparin, warfarin) and aspirin are often tried, but with variable efficacy.
  - Hyperbaric oxygen therapy has been used in intractable cases of LV with good effect in some cases.

Pseudoxanthoma elasticum (PXE)

- PXE is a rare, genetic disorder characterized by progressive calcification and fragmentation of elastic fibres in the skin, the retina, and the cardiovascular system, which is termed as elastorrhexia.
- PXE is caused by mutations in the ATP-binding cassette transporter C6 (*ABCC6*) also known as multidrug resistance-associated protein 6 (*MRP6*) gene.
- Patients present with:
  - Characteristic skin lesions that can appear during childhood. These are small, yellow papules of 1–5mm in diameter in a linear or reticular pattern which may coalesce to form plaques. The skin has a cobblestone-like appearance. These skin changes are first noted on the lateral part of the neck and later can involve any part of the body.
  - Ocular manifestations: angioid streaks of the retina, which are slate grey to reddish brown curvilinear bands radiating from the optic disc.
  - Cardiovascular manifestations include: calcification of the elastica media and intima of the blood vessels leading to a variety of physical findings, mitral valve prolapse.
  - Renal artery involvement leads to hypertension.
  - Mucosal involvement leading to GI haemorrhage.
- There is currently no treatment available for PXE.

Further reading

Eamonn S. Molloy and Carol A. Langford. Vasculitis mimics. *Curr Opin Rheumatol* 2008; **20**:29–34.

JSLE: epidemiology and aetiology

- Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by widespread inflammation and damage to any organ. It is a complex disease with marked heterogeneity, causing mild to life-threatening disease in any combination of organ systems and is remitting and relapsing with an unpredictable natural history.
- Approximately 15–20% of patients with lupus present before the age of 18 and form the cohort known as juvenile-onset SLE (JSLE).This group has a higher severity of disease and accrues more organ damage than adults (Box 4.3).

Box 4.3 Differences between JSLE and adult-onset SLE

- Children have more severe disease at onset than adults.
- Higher rates of organ involvement and more aggressive clinical course.
- Higher use of corticosteroids and immunosuppressive therapies.
- Accrue more organ damage, related to disease and corticosteroid use.
- Higher mortality rates.
- ↑ incidence of renal, neurological, and haematological disease.
- Effects of disease and treatments on growth and physical and psychological development.

Epidemiology

- The annual incidence of SLE per 100,000 children and young people ranges from 0.36–0.8 although this probably underestimates the actual number as many cases go unrecognized, have mild disease, or do not fulfil diagnostic criteria. ♀:♂ ratio varies with age, being 8:1 after puberty and 4:1 before 10yr of age. JSLE is rare before 5yr of age. The incidence of SLE appears to be higher in non-white children especially Black, Hispanic, and Asian children.
- Outcome has improved over recent years from 5yr survival of 60–90% in the 1980s to nearer 95% now. However, long-term outcome and cardiovascular morbidity from premature atherosclerosis is yet to be determined.
- Male children, early-onset of disease and ethnicity are associated with worse outcome.

Aetiology

- JSLE is the archetypal paediatric systemic autoimmune disease, illustrated by its complex clinical, molecular, and genetic characteristics. The cause of JSLE remains unknown. The principal underlying disorder in JSLE is impaired cellular and humoral immune response. Hormonal and environmental factors act on genetically susceptible individuals over time resulting in development of autoimmunity, eventually leading to disease progression (Box 4.4 and Fig. 4.9).
- The multitude of presenting and clinical features of lupus reflects the complex pathogenesis of SLE.

Box 4.4 Genetic, immunological, and environmental factors contributing to the development of lupus

Genetic factors

- Siblings of patients with SLE have 10–20-fold ↑ risk of developing disease.
- Monozygous twins have 24% concordance rate versus 2% heterozygote pairs.
- Familial autoimmunity is a risk factor for SLE (odds ratio 4.1 with 1 relative, 11.3 with 2 or more relatives).
- Homozygous deficiency of C1q, C1r, C1s, C4, and C2 are strongest susceptibility factors for SLE in humans (80% prevalence for C1 or C4 molecules).
- ↑ susceptibility to SLE is associated with an increasing number of recognized candidate genes, including *HLA* haplotypes, *ITGAM*, *IFR5*, *BLK*, *STAT4*, *PTPN22*, and *Fc*γ receptor polymorphisms.

Immune dysfunction

- B cells and autoantibodies: immune complexes containing anti-DNA and anti-RNP antibodies activate dendritic cells to produce IFNα which induces differentiation of B cells into antibody-secreting plasma cells, perpetuating auto-antibody production and immune complex production. B cells secrete cytokines and chemokines enhancing the inflammatory cascade.
- Dendritic cells (DCs): abnormal activation causes selection rather than deletion of T cells that have receptors to self-antigens.
- T cells: hyperactivity and loss of tolerance, in part due to mutations in inhibitory receptors on T cells.
- Proinflammatory cytokines levels elevated: interferon-α, IL-6, IL-10, IL-12, IL-18.
- Apoptosis: impaired clearance of apoptotic cells may lead to over-presentation of nuclear antigens by DCs to T cells.
- Other: abnormalities in monocytes, NK cells, cytokines, and immunoglobulins also identified.

Environmental

- Ultra-violet (UV) light can induce flares, possibly by altering DNA methylation.
- Viruses.
- Hormones.
- Drugs (e.g. procainamide, hydralazine have been shown to impair T cell DNA methylation leading to ↑ autoreactivity).

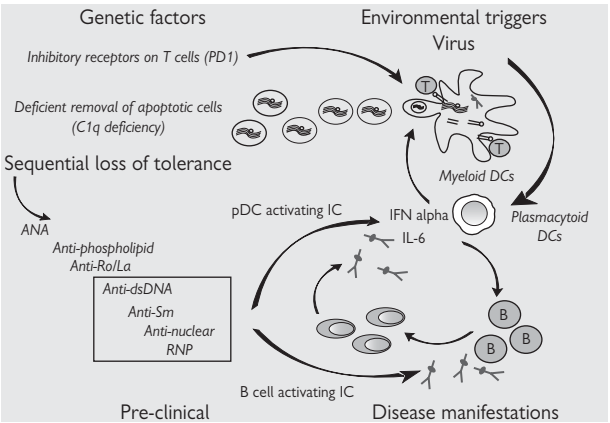

Fig. 4.9 Roles played by both genetic and environmental factors in the development of paediatric SLE. Genetic alterations may contribute to a progressive loss of tolerance to nuclear antigens, which has been shown to precede the development of clinical disease. IFNα will also activate monocytes and other myeloid DC precursors to become immunogenic DCs able to activate T and B cells. Viruses and other environmental triggers can activate DCs to secrete IFNα which amplifies these loops and precipitates the development of clinical disease. Adapted from Stichweh D, Arce E, Pascual V. Update on pediatric systemic lupus erythematosus. *Curr Opin Rheumatol* 2004; **16**:577–87.

Further reading

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JSLE: clinical features and diagnostic criteria

Clinical presentation of JSLE

- The clinical manifestations of JSLE are extremely variable. They range from mild illness characterized by rash, fatigue, and joint pains to life-threatening organ involvement (Box 4.5)
- Symptoms may be incorrectly attributed to problems such as 'being a teenager', exam stress, anorexia nervosa, or chronic fatigue syndrome. Diagnosis may be complicated by the evolution of disease over time.

Box 4.5 Presenting features of JSLE

• Constitutional (fever, malaise, weight loss):	40–74%
• Joint pains/arthritis:	20–74%
• Enlarged liver ± spleen:	15–74%
• Renal involvement:	20–82%
• Malar rash:	44–52%
• Lymphadenopathy:	15–30%

Multisystem presentation of JSLE

Careful, multisystem assessment must be carried out in all patients in whom JSLE is suspected. Potential clinical features are protean, and include:

- Mucocutaneous—malar rash, vasculitic lesions, photosensitive rashes, nasal/oral ulcers, Raynaud's phenomenon, alopecia, discoid lesions.
- Systemic—fever, lethargy, weight loss, arthralgia.
- Arthritis (non-erosive).
- Renal—proteinuria, glomerulonephritis, hypertension, renal failure.
- GI tract: hepatosplenomegaly, autoimmune hepatitis, pancreatitis, diffuse abdominal pain, serositis, colitis, oesophageal dysmotility.
- Cardiopulmonary—pericarditis, myocarditis, pleuritis, interstitial lung disease, pulmonary haemorrhage.
- Neuropsychiatric—headache, migraine, seizures, depression, cognitive impairment, stroke, chorea, cranial and peripheral neuropathies.
- Haematological—anaemia, Coombs positivity, thrombocytopenia, leucopenia.
- Other—lymphadenopathy, ocular (e.g. uveitis, episcleritis, optic neuritis, retinopathy), antiphospholipid antibodies.

Diagnosis of JSLE

- The diagnosis of JSLE is based on a collection of clinical and laboratory features. The American College of Rheumatology (ACR) revised criteria for classification of SLE (Table 4.6) are frequently used for diagnosis and have been shown to be valid in JSLE:
  - The criteria were introduced for the purpose of clinical trials.
  - A person can be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval.
  - The presence of 4 out of 11 gives 96% sensitivity and specificity for (adult-onset) SLE.

Table 4.6 The ACR revised criteria for classification of SLE

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over malar eminences, tending to spare nasolabial folds
Discoid lupus	Erythematous raised patches of adherent keratotic scaling and follicular plugging. Atrophic scarring may be seen in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight
Oral or nasal ulceration	Oral or nasopharyngeal ulcers, usually painless, observed by a physician
Non-erosive arthritis	Non-erosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis—pleuritic pain, rub heard or pleural effusion, or Pericarditis—documented by ECG or rub or pericardial effusion
Nephritis	Persistent proteinuria >0.5g/day or >3+, or: Cellular casts: red cell, haemoglobin, granular, tubular or mixed
Neurological	Seizures in the absence of offending drugs or metabolic derangement (e.g. uraemia, ketoacidosis, electrolyte imbalance), or Psychosis in the absence of offending drugs or metabolic derangement (e.g. uraemia, ketoacidosis, electrolyte imbalance)
Haematological	Haemolytic anaemia with reticulocytes, or Leucopenia <4000 per mm^3 on 2 or more occasions, or Lymphopenia <1500 per mm^3 on 2 or more occasions, or Thrombocytopenia <100,000 per mm^3 in absence of offending drugs
Immunological	Anti-DNA antibody, or Anti-Sm antibody, or Anti-phospholipid antibodies: (i) Abnormal anticardiolipin antibody IgG or IgM (ii) Positive lupus anticoagulant (iii) False positive for syphilis for >6 months
Anti-nuclear antibody	Abnormal titre of ANA at any point in absence of drugs known to be associated with drug-induced lupus

  - The criteria alone are not a pre-requisite for diagnosis or commencing treatment in patients where there is a high index of suspicion of JSLE. Many individuals with 1 or 2 features will develop others later on and may eventually fulfil the criteria.
- The ability to diagnose JSLE correctly may be challenging especially in those with an insidious onset of symptoms that are common in childhood such as joint pains and tiredness.
- Early referral to a clinician with experience and expertise of JSLE is important to allow prompt and correct diagnosis and the timely commencement of appropriate therapy to prevent long-term damage.
- The most common ACR criteria found in children are ANA positivity, arthritis, immunological disorder, haematological disorder, malar rash, and photosensitivity although many children present with or develop renal or neurological disease, even if not strictly meeting the ACR definitions outlined here.

Further reading

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Assessment of the child with JSLE and monitoring of disease activity

Assessing disease severity and monitoring outcome

Optimizing disease control depends on assessing disease activity. The complexity and variability of paediatric lupus makes this difficult. There is no single 'gold standard' biological marker that accurately reflects this. In the assessment of the child with JSLE it is important to determine the following aspects of their disease across all organ systems:

- Disease activity—potentially reversible with correct therapy.
- Organ damage—reversible or irreversible.
- Effect of lupus on the patient's quality of life (QoL).
- Concurrent pathology, e.g. infection, drug side effects, disease complications, concomitant conditions.

Clinical approach to assessment

Careful multisystem assessment must be carried out at each clinical visit:

- ***History***—detailed multi-system symptom enquiry including effect of disease on social and psychological functioning. Enquire about fatigue.
- ***Examination***—cardiovascular including BP, respiratory, abdominal, mucocutaneous, musculoskeletal and neurological. Growth, pubertal staging and development.
- Disease activity score assessment: see Box 4.6.
- SLICC/ACR damage index (annually): see Box 4.6.

Box 4.6 JSLE assessment tools

There are several assessment tools available which can be used serially in the clinical setting or in clinical studies/trials to assess response and outcome and allow comparison of therapies.

Lupus Disease Activity Measures

- BILAG (British Isles Lupus Assessment Group)
- SLEDAI (SLE Disease Activity Index)
- SLAM (Systemic Lupus Activity Measure)
- ECLAM (European Community Lupus Activity Measure).

Most widely used are the BILAG and SLEDAI.

Assessment of damage

- The SLICC/ACR damage index (Systemic Lupus International Cooperating Clinics/American College of Rheumatology).

Function and QoL

- Neither the SLEDAI, BILAG nor SLICC/ACR measure health-related QoL, degree of disability, or impact of disease.
- The Childhood Health Questionnaire (CHQ) and SF36 can be useful in assessing general health and well-being. Specific JSLE-related QoL tools are also being developed.
- The CHAQ (Childhood Health Assessment Questionnaire) measures function and includes a visual analogue scale (VAS) for pain and general evaluation of disease.

Investigations

Routinely at each review, e.g. 3-monthly or more frequently if unwell

- *FBC*—↓Hb (anaemia of chronic disease or autoimmune anaemia), ↓WCC (↑ suggests infection or 2° to stress response/corticosteroids), ↓lymphocytes (due to disease or immunosuppression), ↓platelets.
- ***NB:*** consider macrophage activation syndrome (see 📖 MAS, p 305) if increasing pancytopenia in sick patient.
- ↑ *ESR* (if sudden drop in ESR in sick patient, consider MAS).
- *Urinalysis*—protein or blood in renal involvement. If protein present need quantitative measure such as spot urinary albumin creatinine ratio (UACR) or protein creatinine ratio (UPCR).
- *Urine MC&S*—presence of casts, WCC, RBC, organisms.
- *U&Es, LFTs, bone profile, and glucose* (consider amylase and lipase in presence of abdominal pain).
- *CRP*—if ↑ consider infection. Other causes of raised CRP in the context of SLE include serositis and polyarthritis.
- *Complement*—↓C3 and C4, levels correlate with disease activity.
- *Immunoglobulins*—↑ in acute inflammation.
- *ds-DNA*—possible direct pathogenic role and titres are measure of disease activity. Serial measurements of anti-C1q also marker of disease activity particularly renal disease but test not widely available.

At initial assessment then annually

(*Denotes investigations to perform more frequently in sick patients.)

- *Clotting screen** (prolonged in APLS and MAS), *fibrinogen** (↑in acute inflammation, ↓ in MAS).
- *DAT**—positive in autoimmune haemolytic anaemia.
- *Lupus anticoagulant and anticardiolipin IgG and IgM*—2° APLS.
- *TFTs** *and thyroid antibodies.*
- *Lipid profile** (dyslipidaemia ↑ risk of cardiovascular events; ↑ TGs in MAS).
- *Vitamin D levels.*
- *ANA* (positive in 95% of SLE), *dsDNA* (positive in 60%), *ENAs*—most common include anti-Ro, anti-La associated with neonatal lupus syndromes, anti-Sm (anti-'Smith', not 'smooth muscle' as often erroneously assumed) associated with renal involvement.
- *Immunity status*—e.g. measles and varicella IgG.

Further systems investigation should be undertaken at baseline and when appropriate for select individuals with any disease flare or annual monitoring of progress

- Renal biopsy.
- ECG, echocardiogram, visceral angiogram, MRA.
- CXR, pulmonary function tests including transfer factor, CT chest.
- Renal USS, renal biopsy, measurement of GFR.
- MRI brain, MRA brain, EEG, psychometric testing.
- Abdominal USS, upper and lower GI endoscopy.
- Bone mineral density scan (DEXA) for those at risk from osteoporosis.
- Skin biopsy.
- Ophthalmology assessment.
- Infection screen e.g. viral serology, urine MC&S, blood cultures, lumbar puncture, stool MC&S, and virology.

Further reading

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JSLE: approach to management

(Also see 🕮 Lupus nephritis, p 236.)

General principles

- Management of JSLE requires full MDT engagement by professionals experienced in paediatric rheumatology including prompt liaison with other specialists as dictated by disease manifestations.
- As the survival rates for JSLE improve the late complications of both disease and therapy should be recognized and addressed, such as premature atherosclerosis (Box 4.7), osteoporosis, neurocognitive impairment, and potentially ↑ risk of malignancy.
- ***Early and aggressive therapy*** is key for treatment of JSLE to improve outcome and function and reduce organ damage.
- Management should be individualized taking into account patient preference, tolerance of drugs, and disease presentation. Care should be taken to explore the burden of disease and treatment on QoL, education, physical and emotional development. This should improve patient care and adherence.

Box 4.7 Premature atherosclerosis

- Leads to marked morbidity in young adults—risk to women with SLE of myocardial infarction (MI) or stroke 6–9× that of healthy controls and MI rate of 8% observed in 24–43yr-olds who developed SLE in childhood.
- Risk factors—obesity, smoking, insulin resistance, ↑BP, renal disease, dyslipidaemia, inflammation, APLS, vascular disease. Other as yet undefined non-conventional cardiovascular risk factors arising from SLE and its treatment are areas of ongoing study.
- Prevention in JSLE needs to begin in childhood—importance of modifying risk factors, and potential use of statins in JSLE (NB ongoing trial of atorvastatin in JSLE: The APPLE trial).

Evidence base for management of JSLE

- Paucity of robust epidemiological, clinical cohort studies, and clinical trial data in JSLE hamper evidence-based management of JSLE. To date, no large randomized comparative trials have been published in JSLE, so treatment regimens are based primarily on observational cohort studies and adult data (Box 4.8).
- International organizations (e.g. PRINTO, CARRA) and national, collaborative research groups such as the UK JSLE Study Group seek to improve the evidence base.
- Multinational collaborative paediatric research is essential to define the efficacy and safety of therapies to improve care for JSLE patients.
- Important data from adult studies can help, which may have larger cohorts including patients developing SLE in childhood; however, determining the efficacy and safety within a paediatric population of new and existing therapies is critical.

Box 4.8 UK JSLE Cohort Study & Repository

Established by the UK JSLE Study Group (🔗 http://www.liv.ac.uk/ukjsle/index.htm), the study consists of a comprehensive, prospective clinical data set from patients with JSLE from across the UK. The aims of the UK JSLE Cohort Study & Repository include:

- To determine the demographics of JSLE across the UK and to investigate the clinical characteristics of disease presentation, activity, damage, and response to therapy for a national cohort of JSLE patients.
- To undertake comparative studies with other national lupus cohorts.
- Develop a cohort of patients suitable for recruitment to clinical interventional trials in JSLE.
- Facilitate international collaborative studies and trials in JSLE.

General management of JSLE

- UV light—advise sun avoidance and prescribe sun block factor 50–60 to reduce flares and photosensitive rashes.
- Vaccination—↑ risk of infection in JSLE due to drug therapies and JSLE-associated immune dysfunction. All routine immunizations advised plus pneumococcal and influenza. NB Live vaccines contraindicated if on significant immunosuppression.
- Bone health—ensure adequate dietary intake of calcium and vitamin D. Discourage inactivity. Assess bone density regularly and treat osteoporosis if present.

Corticosteroids in JSLE

- Corticosteroids are needed initially in all but very mild cases to provide rapid control of inflammation but are associated with numerous side effects (osteoporosis, growth retardation, obesity, Cushingoid facies, cataracts, impaired glucose tolerance) and are a risk factor for damage.
- Steroid-sparing immunosuppressive therapy is started early for prompt induction of remission and to allow rapid tapering of steroids as clinical response dictates, with the aim to minimize steroid toxicity.
- Prednisolone used as oral therapy (1–2mg/kg initially then tapered). In control of acute flares and at induction high-dose pulsed IVMP may be required (e.g. 30mg/kg on 3 consecutive days) and repeated as according to response, followed by tapering oral steroids. Weekly pulsed IVMP (e.g. 30mg/kg/day for 4–6 weeks), followed by tapering of oral steroids may also be needed. Oral prednisolone may not be absorbed in gut involvement.

Disease-modifying drugs in JSLE (see 🕮 JSLE: renal involvement, p 236 and 🕮 BSPAR guidelines for treatments used in paediatric rheumatology, p 415)

Choice of DMARDs in JSLE varies with clinician as evidence of superiority is lacking. Multiple DMARDs may be required in refractory disease.

Hydroxychloroquine (HCQ) e.g. 5–6.5mg/kg/day once a day can be given (maximum 400mg)

- Advised in all patients unless contraindicated. Adult studies indicate disease-modifying role and lipid-lowering effect; particularly useful for skin and joint disease; some patients can be managed with HCQ and low-dose corticosteroids only.

Azathioprine (AZA) (e.g. start at 1mg/kg/day, ↑ in increments up to a maximum of 3mg/kg/day)

- Traditionally the 1st-line steroid-sparing DMARD in moderate disease. Side effects uncommon but include nausea, fatigue, hair loss, and bone marrow suppression. Increasingly, many clinicians using MMF before AZA due to anecdotal evidence of ↑ efficacy and tolerability of MMF, and emerging evidence from clinical trials (ALMS trial for both renal and non-renal SLE) in adults (see 🕮 Lupus nephritis, p 236).

Mycophenolate mofetil (MMF): (e.g. 10–20mg/kg/day per dose twice daily; or 600mg/m^2 per dose twice daily)

- Increasingly used as induction and/or maintenance of remission therapy in all but mild disease. Studies in adults with lupus nephritis indicate it to be as effective but less toxic than cyclophosphamide. Published data from the JSLE population is limited, although it offers a significant therapeutic opportunity. It is steroid-sparing, improves renal function, and reduces disease activity in JSLE. Relatively well-tolerated, main side effect is GI upset which can be minimized by slow introduction.

Cyclophosphamide (CPM) (e.g. monthly pulsed IV CPM of 500–1000mg/m^2 [maximum dose 1.2 g] for 3–6 months)

- 'Gold standard' until recently as induction agent for major organ involvement or life-threatening lupus together with pulsed IVMP. Marked side effect profile including bone marrow suppression, gonadal suppression, hair loss, and haemorrhagic cystitis. IV CPM considered superior to oral CPM. More recently, an alternative approach using lower cumulative doses of IV CPM (300–500mg/m^2, maximum dose 500mg, given every 2 weeks for 6 doses), the so-called 'Eurolupus protocol' have been proposed for induction of remission of JSLE.

Biologic therapies in JSLE

- The advent of biological therapies offers a major therapeutic advance in the management of JSLE. To date, rituximab, a B-cell depletor has demonstrated evidence of efficacy in JSLE. Randomized controlled studies are summarized in the separate section on B cell depletion therapy in SLE (🕮 p 241), and are given under expert advice only.

Anti-phospholipid syndrome

- If positive anticardiolipin Ab or lupus anticoagulant on 2 occasions 3 months apart commence *low-dose aspirin* to prevent thrombotic events.

Other therapies used in refractory JSLE

- Methotrexate (skin and joint disease), ciclosporin (lupus nephritis, particularly for membranous nephritis, Class V), infliximab, IVIg.

Treatment of severe refractory lupus

- ***Plasma-exchange***—anecdotal evidence of efficacy in severe refractory lupus.
- ***Haematopoietic stem cell transplantation(autologous and allogeneic stem cell transplant, see 📖 Haematopoietic stem cell transplantation, p 405)***—successfully used in severe refractory disease. Associated with significant mortality rate so only considered in those with severe disease who have failed conventional therapies.

Further reading

von Scheven E, Bakkaloglu A. What's new in paediatric SLE? *Best Pract Res* 2009; **23**:699–708.

JSLE: renal involvement

Introduction

- Renal disease is a major determinant of the long-term outcome of SLE:
  - Present in 60–80% of JSLE cases.
  - Influences management with immunosuppressive agents.
  - Earlier and more severe presentation in patients with JSLE (compared to adult-onset) SLE.
- Presentation of renal involvement:
  - Proteinuria.
  - Microscopic (and rarely macroscopic) haematuria.
  - Nephrotic syndrome.
  - Hypertension.
  - Evidence of renal dysfunction—elevated plasma creatinine or reduced estimated GFR.
- Histopathology of renal involvement with lupus nephritis (LN) cannot be accurately predicted from clinical and serological markers:
  - Renal biopsy is undertaken if deteriorating renal function, significant proteinuria, haematuria or hypertension, or to delineate thrombotic microangiopathy.

Investigations

All JSLE patients should be monitored at least every 3 months for evidence of LN:

- BP measurement.
- Early morning urinary dipstick test.
- Early morning urine albumin:creatinine ratio.
- Consideration of 24h urine collection in adolescent children.
- Markers of renal function (plasma creatinine, estimated GFR, and serum albumin).
- Routine lupus immunological tests.

Histopathology

Classification of LN facilitates clinical management (in guiding treatment and conducting RCTs of therapeutic agents) as well as communication between pathologists and scientists. It standardizes definitions with uniform and reproducible reporting between centres.

The original World Health Organization classification of LN was developed in 1974–1975, and modified in 1982 and 1995 with the current histopathological classification reported by the International Society of Nephrology/Renal Pathology Society working group in 2003 (Fig. 4.10):

- ISN/RPS Class I LN = minimal mesangial LN.
- ISN/RPS Class II LN = mesangial proliferative LN.
- ISN/RPS Class III LN = focal lupus nephritis, subdivided into:
  - III (A) active focal proliferative LN.
  - III (A/C) active and sclerotic focal proliferative LN.
  - III (C) inactive sclerotic focal lupus nephritis.
- ISN/RPS Class IV LN = diffuse segmental (IV-S) or global (IV-G):
  - See Figs. 4.11 and 4.12.
  - IV (A) active diffuse segmental or global proliferative LN.

  - IV (A/C) diffuse segmental or global proliferative and sclerotic.
  - IV (C) diffuse segmental or global sclerotic lupus nephritis.
- ISN/RPS Class V LN = diffuse membranous LN:
  - Class III and Class V changes are reported as Class III + V.
  - Class IV and Class V changes are reported as Class IV + V.
- ISN/RPS Class VI LN = advanced sclerotic LN.
- This classification has been validated in JSLE.

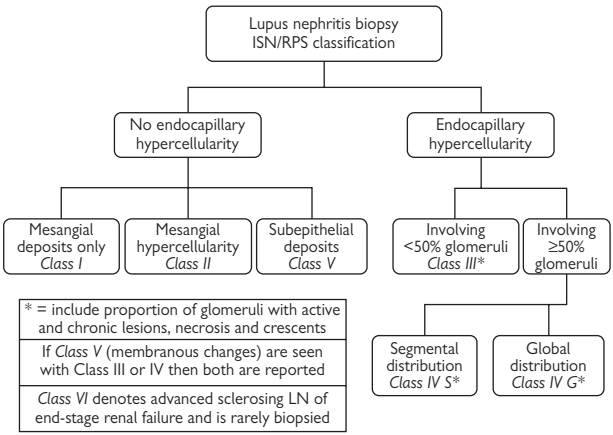

Fig. 4.10 Summary of International Society of Nephrology/Renal Pathology Society classification of lupus nephritis.

Treatment

- The aim of treatment is to induce remission while minimizing side effects (including infectious complications) and flares of disease activity in order to improve patient morbidity and mortality.
- Once induction of remission to gain control of disease activity is achieved then maintenance therapy is utilized to maintain disease control and minimize therapy related toxicity, including corticosteroid exposure.
- However, due to the increasing use of MMF instead of IV CYC for induction of remission, many clinicians are utilizing MMF for both induction and maintenance phases.
- ***ISN Class I and II LN:***
  - The same therapy is employed for those with mild to moderate SLE without LN and may include azathioprine therapy (see 📖 JSLE: non-renal involvement, p 236).
- ***ISN Class III, IV and V LN:***
  - MMF as 1st-line treatment is a safe and efficacious therapy for SLE and LN but can cause more diarrhoea despite less overall side effects than CYC.

- IV CYC may be reserved for patients with severe multisystem disease activity or with poor adherence to oral therapy but is associated with more nausea and vomiting.
- The Aspreva Lupus Management Study (ALMS) showed no difference in response rate in adults with ISN/RPS Class III, IV and V who were randomized to MMF or iv CYC in a 24-week induction study:
  - 56% and 53% responded to MMF and IV CYC respectively.
  - No significant differences in rates of adverse events, including infections.
- Plasmapheresis should be considered for children with rapidly progressive crescentic glomerulonephritis (as well as cerebral vasculitis or pulmonary haemorrhage).
- B cell depletion with IV rituximab has been shown to be useful for JSLE patients with severe renal and non-renal disease activity as well as refractory disease, although its use is not yet supported with RCT data (see 📖 B-cell depletion therapy).

- ***ISN Class VI***
  - The current classification of advanced sclerotic LN implies end-stage renal failure (CKD5) management with renal replacement therapy, although immunosuppressive therapies may be utilized to treat or avoid further non-renal flares of disease activity.
- Maintenance therapy of LN:
  - Oral prednisolone 10–15mg alternate days (where possible; some prefer lower doses of daily prednisolone and there are no hard data to suggest which is superior).
  - Oral hydroxychloroquine 4–6mg/kg/day (maximum dose 400mg/day).
  - Oral AZA 2–3mg/kg once daily, or
  - Oral MMF 300–600mg/m^2/dose twice daily (usual maximum dose of 2g/day although occasionally 3g/day has been used).

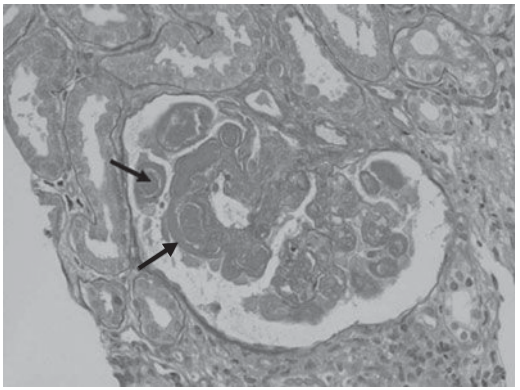

Fig. 4.11 (See also Colour plate 2.) ISN/RPS Class IV LN (PAS stain, original magnification ×250). Wire loop (denoted by lower arrow) and hyaline droplet (upper arrow) change representing massive subendothelial deposits when seen on light microscopy.

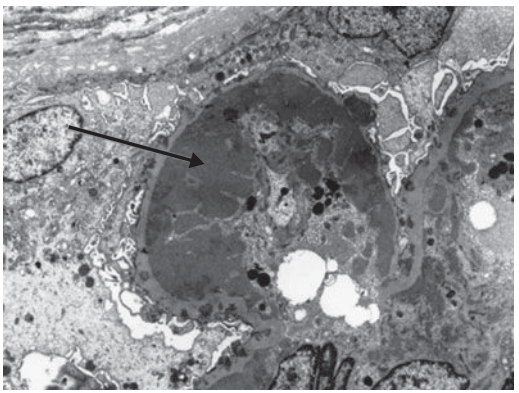

Fig. 4.12 ISN/RPS Class IV LN (electron microscopy). Massive subendothelial deposit corresponding to a wire-loop lesion (see arrow).

Further reading

Appel G, Contreras G, Dooley MA, *et al.* Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009; **20**:1103–12.

Weening JJ, D'Agati VD, Schwartz MM, *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004; **65**:521–30.

Neonatal lupus syndrome

- Autoimmune disease associated with transplacental passage of maternal auto-antibodies (autoAbs) to SSA/Ro and SSB/La antigens.
- Risk of an infant developing NLS in positive mother is 2% (risk to subsequent pregnancy is 25%).

Clinical features

- ***Skin***—subacute cutaneous lupus-like lesions, telangiectasia.
- ***Cardiac***—congenital heart block, cardiomyopathy, prolonged QT interval, sinus bradycardia, cardiac malformations.
- ***Hepatobiliary***—elevation in transaminases, cholestasis, fulminant liver failure.
- ***Haematological***—thrombocytopenia and less commonly other cytopenias.

Investigation

- Diagnosis is made by identifying relevant clinical features with positive NLS-associated antibodies in maternal or neonatal serum.
- Skin biopsy may be useful if diagnosis unclear.

Management

- Careful *in utero* and postnatal monitoring of at-risk pregnancies is important to ensure appropriate treatment (serial fetal echo; postnatal ECG).
- Use of maternal fluorinated corticosteroids (dexamethasone or beclamethasone) which cross the placenta may prevent progression of incomplete heart block.
- Infants with cardiac disease may need cardiac pacing.
- Skin lesions can be treated with sun avoidance, sun block, and topical corticosteroids.

Prognosis

- Skin, hepatic and haematological manifestations tend to resolve spontaneously as maternal autoantibodies disappear from the infant's circulation; complete heart block and cardiomyopathy can be life threatening.
- Affected infants may be at ↑risk of subsequent autoimmune disease.

Further reading

Lee LA. The clinical spectrum of neonatal lupus. *Arch Dermatol Res* 2009; **301**:107–10.
Pain C, Beresford MW. Neonatal lupus syndrome. *Paediatr Child Health* 2007; **17**:223–7.

B-cell-targeted therapies for systemic lupus erythematosus

Why target B cells in SLE?

- A minority of patients with SLE will not have a sufficient clinical response to the present standard treatment with MMF, IV CYC, AZA, 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 4.7.
- The vast majority of the paediatric SLE experience to date is only with rituximab, with little or no data on the role of other agents in paediatric patients. Rituximab should only be used in conjunction with expert advice and in children with SLE resistant to standard therapy; in rare circumstances, rituximab may be considered for 1° induction of remission and there is ongoing controversy as to whether rituximab should be given with IV CYC for 'synergistic' B-cell depletion or not, and what immunosuppression to follow rituximab therapy with.

Clinical trials of B-cell-targeted therapies in adults with SLE

- Very recently, several important prospective RCTs of B cell-targeted therapy have been reported in adults (summarized in Table 4.8), 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 IV CYC 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.
  - Overly optimistic 1° 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 4.7 Different types of B cell-targeted therapy

Drug name	B cell target	Proposed mechanism of efficacy
Rituximab (see 📖 p 441 guidelines)	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 ↓ 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 ↓ 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 ↑ in SLE and correlate with disease activity-blocking BAFF therefore reduces pathological B-cell survival and differentiation
Epratuzumab	Fully human monoclonal antibody against CD 22, a B-cell surface antigen involved in the regulation of signalling	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 reduces autoantibodies but also reduces immunoglobin—very high rate of infections reported in early trials

Table 4.8 Summary of recent 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 1 of AZA, MMF, or MTX. Patients were randomized 2:1 to receive RTX or placebo. Moderate and severe LN or CNS lupus excluded	Pre-defined improvement in BILAG score	No differences between placebo and RTX groups in the 1° 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 pre-defined renal response at 52 weeks: either CRR, PRR, or NR	No difference in 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
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 ↑ 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

(*continued*)

Table 4.8 (*Contd.*)

Trial name	Description	Design	Primary end point	Result	Adverse events
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 ↑ 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

AZA: azathioprine; BILAG: British Isles Lupus Assessment Group score; CNS: central nervous system; CRR: complete renal response; LN: lupus nephritis; MTX: methotrexate; PRED: prednisone; PRR: partial renal response; MMF: mycophenolate mofetil; NR: non-response; RCT: randomized controlled trial; RTX: rituximab; SRI: SLE-response index.

The use of rituximab in paediatric SLE

- Given the negative recent trial data for rituximab, 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 1° 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 IV CYC 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 IV CYC 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 cyclophosphamide (see above), except where cumulative cyclophosphamide toxicity, side effects, or other clinical contraindication preclude this. A suggested protocol is given (also see Guidelines 📖 Chapter, p 441):

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: 30mg, 20mg and 10mg (i.e. days 2, 3, & 4 & days 16, 17, & 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 📖 p 427).

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 ↑ by increments of 25mg/h every 30min up to a maximum of 200mg/h as tolerated.

Rituximab: side effects

- Serum sickness: fevers and rigors, which usually present within the first 2h. Other reported symptoms include pruritis and rashes, dyspnoea, bronchospasm, angio-oedema, 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 leucoencephalopathy caused by JC virus (a polyoma virus).
- Rituximab associated neutropenia—occurring usually several months following the administration of rituximab:
  - Usually not clinically significant and is self-limited but should be differentiated with neutropenia 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:UC (minimum of fortnightly FBC for 6 weeks then monthly).
- ANA, doubled-stranded DNA, C3, C4.
- Screen for B-cell response and hypoagammaglobulinaemia (see Table 4.9). The use of replacement immunoglobulin 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.

Immune monitoring (Table 4.9) is recommended.

Table 4.9 Monitoring rituximab treatment in patients with SLE

Test	Timing (after 1st dose)	Notes
Lymphocyte subsets	• Days 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	• Days 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.

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.

Further reading

Looney RJ. B-cell targeted therapies for systemic lupus erythematosus. *Drugs* 2010; **70**:529–40.
Podolskaya A, Stadermann M, Pilkington C, *et al.* B cell depletion therapy for 19 patients with refractory systemic lupus erythematosus. *Arch Dis Child* 2008; **93**:401–6.

British Isles Lupus Assessment Group (BILAG) 2004 Index

The BILAG Index is a measure of disease activity developed initially for adult-onset SLE using nominal consensus approach and modified several times to improve its validity and reliability (Table 4.10). The BILAG 2004 validation is ongoing. Across 9 domains, clinicians indicate whether each parameter is:

- Not present, 0
- Improving, 1
- Same, 2
- Worse, 3 or
- New, 4.

Scoring refers to manifestations present in the last 4 weeks compared to the previous 4 weeks and to features attributable to SLE disease activity and not due to damage, drugs, or infection.

(NB For detailed descriptions of definitions of manifestations see BILAG 2004 glossary.)

The BILAG rests on the principle of the physicians' intent-to-treat in assigning scores A–E:

- A = Disease necessitating high-dose oral/IV steroids, DMARDs, or biologics.
- B = Low-dose corticosteroids (equivalent to ≤20mg/day prednisolone) and/or HCQ.
- C = Stable mild disease.
- D = Prior involvement of the organ system, no current disease activity.
- E = Organ system never involved.

Several conversion systems have been proposed to translate BILAG A–E ratings into a BILAG disease activity summary score. Newly revised scoring for BILAG 2004 is as follows: A = 12; B = 8; C = 1; D = 0; E = 0.

Use of BILAG in JSLE

The original adult-derived 'Classic' BILAG index has been used in JSLE and shown to be sensitive to change in disease activity. However, it was recognized that adaptation of certain parameters of the original BILAG needed to take place for use in children (e.g. age-adjusted BP). In addition, potential scoring problems were noted due to the differences between paediatric and adult management practices (e.g. timing of renal biopsy). Validation of the revised BILAG 2004 in a JSLE cohort is currently underway but it is summarized here in view of its increasing use in clinical trials of adult-onset SLE.

Further reading

Yee CS, Farewell VT, Isenberg DA *et al.* Numerical scoring for the BILAG 2004 Index. *Rheumatology* 2010; **49**(9):1665–9.

Table 4.10 British Isles Lupus Assessment Group (BILAG) 2004 Index

Domain	Manifestations*		Assessment
Constitutional	1. Pyrexia (documented >37.5°C) 2. Weight loss-unintentional >5% 3. Lymphadenopathy/splenomegaly 4. Anorexia	A	Pyrexia recorded as 2 (same), 3 (worse), or 4 (new) **and** ≥2 recorded as 2–4: weight loss, lymphadenopathy/splenomegaly, anorexia
		B	Pyrexia recorded as 2, 3, or 4 **or** ≥2 recorded as 2–4: weight loss, lymphadenopathy/splenomegaly, anorexia **but** do not fulfil criteria for category A
		C	Pyrexia recorded as 1 (improving) **or** ≥1 recorded as 2 (same), 3 (worse) or 4 (new): weight loss, lymphadenopathy/splenomegaly, anorexia **BUT** does not fulfil criteria for category A or B
		D	Previous involvement
		E	No previous involvement
Mucocutaneous	1. Skin eruption—severe 2. Skin eruption—mild 3. Angio-oedema—severe 4. Angio-oedema—mild 5. Mucosal ulceration—severe 6. Mucosal ulceration—mild 7. Panniculitis/bullous lupus—severe 8. Panniculitis/bullous lupus—mild 9. Major cutaneous vasculitis/thrombosis 10. Digital infarcts or nodular vasculitis 11. Alopecia—severe 12. Alopecia—mild 13. Peri-ungual erythema/chilblains 14. Splinter haemorrhages	A	Any of the following recorded as 2 (same), 3 (worse), or 4 (new): Skin eruption—severe Angio-oedema—severe Mucosal ulceration—severe Panniculitis/bullous lupus—severe Major cutaneous vasculitis/thrombosis
		B	Any category A features recorded as 1 (improving) **or** any of following recorded as 2 (same), 3 (worse), or 4 (new): Skin eruption—mild Panniculitis/Bullous lupus—mild Digital infarcts or nodular vasculitis Alopecia—severe
		C	Any category B features recorded as 1 (improving) **or** any of the following recorded as ≥1: Angio-oedema—mild Mucosal ulceration—mild

(*continued*)

Table 4.10 (*Contd.*)

Domain	Manifestations*		Assessment
			Alopecia—mild Periungual erythema/chilblains Splinter haemorrhages
		D	Previous involvement
		E	No previous involvement
Cardiorespiratory	1. Myocarditis—mild 2. Myocarditis/endocarditis + cardiac failure 3. Arrhythmia 4. New valvular dysfunction 5. Pleurisy/pericarditis 6. Cardiac tamponade 7. Pleural effusion with dyspnoea 8. Pulmonary haemorrhage/vasculitis 9. Interstitial alveolitis/pneumonitis 10. Shrinking lung syndrome 11. Aortitis 12. Coronary vasculitis	A	Any of the following recorded as 2 (same), 3 (worse), or 4 (new): Myocarditis/endocarditis + cardiac failure Arrhythmia New valvular dysfunction Cardiac tamponade Pleural effusion with dyspnoea Pulmonary haemorrhage/vasculitis Interstitial alveolitis/pneumonitis Shrinking lung syndrome Aortitis Coronary vasculitis
		B	Any category A features recorded as 1 (improving) **or** pleurisy/pericarditis or mild myocarditis recorded as 2, 3, or 4
		C	Any category B features recorded as 1 (improving)
		D	Previous involvement
		E	No previous involvement

Neuropsychiatric	1. Aseptic meningitis 2. Cerebral vasculitis 3. Demyelinating syndrome 4. Myelopathy 5. Acute confusional state 6. Psychosis 7. Acute inflammatory demyelinating polyradiculoneuropathy 8. Mononeuropathy (single/multiplex) 9. Cranial neuropathy 10. Plexopathy 11. Polyneuropathy 12. Seizure disorder 13. Status epilepticus 14. Cerebrovascular disease (not due to vasculitis) 15. Cognitive dysfunction 16. Movement disorder 17. Autonomic disorder 18. Cerebellar ataxia (isolated) 19. Lupus headache—severe unremitting 20. Headache from intracranial ↑BP	A Any of manifestations numbered 1–11 or status epilepticus or cerebellar ataxia recorded as 2 (same), 3 (worse), or 4 (new) B Any category A features recorded as 1 (improving) **or** any of the following recorded as 2 (same), 3 (worse), or 4 (new): Seizure disorder Cerebrovascular disease (not due to vasculitis) Cognitive dysfunction Movement disorder Autonomic disorder Lupus headache—severe unremitting Headache due to raised intracranial hypertension C Any category B features recorded as 1 (improving) D Previous involvement E No previous involvement

(*continued*)

Table 4.10 (*Contd.*)

Domain	Manifestations*		Assessment
Musculoskeletal	1. Myositis—severe 2. Myositis—mild 3. Arthritis—severe 4. Arthritis(moderate)/tenosynovitis 5. Arthritis (mild)/arthralgia/myalgia	A	Severe myositis or severe arthritis recorded as 2 (same), 3 (worse), or 4 (new)
		B	Any category A features recorded as 1 (improving) **or** mild myositis or moderate arthritis/tendonitis/tenosynovitis recorded as 2–4.
		C	Any category B features recorded as 1 (improving) **or** mild arthritis/arthralgia/myalgia scored as ≥1
		D	Previous involvement
		E	No previous involvement
Gastrointestinal	1. Lupus peritonitis 2. Abdominal serositis or ascites 3. Lupus enteritis/colitis 4. Malabsorption 5. Protein losing enteropathy 6. Intestinal pseudo-obstruction 7. Lupus hepatitis 8. Acute lupus cholecystitis 9. Acute lupus pancreatitis	A	Any of the following recorded as 2 (same), 3 (worse), or 4 (new): Peritonitis Lupus enteritis/colitis Intestinal pseudo-obstruction Acute lupus cholecystitis Acute lupus pancreatitis
		B	Any category A feature recorded as 1 (improving) **or** abdominal serositis and/or ascites, malabsorption, protein losing enteropathy, lupus hepatitis recorded as 2 (same), 3 (worse) or 4 (new)
		C	Any category B features recorded as 1 (improving)
		D	Previous involvement
		E	No previous involvement

Ophthalmic *(Usually scored by ophthalmologist)*	1. Orbital inflammation/myositis/proptosis 2. Keratitis—severe 3. Keratitis—mild 4. Anterior uveitis 5. Posterior uveitis/retinal vasculitis—severe 6. Post. uveitis/retinal vasculitis—mild 7. Episcleritis 8. Scleritis—severe 9. Scleritis—mild 10. Retinal/choroidal vaso-occlusive disease 11. Isolated cotton-wool spots 12. Optic neuritis 13. Anterior ischaemic optic neuropathy	A	Any of the following recorded as 2 (same), 3 (worse), or 4 (new): Orbital inflammation/myositis/proptosis Keratitis—severe Posterior uveitis/retinal vasculitis—severe Scleritis—severe Retinal/choroidal vaso-occlusive disease Optic neuritis Anterior ischaemic optic neuropathy
		B	Any category A features recorded as 1 (improving) **or** any of the following recorded as 2 (same), 3 (worse), or 4 (new): Keratitis—mild Anterior uveitis Posterior uveitis/retinal vasculitis—mild Scleritis—mild
		C	Any category B features recorded as 1 (improving) **or** episcleritis or isolated cotton-wool spots (cytoid bodies) recorded as ≥1
		D	Previous involvement
		E	No previous involvement

(*continued*)

Table 4.10 (*Contd.*)

Domain	Manifestations*		Assessment
Renal	1. Systolic BP (mmHg) 2. Diastolic BP (mmHg) 3. Accelerated hypertension (Y/N) 4. Urine dipstick protein (+=1, ++=2, +++=3) 5. Urine albumin-creatinine ratio (UACR) mg/mmol 6. Urine protein-creatinine ratio (UPCR) mg/mmol 7. 24h urine protein (gram) 8. Nephrotic syndrome (Y/N) 9. Creatinine (plasma/serum) 10. GFR (calculated) 11. Active urinary sediment (Y/N) 12. Active nephritis	A	**Two or more of the following providing 1, 4, or 5 is included:** 1. Deteriorating proteinuria (severe) defined as: (a) Urine dipstick increased by ≥2 levels **or** (b) 24h urine protein >1g that has not decreased (improved) by ≥ 25%; **or** (c) UPCR >100 mg/mmol that has not decreased (improved) by ≥ 25%; **or** (d) UACR >100 mg/mmol that has not decreased (improved) by ≥ 25% 2. Accelerated hypertension 3. Deteriorating renal function (severe) defined as (a) plasma creatinine >130μmol/L and having risen to >130% of previous value; **or** (b) GFR <80mL/min per 1.73m^2 and having fallen to <67% of previous value; **or** (c) GFR <50mL/min per 1.73m^2, and last time was >50mL/min per 1.73 m^2 or was not measured 4. Active urinary sediment 5. Histological evidence of active nephritis within last 3 months 6. Nephrotic syndrome
		B	**One of the following:** 1. One of the category A criteria 2. Proteinuria (that has not fulfilled category A criteria): (a) Urine dipstick which has risen to ≥2+ or (b) 24h urine protein ≥0.5 g that has not decreased (improved) by ≥25%; or (c) UPCR or UACR ≥50 mg/mmol that has not decreased (improved) by ≥25% 3. Plasma creatinine >130μmol/L and having risen to ≥115% but ≤130% of previous value

		C **One of the following:** 1. Mild/stable proteinuria defined as that which has not fulfilled criteria for category A & B 2. Rising BP (>140/90mmHg) which has not fulfilled criteria for category A & B, defined as systolic rise of ≥30 mm Hg; **and** diastolic rise of ≥15mm Hg D Previous involvement E No previous involvement
Haematological	1. Hemoglobin (g/dL) 2. Total WBC ($\times 10^9$/L) 3. Neutrophils ($\times 10^9$/L) 4. Lymphocytes ($\times 10^9$/L) 5. Platelets ($\times 10^9$/L) 6. TTP 7. Evidence of active haemolysis (Y/N) 8. Coombs test positive (Y/N)	A TTP recorded as 2 (same), 3 (worse), or 4 (new) **or** evidence of haemolysis and Hb <8 g/dL **or** platelets <25 × 10^9/L B TTP recorded as 1 (improving) **or** any of the following: 1. Evidence of haemolysis and Hb 8–9.9g/dL 2. Hb <8g/dL (without haemolysis) 3. WCC <1.0 × 10^9/L 4. Neutrophil count <0.5 × 10^9/L 5. Platelet count 25–49 × 10^9/L C Any 1 of the following: 1. Evidence of haemolysis and Hb ≥10g/dL 2. Hb 8–10.9 g/dL (without haemolysis) 3. WCC 1–3.9 × 10^9/L 4. Neutrophil count 0.5–1.9 × 10^9/L 5. Lymphocyte count <1.0 × 10^9/L 6. Platelet count 50–149 × 10^9/L 7. Isolated Coombs' test positive D Previous involvement E No previous involvement

Table adapted from BILAG 2004 Index (Form, Scoring and Glossary available from *Rheumatology* online via Yee CS, Farewell VT, Isenberg DA *et al*. Numerical scoring for the BILAG 2004 Index. *Rheumatology* 2010; **49**(9):1665–9.).

SLEDAI 2000 Disease Activity Index

Table 4.11 SLEDAI 2K—check box: if descriptor is present at time of visit or past 10 days

Weight		Descriptor	Definition
8	☐	Seizure	Recent onset, exclude metabolic, infectious or drug causes
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behaviour. Exclude uraemia and drug causes
8	☐	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or ↑ or ↓ psychomotor activity. Exclude metabolic, infectious, or drug causes
8	☐	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal haemorrhages, serous exudates or haemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes
8	☐	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
8	☐	Lupus headache	Severe, persistent headache, may be migrainous, but must be non-responsive to narcotic analgesia
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram proof of vasculitis
4	☐	Arthritis	≥2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion)

Table 4.11 (*Contd.*)

Weight		Descriptor	Definition
4	☐	Myositis	Proximal muscle aching weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis
4	☐	Urinary casts	Haem-granular or red blood cell casts
4	☐	Hematuria	>5 red blood cells/high power field, Exclude stone, infection or other cause
4	☐	Proteinuria	>0.5g/24h
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection
2	☐	Rash	Inflammatory type rash
2	☐	Alopecia	Abnormal, patchy or diffuse loss of hair
2	☐	Mucosal ulcers	Oral or nasal ulcerations
2	☐	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	☐	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation
2	☐	Low complement	↓ in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	☐	Increased DNA binding	↑ DNA binding by Farr assay above normal range for testing laboratory
1	☐	Fever	>38°C. Exclude infectious cause
1	☐	Thrombocytopenia	<100,000 platelets/× 10^9/L, exclude drug causes
1	☐	Leucopenia	<3000 white blood cells/× 10^9/L, exclude drug causes
	☐	TOTAL SCORE (Sum of weights next to descriptors marked present)	

*Adapted from: Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; **29**(2):288–91.

SLICC/ACR Damage Index (paediatric)

Table 4.12 SLICC/ACR Damage Index (paediatric)*

	SCORE (circle)
Ocular (either eye, by clinic assessment)	
• Any cataract ever	**0 1**
• Retinal change or optic atrophy	**0 1**
Neuropsychiatric	
• Cognitive impairment or major psychosis	**0 1**
• Seizures requiring therapy for 6 months	**0 1**
• Cerebral vascular accident ever (score 2 if >1), or resection not for malignancy	**0 1 2**
• Cranial or peripheral neuropathy (excluding optic)	**0 1**
• Transverse myelitis	**0 1**
Renal	
• Estimated or measured GFR <50%	**0 1**
• Proteinuria 24h, ≥3.5 g or ACR >1000mg/mm or >10mg/mg	**0 1**
• End-stage renal disease (regardless of dialysis or transplantation)	**3**
Pulmonary	
• Pulmonary hypertension (right ventricular prominence, or loud P2)	**0 1**
• Pulmonary fibrosis (physical and x-ray)	**0 1**
• Shrinking lung (x-ray)	**0 1**
• Pleural fibrosis (x-ray)	**0 1**
• Pulmonary infarction (x-ray) or resection not for malignancy	**0 1**
Cardiovascular	
• Angina or coronary artery bypass	**0 1**
• Myocardial infarction ever (score 2 if >1)	**0 1 2**
• Cardiomyopathy (ventricular dysfunction)	**0 1**
• Valvular disease (diastolic murmur, or a systolic murmur >3/6)	**0 1**
• Pericarditis × 6 months or pericardiectomy	**0 1**
Peripheral vascular	
• Claudication × 6 months	**0 1**
• Minor tissue loss (pulp space)	**0 1**
• Significant tissue loss ever (e.g. loss of digit or limb, resection) (Score 2 if >1)	**0 1 2**
• Venous thrombosis with swelling, ulceration, or venous stasis	**0 1**
Gastrointestinal	
• Infarction or resection of bowel (below duodenum), spleen, liver or gall bladder (score 2 if >1)	**0 1 2**
• Mesenteric insufficiency	**0 1**
• Chronic peritonitis	**0 1**
• Stricture or upper GI tract surgery ever	**0 1**
• Pancreatic insufficiency requiring enzyme replacement or with pseudocyst	**0 1**

Table 4.12 (*Contd.*)

	SCORE (circle)
Musculoskeletal	
• Atrophy or weakness	**0 1**
• Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	**0 1**
• Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	**0 1**
• Avascular necrosis (score 2 if >1)	**0 1 2**
• Osteomyelitis	**0 1**
• Ruptured tendons	**0 1**
Skin	
• Alopecia	**0 1**
• Extensive scarring of panniculum other than scalp and pulp space	**0 1**
• Skin ulceration (not due to thrombosis) >6 months	**0 1**
Diabetes (regardless of treatment)	**0 1**
Malignancy (exclude dysplasia) score 2 if >1 site	**0 1 2**
Premature gonadal failure/secondary amenorrhoea	**0 1**
Pubertal stage	**pre post**
Height (cm)	**Weight (kg)**
Bone age (yr)	
• DEXA scan every 2yr	

*Adapted from: Gutierrez-Suarez R, Ruperto N, Gastaldi R *et al*: *Arthritis Rheum* 2006; **54**:2989–96; scored by summation of scores for each item in the 12 domains (maximum of 47).

Scleroderma

The encompassing term scleroderma (literally 'hard skin') is characterized by skin thickening and ↑ collagen and may involve atrophy of subcutaneous fat and/or deeper tissues. Scleroderma has 2 distinct groupings: localized scleroderma (LS) and the much rarer juvenile systemic sclerosis (jSSc)—Table 4.13. Classifications of LS and jSSC are largely clinical and as yet, there is no universal consensus as to their use in clinical practice or clinical trials (Tables 4.14 and 4.15).

Assessment and monitoring

There are currently no validated outcomes of severity or disease activity in LS or jSSc, either of the skin or organ involvement. Current methods of assessment include;

- Clinical examination (skin, joints, muscles, general examination, growth).
  - Need to consider potential multisystem involvement (Table 4.16): check BP, urinalysis, pulmonary function tests/transfer factor, ECHO as baseline and in jSSc, at least annually pending clinical scenario.
- Imaging:
  - Serial photographs and measurement of lesions.
  - Thermography and capillaroscopy.
  - MRI head (especially if facial lesions present).
  - Skin US, Laser Doppler flowmetry (not yet validated).
- Blood tests: autoantibodies (Table 4.15 and see 📖 p 263). Muscle enzymes (📖 muscle disease, p 266).

Table 4.13 Epidemiology and clinical features

	Localized scleroderma (LS)	Juvenile systemic sclerosis (jSSc)
Estimated incidence	3.4 per million	0.27 per million
Survival	Likely normal	Estimated 4yr survival is 95% (cardiac and pulmonary disease)
♀:♂ ratio	Between 1.7:1–2.4:1 (largest cohort 2.4:1)	2.8:1 or greater (largest cohort 3.6:1)
Ethnicity	82–90% Caucasian	
Mean age of onset	Approx 8yr (range: birth–16yr) Delay in diagnosis is common especially in LS as presentation is often insidious	
Clinical features	Articular (19%)—often distant to skin lesions	More generalized skin changes and may include widespread visceral involvement
	Neurological (4%)—e.g. epilepsy, headaches, behavioural change, learning disabilities	Raynaud's phenomenon (76%), skin induration (66%), sclerodactyly (55%), digital tip ulceration (35%), dysphagia (13%)
	Vascular—Raynaud's	3 subtypes recognized:
	Ocular—e.g. uveitis, episcleritis, eyelid or eyelash abnormality	Limited cutaneous systemic sclerosis (lcSSc)—skin change usually confined to distal arm or leg >head and neck. *Previously often termed 'CREST' (calcinosis, Raynaud's, oesophageal involvement, sclerodactyly, telangiectases)*
	GI (2%) (reflux oesophagitis)	
	Respiratory, renal & cardiac (<1%)	Diffuse cutaneous (dcSSc)—skin involvement extends to proximal limb and/or trunk
		Overlap syndromes—both lcSSc and dcSSc may overlap with other connective tissue diseases (e.g. SLE, Sjögren's syndrome and inflammatory muscle disease)
Differential diagnosis	Amyloidosis, eosinophilic faciitis, graft-versus-host-disease, juvenile dermatomyositis, juvenile idiopathic arthritis, [lichen sclerosus et atrophicus], lipodystrophy, Lyme disease, lupus erythematosus, mixed connective tissue disease, phenylketonuria, scleredema	

Table 4.14 Localized scleroderma (Mayo Clinic classification)

Localized scleroderma type (relative frequency, %)	Subdivision	Comment
Plaque morphoea (26%)	Plaque morphoea	Most benign subtype (usually on the trunk), lesions may be single or multiple. Often start as localized patch of erythema, induration with erythematous halo or altered skin pigment
	Others—Guttate morphoea, atrophoderma of Pasini and Pierini, Keloid morphoea (nodular morphoea), [lichen sclerosus et atrophicus]	Skin lesion patterns are variable and differing patterns may coexist
Generalized morphoea (7%)		No subdivisions. Plaques confluent or affecting >2 separate anatomical sites
Bullous morphoea (<1%)		No subdivisions
Linear morphoea (65%)	Linear morphoea/ scleroderma	Commonest subtype usually affecting limbs. May also involve face
	En coup de sabre (Parry-Romberg)	When face is affected, changes are often disfiguring
	Progressive hemifacial atrophy	'En coup de sabre' refers to cranial linear lesion with lack of hair growth in the involved skin; 'Parry–Romberg syndrome' refers to hemifacial atrophy. Intracranial brain lesions are rare (e.g. gadolinium-enhancing lesions, cerebral vasculitis, raised oligoclonal bands, or intracranial calcification)
Deep morphoea (2%)	Various descriptions	Subcutaneous morphoea, eosinophilic fasciitis, morphoea profunda, disabling pansclerotic morphoea of children

Table 4.15 Proposed provisional classification criteria of jSSc (http://www.pres.org)

Major criterion (1 required)	
Proximal skin sclerosis/induration of the skin	
Minor criterion (>2 required)	
Cutaneous	Sclerodactyly
Peripheral vascular	Raynaud's phenomenon, nailfold capillary abnormalities, digital tip ulcers
Gastrointestinal	Dysphagia, gastroesophageal reflux
Cardiac	Arrhythmias, heart failure
Renal	Renal crisis, new-onset arterial hypertension
Respiratory	Pulmonary fibrosis (high-resolution CT/radiography) with ↓ transfer factor and restrictive lung disease on pulmonary function tests, pulmonary arterial hypertension
Neurologic	Neuropathy, carpal tunnel syndrome
Musculoskeletal	Tendon friction rubs, arthritis, myositis
Serological	Antinuclear antibodies, jSSc-selective autoantibodies (anticentromere, anti–topoisomerase I [Scl-70], antifibrillarin, anti–PMScl, antifibrillin or anti–RNA polymerase I or III)

These criteria still require validation and particularly with regard to disease subtypes.

Approach to management

- Early disease recognition and referral to an experienced paediatric rheumatology MDT. There are few placebo controlled trials in children with scleroderma; therapy decisions are based on reports of clinical cohorts. Physiotherapy and occupational therapy optimize physical function to treat and prevent contractures and muscle weakness and facilitate access to make up and cosmetic approaches if there are disfiguring skin lesions. Surgery may be complicated by problems with healing and ischaemia.
- Raynaud's phenomenon—avoidance of smoking, certain drugs (e.g. beta blockers) and may be helped by gloves, topical GTN or oral medication (calcium channel blockers) or iloprost (see Clinical guidelines p 409, and Overlap syndromes, p 275).
- Treatment of skin lesions in LS depends largely on lesion site, size, depth, and potential for growth impairment when the lesions are deep and/or over joints and the presence of extra-cutaneous features. Options include topical treatments (e.g. moisturizers, corticosteroids), UV phototherapy and systemic immunosuppression are increasingly used (e.g. corticosteroids, MTX, MMF, and anti-TNF treatment—see p 409)—case series have demonstrated efficacy in halting

progression of skin involvement. Cosmetic procedures in localized scleroderma may be helpful when growth is complete and lesions inactive.

- EULAR have recently proposed evidenced-based treatment recommendations for jSSc (Table 4.16). Treatment of jSSc requires specialist evaluation and treatment (including iloprost (see 📖 Epoprostenol/iloprost, p 433, and 📖 Overlap syndromes, p 275) for Raynauds, DMARDs, and cytotoxics for organ involvement and proton pump inhibitors for GI symptoms). There are successful case reports of bone marrow transplantation and autologous haematopoietic stem cell transplantation (see 📖 AHSCT, p 405).
- Long-term monitoring is imperative and LS often progresses insidiously and frequently relapses following cessation of drug treatment. LS evolving into jSSc is reported, albeit very rarely (and possibly cases were atypical from onset).

Table 4.16 EULAR recommendations for the treatment of SSc (recommendations for adult and paediatric populations)

Organ system	Recommendation	Category of evidence
SSc-related digital vasculopathy (Raynaud's phenomenon (RP), digital ulcers)	Dihydropiridine-type calcium antagonists, usually oral nifedipine, should be considered for first-line therapy for SSc-RP, and IV iloprost, or other available IV prostanoids for severe SSc-RP	A
	IV prostanoids (in particular iloprost) should be considered in the treatment of active digital ulcers in patients with SSc	A
	Bosentan should be considered in diffuse SSc with multiple digital ulcers after failure of calcium antagonists and, usually, prostanoid therapy	A
SSc-related pulmonary arterial hypertension (PAH)	Bosentan should be strongly considered to treat SSc-PAH (pulmonary hypertension)	A/B
	At present, sitaxentan may also be considered to treat SSc-PAH	A/B
	Sildenafil may be considered to treat SSc-PAH	A/B
	Intravenous epoprostenol should be considered for the treatment of patients with severe SSc-PAH	A
SSc-related skin involvement	MTX may be considered for treatment of skin manifestations of early diffuse SSc	A
SSc-related interstitial lung disease (ILD)	In view of the results from 2 high-quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SSc-ILD (interstitial lung disease)	A

Table 4.16 (*Contd.*)

Organ system	Recommendation	Category of evidence
SSc-related renal crisis (SRC)	Despite the lack of RCT, expert consensus is that ACE inhibitors should be used in the treatment of SRC	C
	4 retrospective studies suggest that steroids are associated with a higher risk of SRC. Patients on steroids should be carefully monitored for BP and renal function	C
SSc-related gastrointestinal disease	Despite the lack of specific RCT, experts believe that proton pump inhibitors should be used for the prevention of SSc-related gastro-oesophageal reflux, oesophageal ulcers, and strictures	B
	Despite the lack of specific RCTs, experts believe that prokinetic drugs should be used for the management of SSc-related symptomatic motility disturbances (dysphagia, gastrointestinal reflux disease, early satiety, bloating, pseudo-obstruction)	C
	Despite the lack of specific RCT, experts believe that, when malabsorption is caused by bacterial overgrowth, rotating antibiotics may be useful in SSc patients	D

Further reading

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Kowal-Bielecka O, Landewé R, Avouac J, *et al.* EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group EUSTAR). *Ann Rheum Dis* 2009; **68**(5):620–8.

Zulian F, Athreya BH, Laxer R, *et al.*; Juvenile Scleroderma Working Group of the Pediatric Rheumatology European Society (PRES). Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology (Oxford)* 2006; **45**(5):614–20.

Zulian F, Woo P, Athreya BH, *et al.* The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. *Arthritis Rheum* 2007; **57**(2):203–12.

Juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is a rare small-vessel vasculopathy of childhood. It characteristically affects the skin and muscle but can also involve the GI system, heart, joints, and other organs. JDM is the most common of the idiopathic inflammatory myopathies of childhood.

Epidemiology

- The incidence of JDM is between 2 and 3 children per million per year.
- JDM is more commonly seen in girls than boys (2.3:1).
- The mean age of onset is ~7yr; however 25% of cases present before the age of 4.
- Ethnicity largely reflects that of the population. An analysis of cases from Great Britain and Ireland has shown an over-representation amongst the black population relative to population demographics.
- Seasonality, most notably in birth distribution in certain populations, suggests a role for perinatal environmental factors in the onset of the illness in later childhood.

Clinical features

- Clinical features form the central basis of the diagnosis of all cases of JDM. The typical picture is one of:
  - Heliotrope rash, periorbital oedema
  - Gottron's papules over the extensor surfaces
  - Proximal muscle weakness
- In reality patients can present with any of a number of clinical pictures including:
  - Systemic symptoms (fever, malaise, anorexia, weight loss or irritability)
  - Arthritis, myalgia, contractures
  - Dysphagia, dyspnoea, dysphonia
  - Lipoatrophy, calcinosis, skin ulceration, oedema.

Diagnostic criteria

- The diagnostic criteria defined by Bohan and Peter in 1975 remain the most widely used today. These criteria require, for a diagnosis of definite JDM, the presence of 1 of the characteristic rashes in combination with 3 of the following:
  - Symmetric proximal muscle weakness
  - Raised serum muscle enzymes (creatine kinase, transaminases, lactate dehyrogenase, and aldolase)
  - Abnormal findings on a muscle biopsy (Fig. 4.13) or electromyogram (EMG).
- The presence of 1 of the characteristic rashes plus 2 of the other features provides a diagnosis of probable JDM; rash +1 feature gives possible JDM.
- Over time, changes in clinical practice have made these criteria less reliable as many children with a diagnosis of JDM may not fulfil the criteria as a result of a lack of muscle biopsy or EMG. As such the classification criteria for JDM is under discussion, but may include:
  - Abnormal MRI
  - Abnormal nailfold capillaroscopy
  - Calcinosis
  - Dysphonia.

Monitoring during follow-up

Monitoring of disease activity in JDM involves both global activity monitoring, organ specific monitoring and includes the following:

- Assessment of muscle disease activity: muscle strength, contractures, reduced muscle length.
- Assessment of skin disease activity: rashes, nailbed erythema and swelling.
- Assessment of other organ disease: arthritis, lung/liver/heart, calcinosis. inflammation, cuticular overgrowth, nailbed capillary abnormalities.

Global assessment

- JDM Disease Activity Score—assesses the extent and distribution of cutaneous involvement, muscle weakness, functional status and vasculopathic manifestations.
- Parent/Patient global assessment of disease activity assessment by Visual Analogue Score (VAS).

Functional ability

Childhood Health Assessment Questionnaire—see 🕮 Outcome measures, p 41.

Health-related quality of life

Child Health Questionnaire—see 🕮 Outcome measures, p 41).

Assessment of muscle disease

The assessment of the extent and severity of muscle involvement is pivotal to the monitoring of JDM. Assessment of muscle disease activity and response to therapy can be subdivided.

- Measures of muscle strength—MMT8 (tests 8 muscle groups).
- Measures of muscle functional ability—CMAS.
- Serological measurement of muscle enzymes (this does not always accurately assist with disease activity monitoring particularly in long-standing disease).

Childhood Myositis Assessment Scale (CMAS)—(Table 4.17)

- This is an excellent assessment and monitoring tool to assess muscle strength and function, stamina of muscles, task orientated function.
- The CMAS assesses quality of movement as well as whether the task can be completed.
- The maximum score is 53 and this indicates a well, fit, young person.

Manual Muscle Test (MMT8)

JDM affects both proximal muscles and distal muscles and so muscle test have been validated to provide an outcome tool that measures 8 specific muscle groups, and gives an overall score which can be followed over time. Current Scoring scales include the Oxford MMT and the Kendall MMT (Table 4.18).

Assessment of skin disease

- Cutaneous Assessment Tool—assesses skin activity and damage.
- Disease Activity Score.

Monitoring of extramuscular disease

Myositis Disease Activity Assessment—a combination of a series of organ specific visual analogue scales and a myositis intention to treat activity index.

Assessment of damage

Myositis Damage Index—assess the extent of damage in many organ systems and includes a VAS to quantify the extent of damage (it includes the assessment of linear growth and pubertal development).

Imaging

MRI is accepted as the most valuable tool in the evaluation of myositis activity and in differentiation between activity and damage (Fig. 4.14).

Capillaroscopy (see 🕮 Nailfold capillaroscopy in rheumatic disease) Nailfold capillary changes correlate strongly with measures of disease activity.

Treatment

- The aims of therapy for JDM are to treat the disease, prevent mortality, and reduce long-term disability and calcinosis.
- The management of JDM continues to vary widely from centre to centre and evidence base is scant.
- Corticosteroids are the accepted 1st-line therapy, however mode of administration, dosage, and duration of therapy still varies.
- The early introduction of agents beyond corticosteroids may shorten disease duration, reduce calcinosis, reduce the likelihood of flares later in the disease course, and ↑ the chance of remission.
- Corticosteroid therapy is preferably administered by the parenteral route rather than oral, particularly in patients with vasculopathy as evidenced by periungal nailfold capillary abnormalities.
- *Accepted 1st-line management for a typical case of JDM in the UK (see 🕮 for guidelines)*
  - Corticosteroids—IV methylprednisolone 10–30mg/kg/day for 3 days followed by 1–2mg/kg oral prednisolone (weaning dose).
  - MTX 15mg/m^2 preferably by the subcutaneous route.
  - Physical therapy.
  - Photoprotective measures.
  - Calcium and vitamin D supplementation.
  - Hydroxychloroquine at 3–6mg/kg/day.
- *2nd-line agents*
  - IVIg
  - Ciclosporin
  - AZA.
- *3rd-line agents*
  - Cyclophosphamide
  - MMF
  - Tacrolimus
  - Rituximab
  - Anti-TNFα agents.

Table 4.17 Childhood Myositis Assessment Scale (CMAS) scoring sheet

1. Head elevation (neck flexion): 0 = Unable 1 = 1–9sec 2 = 10–29sec 3 = 30–59sec 4 = 60–119sec 5 = >2min No. of seconds	Item score . . .
2. Leg raise/touch object: 0 = Unable to lift leg off table 1 = Able to clear table, but cannot touch object 2 = Able to lift leg high enough to touch object	Item score . . .
3. Straight leg lift/duration: 0 = Unable 1 = 1–9sec 2 = 10–29sec 3 = 30–59sec 4 = 60–119sec 5 = >2min No. of seconds	Item score . . .
4. Supine to prone: 0 = Unable. Has difficulty even turning onto side; able to pull arms under torso only slightly/not at all 1 = Turns onto side fairly easily, but cannot fully free arms, but not able to fully assume a prone position 2 = Easily turns onto side; some difficulty freeing arms, but fully frees them and fully assumes prone position 3 = Easily turns over, free arms with no difficulty	Item score . . .
5. Sit-ups: for each type of sit-up enter either '0' (unable) or '1' (able). Then enter the total subscore. Maximum possible item score 6. Hands on thighs, with counterbalance Hands across chest, with counterbalance Hands behind head, with counterbalance Hands on thighs, without counterbalance Hands across chest, without counterbalance Hands behind head, without counterbalance	Item score . . .

(*continued*)

Table 4.17 (*Contd.*)

6. Supine to sit: 0 = Unable by self 1 = Much difficulty. Very slow, struggles greatly, barely makes it. Almost unable 2 = Some difficulty. Able, but is somewhat slow, struggles some 3 = No difficulty	Item score . . .
7. Arm raise/straighten: 0 = Cannot raise wrists 1 = Can raise wrists at least up to the level of the acromioclavicular joint. but not above top of head 2 = Can raise wrists above top of head. but cannot raise arms straight above head so that elbows are in full extension 3 = Can raise arms straight above head so that elbows are in full extension	Item score . . .
8. Arm raise/duration: Can maintain wrists above top of head for: 0 = Unable 1 = 1–9sec 2 = 10–29sec 3 = 30–59sec 4 = 60–119sec 5 = >120sec No. of seconds	Item score . . .
9. Floor sit: Going from a standing position to a sitting position on the floor. 0 = Unable. Afraid to even try, even if allowed to use a chair for support. Child fears that he/she will collapse, fall into a sit, or harm self. 1 = Much difficulty. Able, but needs to hold onto a chair for support during descent. (Unable or unwilling to try if not able to use a chair for support.) 2 = Some difficulty. Can go from stand to sit without using a chair for support, but has at least some difficulty during descent. Descends somewhat slowly and/or apprehensively; may not have full control or balance as manoeuvres into a sit. 3 = No difficulty. Requires no compensatory manoeuvring.	Item score . . .

Table 4.17 (*Contd.*)

10. All-fours manoeuvre: 0 = Unable to go from a prone to an all-fours position. 1 = Barely able to assume and maintain an all-fours position. 2 = Can maintain all-fours position with straight back and head raised (so as to look straight ahead). But, cannot creep (crawl) forward 3 = Can maintain all fours, look straight ahead, and creep (crawl) forward 4 = Maintains balance while lifting and extending leg.	Item score . . .
11. Floor rise: Going from a kneeling position on the floor to a standing position. 0 = Unable, even if allowed to use a chair for support 1 = Much difficulty, Able, but needs to use a chair for support. Unable if not allowed to use a chair 2 = Moderate difficulty. Able to get up without using a chair for support, but needs to place one or both hands on thighs/knees or floor. Unable without using hands 3 = Mild difficulty. Does not need to place hands on knees, thighs, or floor, but has at least some difficulty during ascent 4 = No difficulty.	Item score . . .
12. Chair rises: 0 = Unable to rise from chair, even if allowed to place hands on sides of chair seat l = Much difficulty. Able, but needs to place hands on sides of seat. Unable if not allowed to place hands on knees/thighs. 2 = Moderate difficulty. Able, but needs to place hands on knees/ thighs. Does not need to place hands on side of seat. 3 = Mild difficulty. Able; does not need to use hands at all, but has at least some difficulty; 4 = No difficulty	Item score . . .
13. Stool step: 0 = Unable 1 = Much difficulty. Able, but needs to place one hand on exam table or examiner's hand 2 = Some difficulty. Able; does not need to use exam table for support, but needs to use hand(s) on knee/thigh 3 = Able. Does not need to use exam table or hand(s) on knee/thigh	Item score . . .

(*continued*)

Table 4.17 (*Contd.*)

14. Pick up:	Item score . . .
0 = Unable to bend over and pick up pencil off floor	
1 = Much difficulty. Able, but relies heavily on support gained by placing hand(s) on knees/thighs	
2 = Some difficulty. Needs to at least minimally and briefly place hand(s) on knees/thighs for support and is somewhat slow	
3 = No difficulty. No compensatory manoeuvre necessary	
TOTAL SCORE (Max = 53)	

Table 4.18 The MMT Standard Scoring systems (Oxford and Kendall) (0–10 scale)

	Function of the muscle	**0–10 scale**
No movement		0
Test movement	**Movement in horizontal plane**	
	Moves through partial range of motion	1
	Moves through complete range of motion	2
	Moves to completion of range against resistance Or	
	Moves to completion of range and holds against pressure Or	3
	Antigravity position	
	Moves through partial range of motion	
Test position	Gradual release from test position	4
	Holds test position (no added pressure)	5
	Holds test position against slight pressure	6
	Holds test position against slight to moderate pressure	7
	Holds test position against moderate pressure	8
	Holds test position against moderate to strong pressure	9
	Holds test position against strong pressure	10

Oxford MMT:
- 0=no muscle action,
- 1=flicker of muscle action,
- 2=muscle action with gravity counterbalance,
- 3=muscle action against gravity,
- 4=muscle action against gravity with some resistance,
- 5=full muscle strength,
- (9=not done)

Table 4.18 (*Contd.*)

Function of the muscle	0–10 scale
The 8 muscle groups assessed are: • Neck flexors (this must be assessed lying flat as this includes gravity) • Shoulder abductors • Elbow flexors • Wrist extensors • Hip abductors • Hip extensors • Ankle dorsiflexors • Knee extensors	
All 8 muscle groups are assessed and the score is added up to give a global score (out of 80).	

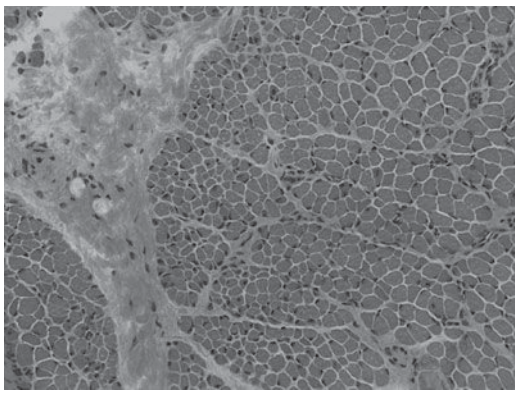

Fig. 4.13 (Also see Colour plate 3.) Muscle biopsy in JDM.

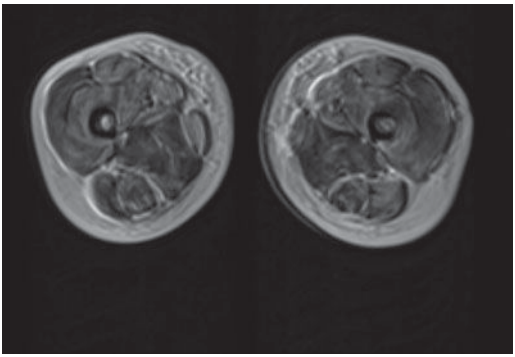

Fig. 4.14 MRI of muscles in JDM.

Further reading

Isenberg DA, Allen E, Farewell V, *et al.* International consensus outcome measures for patients with idiopathic inflammatory myopathies. Development and initial validation of myositis activity and damage indices in patients with adult onset disease. *Rheumatology (Oxford)* 2004; **43**:49–54.

Lowry CA, Pilkington CA. Juvenile dermatomyositis: extramuscular manifestations and their management. *Curr Opin Rheumatol* 2009; **2**: 575–580.

Pilkington C. Clinical assessment in juvenile idiopathic inflammatory myopathies and the development of disease activity and damage tools. *Curr Opin Rheumatol* 2004; **16**:673–7.

Overlap syndromes

Background

- Paediatric and adolescent rheumatology patients may exhibit features of >1 of the classical autoimmune rheumatic diseases (JIA, SLE, JDM, systemic sclerosis) (Fig. 4.15). Such patients are often described as having 'overlap' syndromes or 'undifferentiated' autoimmune rheumatic disease (UAIRD)/connective tissue disease.
- Over time, UAIRD may 'evolve' so the features of one of the classical autoimmune diseases predominate.
- Sometimes one AIRD e.g. JDM may 'evolve' into another, e.g. SLE.
- Variability of the clinical manifestations over time is a particular feature of paediatric overlap syndromes, and is more common than in adult patients.

The paediatric rheumatologist needs to remain vigilant for features of SLE, myositis, systemic sclerosis, inflammatory arthritis, and vasculitis in any child with an overlap syndrome, and should avoid a rigid diagnostic label.

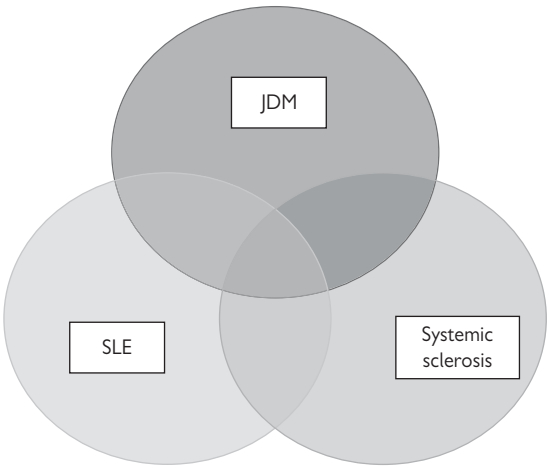

Fig. 4.15 Overlap syndromes.

Mixed connective tissue disease (MCTD)

This specific overlap syndrome is more clearly defined, and characterized by:

- Puffy, swollen hands ('sausage fingers'—diffuse swelling of the entire digit distinct from the articular swelling seen in JIA).
- Raynaud's phenomenon.

- High titre speckled pattern ANA on immunofluorescence with antibodies to U1-RNP:
  - A variety of formal diagnostic criteria have been proposed for MCTD in adults (e.g. Sharp's, Kasukawa, Porter's); none have been validated in children.
  - Controversy exists over whether MCTD is a discrete diagnostic entity because U1-RNP antibodies are also found in SLE, and follow-up of adult MCTD patients shows that many differentiate into SLE or SSc. Proponents of MCTD argue that antibodies to U1-RNP and MCTD have specific immunogenetic associations (e.g. HLA-DR4) suggesting a distinct pathogenesis.
- Clinical features and their frequencies (derived from synthesis of data from a number of case series) in juvenile onset MCTD are shown in Table 4.19.
- Mean age of onset of paediatric MCTD is 9–12yr.
- ♀ to ♂ ratio ~6:1.
- In children, evolution of MCTD is common. Over time arthritis, myositis, and SLE-like manifestations transition to scleroderma-type features.
- Inflammatory manifestations (e.g. arthritis, myositis) respond better to immunosuppression and result in less permanent damage than scleroderma-type manifestations.
- There are conflicting observations from small case series of paediatric MCTD over whether SLE-like or sclerodermatous features are more common than in adult MCTD.
- Some studies report a more benign prognosis in paediatric MCTD compared to adult disease, but other series show the opposite.
  - Pulmonary hypertension, a cause of serious morbidity and mortality in adults, is rare in paediatric disease.

Table 4.19 Clinical features of MCTD

Manifestation	Frequency (%)*
Raynaud's phenomenon	91%
Arthritis	81%
Sclerodermatous skin changes/sclerodactyly	60%
Rash (may be lupus-type or JDM-type)	50–60%
Myositis	52%
Sicca symptoms/parotiditis	40%
Interstitial lung disease	28%
Oesophageal dysmotility	15%
Thrombocytopenia	12%
Pericarditis	12%
Haemolytic anaemia	5%
Pulmonary arterial hypertension	5%

*Frequencies are derived from synthesis of data from a number of case series

Sjögren's syndrome overlap

- 1° Sjögren's syndrome (pSS) is an autoimmune exocrinopathy characterized pathologically by focal lymphocytic infiltration of glandular tissue eventually leading to glandular destruction.
- Some patients have overlapping features of SS and other connective tissue diseases. The term 'Sjögren overlap' has been used to describe these patients.
- The syndrome manifests clinically as sicca symptoms (dryness of mucosal surfaces, particularly eyes and mouth).
- Extraglandular features such as arthralgia, hepatic involvement, and renal tubular acidosis may also occur.
- Both pSS and Sjögren overlap are very rare in children.

Overlap with organ-specific autoimmunity

- Systemic autoimmune disease may overlap with organ-specific autoimmune disease.
- SLE/autoimmune hepatitis (AIH) overlap is well described.
  - Autoimmune hepatitis occurs in 9% of juvenile SLE patients (compared to only 1% of adult SLE patients).
  - In juveniles AIH usually precedes the development of SLE; in adults the converse is true.

Investigations in patients with overlap syndromes:

These depend on the clinical manifestations. However, consideration should be given to the following:

- Full immunological work-up at initial presentation to best characterize disease:
  - RF, ANA, ENA, dsDNA, ANCA, anticardiolipin antibodies and lupus anticoagulant, complement (C3, C4), immunoglobulins G, A, and M.
- Serial measurement of dsDNA & C3/C4; repeat ENA every 2yr as the autoantibody profile may evolve with time.
- TFTs and anti-thyroid antibodies.
- Coombs' test.
- Muscle enzymes (CK, LDH, AST).
- Urine dip at all clinic visits; if abnormal request urine microscopy to look for casts, urine culture, and urine protein:creatinine ratio.
- MRI is a useful non-invasive tool for assessing myositis. Muscle biopsy remains the 'gold standard' but is painful and so often avoided in children.
- CXR.
- Lung function tests with gas transfer (depending on the age of the child) to identify interstitial lung disease—consider high resolution CT of the chest if abnormal.
- Echocardiography to estimate pulmonary artery pressure (PAP) if pulmonary hypertension suspected.

Treatment

Treatment is tailored to individual manifestations of the child's disease:

- ***Arthritis***—NSAIDs, MTX, hydroxychloroquine, corticosteroids.
- ***Rash***—hydroxychloroquine, topical treatments including steroids and tacrolimus.

- ***Raynaud's phenomenon***—calcium channel blockers (e.g. nifedipine), GTN patch, angiotensin II receptor blockers in addition to conservative measures.
  - IV epoprostenol or eporostenol analogue (e.g. iloprost) may be used in severe cases with digital ischaemia.
- ***Myositis***—steroids, AZA, MTX. IVIg and cyclophosphamide may be used in severe cases. Rituximab may have a role.
- ***Interstitial lung disease***—steroids, AZA, or MMF, or CPM
- ***Pulmonary arterial hypertension (PAH)***—this carries a poor prognosis. Consult a cardiologist with experience of PAH.

Iloprost administration: standard regimen is an infusion lasting 6h per day for 5 consecutive days. See also 📖 BSPAR guidelines for treatments uses in paediatric rheumatology, p 415.

50 micrograms (0.5mL) Iloprost is mixed with 49.5mL of normal saline in a syringe driver, giving a solution of 50mcg in 50mL. A fresh solution should be prepared daily.

Day1

- Commence at 0.5 nanogram/kg/min (1mcg = 1000ng).
- If tolerated, after 30min ↑ to 1 ng/kg/min.
- If tolerated, after further 30min ↑ to 1.5ng/kg/min.
- If tolerated, after further 30min ↑ to 2ng/kg/min. Run at this rate for the remaining 4.5h.

On subsequent days commence rate at the highest rate tolerated on the previous day.

Check P/BP/T prior to infusion, every 30min during infusion, and 1h post infusion.

Common side effects: facial flushing, headaches, nausea & vomiting, diarrhoea, sweating, paraesthesia, erythema around infusion site, hypotension. If mild, reduce rate by 0.5ng/kg/min. If moderate/severe stop the infusion. It may be possible to re-start at the lowest rate following premedication with paracetamol and an antiemetic.

NB Iloprost is renally excreted: use ½ dose in patients on dialysis.

Antiphospholipid syndrome (APS)

Background

- APS is a multisystem autoimmune disease characterized by persistent positivity of antiphospholipid (aPL) antibodies in the presence of vascular thrombotic events, pregnancy morbidity, and other clinical manifestations.
- The APS may occur as an isolated clinical entity (1° APS) or in association with an underlying systemic disease (2° APS), most commonly SLE.
- Paediatric 1° APS is very rare whilst the prevalence of 2° APS in children with SLE is estimated to be 9–14%.

Classification criteria

Preliminary criteria for the classification of paediatric APS are based on the recently revised classification criteria for the diagnosis of APS in adults, and include:

- *Clinical criteria*—vascular thrombosis: 1 or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
- *Laboratory criteria* must be present on 2 or more occasions, at least 12 weeks apart and include:
  - Anticardiolipin antibody (ACL) of IgG and/or IgM isotype in serum or plasma: must be present in medium or high titre (i.e. >40 GPL or MPL, or >99th percentile)
  - Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma: must be present in titre >99th percentile.
  - Lupus anticoagulant (LA) in plasma.

Paediatric APS is considered to be present if the clinical criterion and at least 1 of the laboratory criteria are met.

Pathogenesis

- Exactly how aPL antibodies cause thrombosis, and why some patients develop thromboses rather than pregnancy morbidity is currently not known.
- One hypothesis postulates that pathogenic aPL antibodies target and bind cellular and platelet phospholipids in the presence of certain serum cofactors such as beta-2 glycoprotein I, leading to cellular activation and biological effects such as promotion of thrombosis.
- In addition, aPL antibodies cause an ↑ in expression of tissue factor (a critical pro-thrombotic intermediate in the clotting cascade) in both monocytes and endothelial cells.

Furthermore, platelet and complement activation as well as endothelial activation and a 'second hit' inflammatory signal may play a role, particularly in those with catastrophic APS (CAPS).

Clinical features

The clinical manifestations of APS in children include:

- ***Vascular thrombosis:***
  - Most commonly this is deep vein thrombosis of the lower limbs.
  - More rare are thromboses in the superficial and upper extremity veins, inferior and superior vena cava, hepatic (Budd–Chiari syndrome) and portal veins, renal, adrenal, retinal, and intracranial veins.
  - Arterial thrombosis, resulting mainly in stroke (20% of all thrombotic events thromboses) and transient ischaemic attacks (11% of all thrombotic events), are less common. Other involved vessels include coronary, subclavian, mesenteric, renal, retinal, and pedal arteries. Of note is that arterial thrombosis is much more common in children than in adults.
- ***Central nervous system symptoms***—chorea (always consider APS in the differential diagnosis of Sydenham's chorea), dementia, migraine, intracranial hypertension, neurocognitive deficits, psychosis and depression, epilepsy, Guillain–Barré syndrome, transverse myelopathy and optical neuritis.
- ***Cardiac manifestations***—valvulopathy (mitral/aortic valves), intracardiac thrombosis, coronary artery thrombosis and cardiomyopathy.
- ***Haematological disorders***—mainly thrombocytopenia and haemolytic anemia (direct Coombs testing is usually positive in the latter).
- ***Skin manifestations***—livedo reticularis, cutaneous gangrene, skin ulcers, livedoid vasculopathy (an important occlusive vasculopathy mimicking vasculitis, although not vasculitic in nature), palmar and plantar erythema, anetoderma (focal loss of dermal elastic tissue, resulting in localized areas of flaccid or herniated saclike skin), Raynaud's phenomenon.
- ***Renal manifestations*** include:
  - Renal artery thrombosis.
  - Thrombosis in smaller-diameter renal parenchymatous vessels, resulting in areas of focal cortical, ischaemia and/or necrosis.
  - Thrombotic microangiopathy—most characteristic lesion of APS nephropathy, with distinctive microscopic and ultrastructural changes.
  - Thrombosis of the renal veins and inferior vena cava.
- ***Pulmonary involvement*** is rare in children with APS, but includes: pulmonary embolism, intra-alveolar haemorrhages, 1° thrombosis of lung vessels, both major and minor, as well as pulmonary capillaritis, pulmonary hypertension.
- ***Various GI manifestations*** have been reported including intestinal and oesophageal ischaemia and infarction, ischaemic colitis, colonic ulceration, infarction of the liver, cholecystitis, and mesenteric, hepatic, and portal vein thrombosis.
- ***Perinatal APS***—rare cases of perinatal thrombosis in infants born to mothers with APS or mothers with aPL antibodies have been reported, with the clinical presentation consisting of arterial and venous thromboses in multiple localizations. Although patients in this subgroup have diagnostic criteria of APS, their disease behaves differently, is transitory and does not recur, similar to patients with neonatal SLE.

Laboratory investigations

- Clotting screen:
  - The first clue to the presence of aPL antibodies is the finding of a prolonged APTT. If the clotting remains abnormal when the patient's plasma is mixed with normal pooled plasma, this is suggestive of the presence of an inhibitor, the lupus anticoagulant (LA).
  - The presence of LA is then confirmed with a phospholipid-sensitive functional clotting testing, such as the dilute Russell viper venom test (dRVVT). In part one of the test Russell viper venom directly activates factor X, but phospholipid is still required to generate thrombin, so in the presence of PL binding anticardiolipin antibodies (the LA) clotting is delayed. In the second part of the test the inhibitory effect of LA on phospholipids can be overcome by adding an excess of phospholipid to the assay. The clotting times of both the initial dRVVT assay and the second part of the test are used to determine a ratio of time with or without phospholipid excess. A ratio >1.2 is considered positive and implies that the patient may have aPL antibodies.
- Other tests for measuring aPL antibodies are the enzyme-linked immunosorbent assay which detects different isotypes of anticardiolipin antibodies and antibodies to many other phospholipids (phosphatidylserine, phosphatidylinositol, phosphatidylcholine).
- Another group of antibodies are directed against protein co-factors that bind the phospholipids, such as beta-2 glycoprotein-1 and annexin.
- Although there is some overlap between all these antibodies, it is important to use >1 test to detect them.

Treatment

The risk of thrombosis is low in asymptomatic children who are incidentally found to have positive aPL; high among those in whom thrombosis already occurred and extremely high in patients with CAPS.

- Aspirin at low doses (2–5mg/kg/once daily) has been used as prophylaxis in aPL-positive children with autoimmune diseases but without previous thromboses and in particular to prevent arterial thromboses.
- Hydroxychloroquine may be protective against the development of thrombosis in aPL-positive patients with SLE.
- Warfarin: lifelong treatment if one major thrombotic episode has occurred (such as pulmonary or femoral arterial thrombus) is recommended, aim for INR 2–3.

Dosing regimen for warfarin is:

- 200 micrograms/kg (max. 10mg) as a single dose on first day.
- Reduce dose to 100 micrograms/kg (max. 5mg) once daily for following 3 days. Note that:
  - If INR still below 1.4 use 200 micrograms/kg (max. 10mg) once daily, or
  - If INR above 3 use 50 micrograms/kg (max. 2.5mg) once daily, or
  - If INR above 3.5 omit dose;
- Dose is then adjusted according to INR, usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg).

NB initial warfarinization should be covered with full heparinization to prevent warfarin-induced thrombosis due to inhibition of protein C and S which occurs at INR levels <2. Heparin is usually given in its low-molecular-weight forms (LMWH) subcutaneously at therapeutic doses. It will often take up to 10 days to adjust warfarin treatment to obtain the recommended INR. During this time LMWH treatment is assessed through monitoring anti-Xa levels to ensure a therapeutic range (0.5–1.0 anti-Xa units/ml plasma). This is of particular importance in children with renal or hepatic impairment and severely ill children. Note that LMWH is not as easy to reverse as unfractionated heparin.

In cases of 2° *APS*, treatment of the underlying condition should be initiated in addition to anticoagulation and anti-platelet therapy.

Outcome

In one study, of a large paediatric APS cohort at follow-up of 6.1yr:

- 19% developed recurrent thromboses, which usually occurred in a similar blood vessel type as initial thrombosis.
- 5% presented with life threatening widespread thrombotic disease suggestive of CAPS.
- 7% died mainly due to aPL-related thrombotic complications.

Catastrophic APS (CAPS)

- CAPS is a rapidly progressive life-threatening disease causing multiple organ thromboses and dysfunction in the presence of aPL antibodies, and is associated with an ↑ mortality despite treatment. The syndrome is characterized by a diffuse thrombotic microvasculopathy.
- The exact pathogenesis of CAPS remains unclear. One hypothesis postulates that clots continue to generate thrombin, fibrinolysis is depressed by an ↑ in plasminogen activator inhibitor type-1 (PAI-1), and there is consumption of the natural anticoagulant proteins such as protein C and antithrombin III. In addition, manifestations of the systemic inflammatory response syndrome are presumed to be due to excessive cytokine release from affected and necrotic tissues.
- Another specific characteristic of CAPS is that 60% of patients appear to have a triggering factor especially infections, the commonest identifiable trigger for CAPS and present in about 25% of cases.
- For treatment of CAPS *seek expert advice* and consider IVIg (2g/kg), Pulsed IV methylprednisolone, cyclophosphamide and/or rituximab and plasma exchange, in addition to full anticoagulation and anti-platelet therapy as per APS.
- Despite treatment, mortality in CAPS is reported to be as high as 48%.

Further reading

Avcin T, Silverman ED. Antiphospholipid antibodies in pediatric systemic lupus erythematosus and the antiphospholipid syndrome. *Lupus* 2007; **16**; 627.

Avcin T, Cimaz R, Rozman B; Ped-APS Registry Collaborative Group Lupus. The Ped-APS Registry: the antiphospholipid syndrome in childhood. *Lupus* 2009; **18**:894–9.

Paediatric uveitis

- Uveitis is the term for intraocular inflammation, i.e. those layers internal to the sclera and cornea (see Fig. 4.16 for a diagram of eye anatomy).
- The uveal tract is the vascular layer including the choroid, ciliary body, and iris (uvea = grape in Greek).
- The term uveitis referred to inflammation of the uveal tract but can also refer to inflammation of the retina and vitreous.

Aetiology

- The causes can be infectious and non-infectious (Tables 4.20 and 4.21).
  - Non-infectious uveitis has an approximate incidence of 4–7/100 000 children.
- The appearance and site of the inflammation may help to determine the cause, e.g. sarcoidosis is typically a granulomatous anterior or panuveitis. The investigations to consider depend on the clinical presentation (Table 4.22).

Masquerade syndromes include:

- Juvenile xanthogranulomatosis—typical histiocytic skin lesions which may involve the eye, particularly iris
- Diffuse retinoblastoma
- Intraocular foreign body
- Leukaemia
- 1° retinal detachment
- Retinal dystrophy.

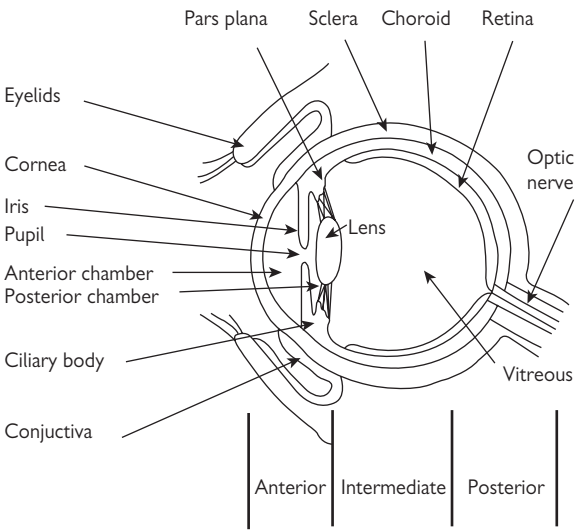

Fig. 4.16 Anatomy of the eye: Reproduced from http://www.uveitis.net/patient/glossary.php, with permission.

Table 4.20 Infectious causes of paediatric uveitis

Relatively common	Relatively uncommon but with geogrphical variation
• *Toxoplasmosis gondii* • Varicella zoster • Herpes simplex virus • Cytomegalovirus • Tuberculosis • *Bartonella*	• Lyme disease • Toxocara • Histoplasmosis • Ascaris • Echovirus • Fungal infection • Syphilis

Table 4.21 Non-infectious types of paediatric uveitis

No systemic disease association	Associated with systemic disease
Idiopathic uveitis: the most common type in population-based cohorts. In children <8yr of age idiopathic chronic anterior uveitis is by far the most common. In those with onset between 8–15yr of age intermediate uveitis is relatively more common, and in older patients acute anterior uveitis is the most frequent type, as in adults. **Named uveitis syndromes are very rare in childhood**: • Sympathetic ophthalmia—trauma to one eye causes uveitis in the other eye, typically multifocal choroiditis and panuveitis	**Common:** • **Juvenile idiopathic arthritis (JIA)**—typically chronic asymptomatic anterior uveitis. The most common systemic disease associated with paediatric uveitis worldwide • **Enthesitis related arthritis**—usually acute anterior uveitis and often carry HLA B27 • **Inflammatory bowel disease**—anterior and intermediate uveitis • **Sarcoidosis**—anterior and pan uveitis. Granulomas of uvea frequent • **Blau syndrome**—if there is a family history of granulomatous disease consider this autosomal dominant genetic granulomatous condition involving arthritis, uveitis and dermatitis with a typical skin rash (*NOD2* gene; see 📖 p 300 sarcoid) • **Tubulointerstitial nephritis uveitis (TINU)**—bilateral anterior uveitis and acute interstitial nephritis; occasionally associated with deafness.

Table 4.21 (*Contd.*)

No systemic disease association	Associated with systemic disease
	Less common
• Acute multifocal placoid pigment epitheliopathy • Fuch's cyclitis • Birdshot retinochoroidopathy	• **Kawasaki disease**—an acute non-granulomatous bilateral uveitis which usually resolves without any specific ocular therapy and without visual complication • **Other childhood-onset vasculitides:** WG, PAN, scleroderma, SLE, Cogan's syndrome (atypical; typical Cogan's is associated with interstitial keratitis) • **Behçets disease**—posterior and anterior uveitis is recognized. Rare to have onset of uveitis in childhood • **Chronic inflammatory neurologic cutaneous and articular syndrome (CINCA)**—uveitis and papillitis with chronic disc swelling • **Other periodic fever syndromes** • **Vogt–Koyanagi–Harada syndrome**—uveitis, vitiligo, poliosis (= ↓ or absence of melanin in head hair, eyebrows, or eyelashes), neurological and auditory findings • **Multiple sclerosis** with intermediate uveitis is rare in childhood, although intermediate uveitis is common

Table 4.22 Anatomical classification of uveitis

Uveitis type	Inflammation site
Anterior uveitis	Anterior segment (i.e. iris ± ciliary body)
Intermediate uveitis	Vitreous and retina
Anterior and intermediate uveitis	Intermediate uveitis with significant anterior uveitis
Posterior uveitis	Retina or choroid only
Panuveitis	Anterior uveitis and posterior uveitis

Uveitis associated with JIA

- JIA is the commonest systemic disease associated with paediatric uveitis. 15% of children with JIA have uveitis, usually chronic anterior uveitis and it can occur before, or up to 7yr after the onset of arthritis.
- Predisposing factors include:
  - Oligoarticular rather than polyarticular onset.

  - Age at JIA onset <7yr (and especially <4yr), and ANA positivity.
  - Uveitis is much less common in sJIA and chronic anterior uveitis is not typically associated with childhood onset ERA or RA. The presence of psoriasis may ↑ the risk of chronic anterior uveitis.
- There is no difference known in the course or pattern of uveitis seen in JIA other than the almost exclusive association of acute anterior uveitis in those with clinical enthesis related arthritis. All other JIA types, other than early onset RA develop chronic anterior or chronic anterior and intermediate uveitis.
- Children <8yr rarely describe unilateral visual loss reliably so screening for vision in each eye is required.
- JIA uveitis can cause irreversible blindness without changes in the appearance of the eye or reliably reported symptoms.
- All JIA children should have eye screening with a slit lamp examination according to the Royal College of Ophthalmologists and BSPAR (see 📖 Screening, p 148).
- Poor prognostic features for vision include uveitis present prior to arthritis, severe uveitis at presentation and the failure to achieve early remission.
- Irreversible complications may occur after only a few weeks of uncontrolled eye inflammation.
- Complications include raised intraocular pressure, glaucoma, posterior synechiae, band keratopathy, cataract, retinal detachment, macular oedema, and hypotony.
- Visual loss may affect up to 25% of JIA uveitis.
- Reducing JIA medication given for arthritis, e.g. MTX may result in a uveitis flare.
- Raised inflammatory markers in the absence of corresponding articular signs may represent ocular inflammation.

Treatment modalities in paediatric uveitis (Table 4.23)

The correct treatment of uveitis balances the long-term risk, and effects of visual loss with the short- and long-term risks of treatment. In most cases these are not well established. About half of children with JIA-uveitis or intermediate uveitis do not suffer visual loss despite prolonged inflammation. Aggressive treatment should be confined to those with a significant risk of permanent visual loss, and this risk (and the efficacy of available treatments) may change considerably over the course of disease.

Treatment will depend on causes identified from the investigations previously described. For idiopathic and autoimmune/autoinflammatory causes, including uveitis associated with JIA:

- Topical corticosteroids are invariably used when the predominant site of inflammation is anterior, e.g. prednisolone or dexamethasone 1% drops. They are not indicated when the predominant site is intermediate or posterior.
- Topical mydriatics are used to reduce the risk of synechiae formation in anterior uveitis.
- Topical glaucoma agents may be required to reduce intraocular pressure.
- Systemic corticosteroids, e.g. oral prednisolone, short-term high dose to gain control followed by a reducing course over 4–6 weeks. The need for long-term systemic steroids needs regular review in growing children.

- Periocular corticosteroids, e.g. orbital floor steroid injection may be used where topical steroids are ineffective. Intravitreal steroids are occasionally used where risk of cataract and glaucoma are low.
- MTX 15mg/m^2 once weekly (SC or PO) when topical steroids are insufficient is frequently used in patients with JIA. Other steroid-sparing agents used in adult uveitis may be more appropriate in other types of uveitis.
- Inhibitors of tumour necrosis factor alpha (anti-TNFα) i.e. infliximab and adalimumab have been used in JIA—uveitis poorly controlled with MTX. They may be more effective than etanercept or other 2nd-line immunosuppressants but there is no trial data to confirm this—see 🕮 Biologics, p 393.
- The Interleukin 1 inhibitors, anakinra and canakinumab, have been used to treat uveitis associated with CAPS (which includes the severe variant chronic infantile neurological cutaneous arthritis, CINCA).

Table 4.23 Suggested investigations in paediatric uveitis

Suggested first line investigations	Suggested second line investigations

• FBC, blood film
• ESR, CRP
• Renal function: plasma creatinine and consider formal GFR if abnormal
• Immunoglobulins
• ASO titre
• ANA
• Urine analysis for blood and protein; UA:UC if proteinuria on dip test
• Mantoux and or Quantiferon (or equivalent gamma interferon release assay)
	• Tissue biopsy—especially of rashes; other including renal biopsy
	• CXR
	• Chest CT
	• Serum ACE
	• ANCA
	• MRI/MRA brain
	• Selective visceral arteriography (particularly for PAN, see 🕮 p 168 Vasculitis)
	• Pure tone audiometry and assessment of vestibular function (Cogan's)
	• Many others—including specific genetic tests dependent on the clinical presentation
	• To pursue the diagnosis of infectious/malignant causes where the clinical diagnosis is in doubt:
	  • PCR (including 16S and 18S ribosomal PCR as screening tests for bacterial and fungal infection respectively) and cytology of ocular fluids is usually necessary.
	  • Serology for infectious agent may be helpful to exclude, but not diagnose, causes of ocular infection.

Standardizing uveitis measurement for research

- Currently there are no standardized criteria for measuring paediatric uveitis activity in clinical studies.
- Proposed standardized terms and grades for adult uveitis were published in 2005.

Further reading

Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First Workshop. *Am J Ophthalmol* 2005; **140**:509–16.

Periodic fever syndromes/ autoinflammatory disease

Introduction

The periodic fever syndromes are disorders of innate immunity, sometimes referred to as autoinflammatory diseases.

They are characterized by the following:

- Recurring episodes of fever and constitutional upset, but with normal health between attacks.
- Systemic inflammatory symptoms affecting the:
  - Serosal surfaces
  - Joints
  - Skin
  - Eyes.
- Symptoms are always accompanied by biochemical markers of inflammation such as raised ESR, CRP, and leucocytosis.
- The various syndromes are compatible with near-normal life expectancy, except for the risk of developing amyloid A (AA) amyloidosis in later life.
- Despite similarities in symptoms, the syndromes have differing aetiologies, inheritance, duration, and clinical features.
- The *hereditary* periodic fever syndromes are associated with mutations in genes involved in innate immunity and generally the onset is early in childhood affecting both sexes equally. 7 major syndromes are currently recognized (summarized in Table 4.24):
  - Familial Mediterranean fever (FMF)
  - TNF receptor-associated period syndrome (TRAPS)
  - Mevalonate kinase deficiency (MKD) (also known as hyperimmunoglobulin D and periodic fever syndrome (HIDS))
  - Cryopyrin associated periodic syndrome (CAPS) (subdivided into Familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and chronic infantile, neurological, cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease (CINCA/NOMID))
  - Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome
  - Deficiency of IL-1 receptor antagonist (DIRA)
  - Blau syndrome/early onset sarcoidosis (EOS).
- There are now completely effective treatments for most patients with FMF, CAPS, and DIRA and although not always quite as effective, good treatments are available for the majority of the other syndromes too.
- Disorders of unknown aetiology which share some features with the inherited syndromes include:
  - Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome
  - Behçet's disease
  - Chronic recurrent multifocal osteomyelitis (CRMO)—(see 🕮 CRMO, p 297)
  - Systemic juvenile idiopathic arthritis (sJIA)—see 🕮 JIA and MAS, p 305.

Table 4.24 Hereditary periodic fever syndromes

Periodic fever syndrome	Gene	Mode of inheritance	Predominant ethnic groups	Usual age at onset	Potential precipitants of attacks	Distinctive clinical features	Typical duration of attacks	Typical frequency of attacks	Characteristic laboratory abnormalities	Treatment
FMF	*MEFV* Chromosome 16	Autosomal recessive (dominant in rare families)	Eastern Mediterranean	Childhood/ early adult	Usually none Occasionally menstruation, fasting, stress, trauma	Short severe attacks Colchicine responsive Erysipelas like erythema	1–3 days	Variable	Marked acute phase response during attacks	Colchicine
TRAPS	*TNFRSF1A* Chromosome 12	Autosomal dominant, can be *de novo*	Northern European but reported in many ethnic groups	Childhood/ early adult	Usually none	Prolonged symptoms	More than a week, may be very prolonged	Variable, may be continuous	Marked acute phase response during attacks. Low levels of soluble TNFR1 when well	Etanercept High-dose corticosteroids
HIDS	*MVK* Chromosome 12	Autosomal recessive	Northern European	Infancy	Immunizations	Diarrhoea and lympha-denopathy	3–7 days	1–2-monthly	Elevated IgD & IgA, acute phase response, and mevalonate aciduria during attacks	Anti-TNF and anti IL-1 therapies

(*continued*)

Table 4.24 (*Contd.*)

Periodic fever syndrome	Gene	Mode of inheritance	Predominant ethnic groups	Usual age at onset	Potential precipitants of attacks	Distinctive clinical features	Typical duration of attacks	Typical frequency of attacks	Characteristic laboratory abnormalities	Treatment
CAPS	*NLRP3* Chromosome 1	Autosomal dominant or sporadic	Northern European	Neonatal/ infancy	Marked diurnal variation Cold environment but less marked than in FCAS	Severity spectrum including: Urticarial rash Conjunctivitis Sensorineural deafness Aseptic chronic meningitis Deforming arthropathy	Continuous often worse in the evenings	Often daily	Varying but marked acute phase response most of the time	

PAPA	*PSTPIP1 (CD2BP1)* Chromosome 15	Autosomal dominant	Northern European (only 3 families reported)	Childhood	None	Pyogenic arthritis, pyoderma gangrenosum Cystic acne	Intermittent attacks with migratory arthritis	Variable, and may be continuous	Acute phase response during attacks	Anti-TNF therapy or anti IL-1 therapies
DIRA	*IL1RN* Chromosome 2	Autosomal recessive	Hispanic and European (few families reported)	Neonatal	None	Sterile multifocal osteomyelitis, periostitis, and pustulosis	Continuous	Continuous	Marked acute phase response	IL-1ra
Blau syndrome	*NOD2 (CARD15)* Chromosome 16	Autosomal dominant	None	Childhood	None	Granulomatous polyarthritis, iritis, and dermatitis	Continuous	Continuous	Sustained modest acute phase response	Corticosteroids

Inherited fever syndromes

Familial Mediterranean fever is commonest in Middle Eastern populations (prevalence 1/250 to 1/1000) but occurs worldwide. It is inherited recessively due to mutations in the *MEFV* gene on chromosome 16.

Clinical features

- Attacks occur irregularly and may be precipitated by minor physical or emotional stress, the menstrual cycle, or diet.
- Attacks resolve within 72h and the clinical features are:
  - Fever
  - Aseptic peritonitis in 85%
  - Pleuritic chest pain in 40%
  - Erysipelas-like rash occurs in 20%
  - Meningitic headache rarely
  - Orchitis rarely
  - Joint involvement is rare and generally mild affecting the lower limbs.
- Acute attacks are accompanied by a neutrophil leucocytosis and a dramatic acute phase response.
- Protracted febrile myalgia is a very rare complication, characterized by severe pain musculature and can be accompanied by a vasculitic rash; it usually responds to high-dose corticosteroid therapy.

Diagnosis

Supported by DNA analysis but remains clinical and centres on the history of recurrent self-limiting attacks of fever and serositis that are prevented by colchicine.

Treatment

- Colchicine has now been licensed by the US Food and Drug administration for the prophylactic treatment of FMF from the age of 4yr upwards.
- Continuous use prevents or substantially reduces symptoms of FMF in at least 95%, and almost completely eliminates the risk of developing AA amyloidosis.
- The mechanism of action of colchicine remains incompletely understood but most patients respond to between 250 microgrammes and 2mg daily.

Long-term complications

- Life-long treatment is required but in general the long-term outlook is excellent.
- Prior to colchicine, 60% of Turkish patients developed AA amyloidosis, effective long-term colchicine prophylaxis should completely prevent this.
- Destructive arthritis is very rare.
- Growth, educational achievement and fertility appear to be normal for both sexes once treated, but otherwise severe disruption to development, education and family life results from the recurrent attacks.

Tumour necrosis factor-receptor associated periodic syndrome (TRAPS) is very rare with an estimated prevalence of about 1 per million in Europe. It is an autosomal dominant disease where there is usually a family history. It occurs in many ethnic groups and presentation is usually before the age of 4yr.

Clinical features

TRAPS attacks are often far less distinct than in FMF and may be precipitated by minor stress, travel, the menstrual cycle or diet. Typical features are:

- Prolonged attacks lasting 1–3 weeks (symptoms are near continuous in 30%).
- ~50% give no clear family history.
- >95% of patients experience fever.
- 80% classically have arthralgia and myalgia often with centripetal migration.
- Abdominal pain occurs in 80% of patients.
- Rash (erythematous, oedematous plaques, discrete reticulate or serpiginous lesions) occurs in 70% of patients.
- Other features include:
  - Headache
  - Pleuritic pain
  - Lymphadenopathy
  - Conjunctivitis and periorbital oedema.
- Symptoms are accompanied by a marked acute phase response.

Diagnosis

Genetic testing is central to diagnosis. One difficulty is interpretation of the significance of 2 common polymorphisms, R92Q (Caucasian) and P46L (African/Arab origin). Both are present in ~4% of normal population but can be associated with a mild inflammatory syndrome.

Treatment

- Acute attacks respond to high-dose corticosteroids but this does not reduce the frequency of attacks.
- Etanercept is useful in some patients, but infliximab and other monoclonal antibodies to TNF exacerbate the attacks.
- IL-1 blockade seems to be the most effective treatment: recombinant IL-1 Ra (anakinra) is effective in ~80% cases but needs to be injected daily. Long-acting IL-1 blocking agents such as canakinumab may be used more frequently for TRAPS in the future.

Long-term complications

- Life-long treatment is required but, in general, the long-term out look is good.
- Without effective long-term treatment >25% patients developed AA amyloidosis.
- Growth, educational achievement, and fertility appear to be near normal for both sexes only if treated. Otherwise the child's development, education, and family life are severely compromised.

Mevalonate kinase deficiency (MKD) also known as hyperimmunoglobulin D periodic fever syndrome (HIDS) is an autosomal recessive disease. MVK is the enzyme after HMG CoA reductase, most mutations found in this syndrome reduce enzyme activity by >90%. Mutations resulting in near complete absence of enzyme activity cause a much more severe disease called mevalonic aciduria (MVA) with severe mental retardation. MKD is extremely rare, most patients are North European with a concentration in Holland and indeed it used to be called 'Dutch fever', although it occurs in other ethnicities. Usually the onset of MKD is below 1yr of age.

Clinical features

- Attacks occur irregularly and may be precipitated by vaccination, minor trauma, surgery, or stress.
- Attacks last 4–7 days and consist of:
  - Fever
  - Unilateral or bilateral cervical lymphadenopathy
  - Abdominal pain with vomiting and diarrhoea
  - Headache, arthralgia, large joint arthritis, erythematous macules and papules, and aphthous ulcers are also common
  - History of high fevers or a full attack with vaccination.
- Attacks are often less severe in adult life.

Diagnosis

- A high serum IgD, IgE, and IgA concentration are seen although these are not specific.
- Presence of mevalonic acid in the urine during attacks.
- A mutation in both alleles of the *MVK* gene can be identified in most patients.

Treatment

- Etanercept is useful in some patients.
- IL-1 blockade seems to be the most effective treatment anecdotally. Recombinant IL-1 Ra (anakinra) can either be used continuously or to abort attacks.
- Statins do not appear to be useful

Long-term complications

- Symptoms may partially improve with age.
- AA amyloidosis has been reported but appears less common than in FMF, TRAPS, or CAPS.

Cryopyrin associated periodic syndrome (CAPS)

CAPS comprises an overlapping severity spectrum ranging from mild to severe otherwise known as familial cold autoinflammatory syndrome (FCAS); Muckle–Wells syndrome (MWS); and chronic infantile neurological, cutaneous, and articular syndrome (CINCA), which is known in the US as neonatal onset multisystem inflammatory disease (NOMID). CAPS is associated with mutations in NLRP3/CIAS1 on chromosome 1q44, encoding a key component of the IL-1 activation complex, called the inflammasome. Dominant inheritance occurs in about 75% of patients with FCAS and MWS, whereas CINCA is usually due to *de novo* mutations. Most reported patients are Caucasian but cases have been described from

South Asia and elsewhere. Onset of disease is usually in early infancy, often from birth, and there is no sex bias.

Clinical features

- In FCAS, attacks of fever, urticarial rash, arthralgia, and conjunctivitis are precipitated by exposure to cold or damp conditions.
- In MWS, attacks usually occur daily often in the afternoon and evenings although there may be a degree of cold exacerbation. Acute symptoms are fever, urticarial rash, arthralgia and myalgia, conjunctivitis, headache, and fatigue. The rash can be persistent. Deafness occurs later and is often missed in the early stages.
- In CINCA/NOIMID there is continuous inflammation with additional severe chronic aseptic meningitis, raised intracranial pressure, uveitis, deafness, and arthropathy.

Diagnosis

Patients with FCAS and MWS have mutations in *NLRP3*. Mutations are present in only 50% of CINCA/NOMID patients.

Treatment

The treatment of choice is IL-1 blockade with anakinra or with 2 other licensed therapies: the fully human anti-IL-1beta antibody canakinumab; or IL-1 Trap (rilonacept).

Long-term complications

- AA amyloidosis occurs in ~25% of patients.
- Complications of chronic CNS inflammation—these are most severe in CINCA but are also seen in MWS:
  - Sensorineural deafness in 40%
  - Blindness due to optic atrophy or uveitis
  - Developmental delay.
- Arthropathy causes cartilage and bony overgrowth especially affecting the patella. Joint destruction can occur. In 17%, clubbing of the finger nails is seen.

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome

- This is an exceptionally rare autosomal dominant disease caused by mutations in the proline serine threonine phosphatase-interacting protein 1 (*PTSTPIP*) gene encoding a protein also known as CD2 binding protein 1 (CB2BP1).
  - The underlying pathogenesis remains poorly understood although there is evidence that CD2BP1 interacts with pyrin.
- It is characterized clinically by severe acne and recurrent pustular sterile arthritis which typically occurs after minor trauma.
- Early reports suggest that therapy with anakinra may be effective, especially for the skin lesions.

Deficiency of the IL-1 receptor antagonist (DIRA)

- This autosomal recessive disease was first described in 2009 with very few affected families known and is due to mutations in *IL1RN* resulting in a total deficiency of IL-1 receptor antagonist.

- Presents in the immediate neonatal period with a pustular rash, joint swelling, osteolytic lesions, and periosteitis typically affecting the distal ribs and the long bones.
- Treatment is anakinra with good responses seen in all cases treated so far.

Blau syndrome (see 🕮 Sarcoidosis, p 300)

- A sarcoid-like autosomal dominant syndrome with granulomatous infiltration of the skin, joints and sometimes viscera associated with uveitis.
- Histologically it is indistinguishable from sarcoid and is associated with missense mutations in *NOD2/CARD15*.
- Treatment is with corticosteroids.

Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA)

- This was first described in 1987 (as Marshall's syndrome) and is of unknown aetiology. It is the most common periodic fever syndrome in the paediatric age group and does not appear to be a monogenetic disease.
- The diagnosis is clinical and is suggested by the presence of the following in the absence of evidence of recurrent upper respiratory tract infections or cyclic neutropenia:
  - Regular recurrent fever of early onset
  - Oral apthous ulcers
  - Cervical lymphadenopathy
  - Pharyngitis
- The 1st-line treatment of PFAPA is a single dose of corticosteroid (1–2mg/kg given at the start of the attack). Alternative treatments include tonsillectomy (approximately 50% success reported. Colchicine, cimetidine, or anakinra maybe useful but the response is unpredictable.
- In general the prognosis is good and most children will outgrow their symptoms by adolescence.

Chronic recurrent multifocal osteomyelitis

Background

- CRMO is an auto-inflammatory disorder associated with non-infective painful inflammation of bones and may be associated with SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), sacroiliitis, psoriasis, or inflammatory bowel disease, with reported frequency of association of CRMO with SAPHO syndrome or psoriasis varying from 7.5–23%.
  - The presence of HLA-B27 is ↑ (21% reported) suggesting an overlap between CRMO/SAPHO and spondyloarthropathies; indeed some patients may develop persistent arthritis typical of enthesitis related arthritis (see 🕮 JIA, p 129).
- The diagnosis of CRMO is based on a combination of clinical, radiological, and histopathological features. The major and minor diagnostic criteria of non-bacterial osteitis (NBO) are included in Table 4.25.

Clinical presentations

- Predominantly a disease of young ♀ (85% girls, mean age of 10yr) although can occur *de novo* in adults.
- Typically, acute or insidious onset with unifocal or multifocal bone pain, nocturnal pain, and sometimes fever and bony lesions may be associated with an asymmetrical inflammatory arthritis. Inflammatory markers may be raised and are useful to follow disease activity. ANA is usually negative and HLA B27 may be positive.
- Lesions can occur at any site, lower limbs are most frequently affected, followed by clavicle, spine, ribs, and mandible (median number of bony lesions is 3.5). Isolated swelling of the medial clavicle is common.
- Persistence of disease is ↑ with greater number of initial bony lesions and in younger children (median duration of active disease 2–3yr).

Management

- The main differential is exclusion of infection and malignancy and often requires multi-specialist input (including radiology, infectious diseases, orthopaedics, and paediatric rheumatology).
- X-ray may be non-specific (e.g. soft tissue swelling, localized osteopenia, periosteal reaction or bony expansion)—typically lytic and sclerotic lesions in the metaphyses of long bones and medial clavicles are observed (Fig. 4.17).
- Radioisotope bone scan detects 'hot spots' as evidence of inflammatory change (Fig. 4.18).
- MRI with gadolinium contrast is very sensitive to inflammatory changes and best identified on T1 sequences.
- Bone biopsy may be necessary to exclude infection or malignancy, and is recommended in most cases.
- There are no validated disease activity scores in CRMO, but in practice, the degree of clinical involvement, pain scores, acute phase reactants,

impact on physical function (e.g. CHAQ see 📖 p 45), and imaging (and especially MRI) are most helpful.

- There are no clinical trials to guide medical therapy:
  - Antibiotics have not been shown to be effective.
  - NSAIDS may be an effective 1st-line treatment for symptom control.
  - Pamidronate (see 📖 p 431), helps reduce symptoms in acute CRMO and efficacy may be related to anti-osteoclastic and/or anti-inflammatory activity. Regular infusions do not appear to reduce the frequency or severity of flares.
  - Corticosteroids can be useful particularly if there is associated arthritis or synovitis.
  - MTX has not been shown to reduce the severity or frequency of flares but may improve any associated arthritis.
  - Anti-TNF therapy (see 📖 p 393) is used in severe cases unresponsive to pamidronate with clinical improvement reported albeit in small case series only.

Table 4.25 Major and minor criteria for non-bacterial osteitis (NBO)

Major diagnostic criteria	Minor diagnostic criteria
Radiologically proven osteolytic/sclerotic bone lesion	Normal blood count, systemically well
Multifocal bone lesions	Mild/moderate elevation CRP or ESR
Palmoplantar pustulosis (PPP) or psoriasis	Observation time >6 months
Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis	Hyperostosis
	Other autoimmune disease (excluding PPP or psoriasis)
	1st- or 2nd-degree relatives with autoimmune, auto-inflammatory disease or NBO

NBO confirmed by 2 major criteria or 1 major and 3 minor criteria.

Further reading

Jansson A, Renner ED, Ramser J, *et al.* Classification of non-bacterial osteitis. *Rheumatology* 2007; **46**:154–60.

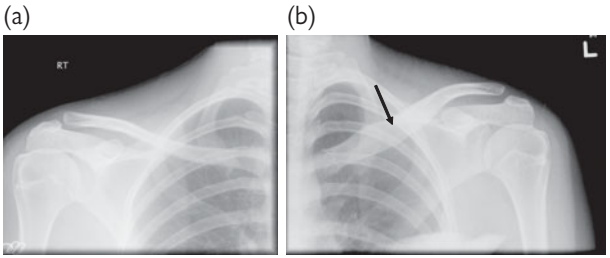

Fig. 4.17 Plain radiographs of (a) right and (b) left clavicle. Left clavicle shows cortical expansion and sclerosis (arrow).

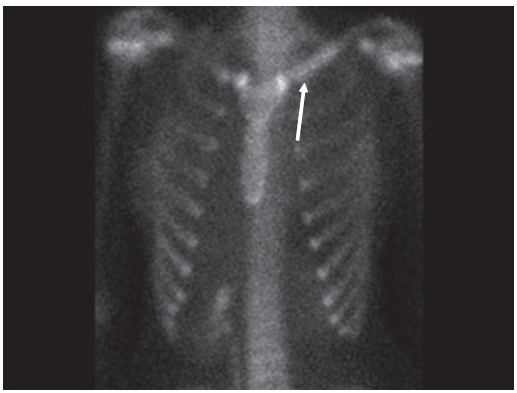

Fig. 4.18 Radioisotope bone scan showing ↑ uptake in left clavicle.

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 hypotheses. Candidate genes may reside in loci that influence regulation of antigen presentation and/or T-cell function resulting in ↑ granulomata formation and fibrosis.
- There is an ↑ incidence of other autoimmune diseases in patients with sarcoidosis.

Epidemiology

- Prevalence varies worldwide and by age: primarily a disease of 20–40yr-olds. Twice as common in ♀.
- 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.
- In Denmark, where the disease has a high prevalence, the incidence in children <15yr was 0.22–0.27 per 100 000/yr; 0.06 per 100,000 children aged <4yr; and ↑ gradually with age to 1.02 per 100,000 in children aged 14–15yr.

Genetics of sarcoidosis

- There is an ↑ incidence of sarcoidosis in certain families.
- An HLA association has been described including DQB1*0603, DQB1*0604, and DPB1*0201.
- In the USA, familial clusters are observed in African Americans in 19%, compared to 5% in white families.
- Monozygotic twins are 2–4× more concordant for disease than dizygotic twins.
- Recent studies suggest a unique candidate gene *BTNL2* in the MHC II region on chromosome 6.
- Specific HLA genotypes appear to confer a predisposition to disease phenotype. For example, HLA-DQB1*0201 and HLA-DRB1*0301 are associated with acute disease and a good prognosis.

Relationship between early-onset sarcoidosis (EOS) and Blau's syndrome

- EOS refers to young children with disease onset in the first 5yr 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 1st 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—autosomal dominant granulomatous disease with 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

Multisystemic disease so presentation can vary greatly.

- *Multisystemic 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 described previously.
- *Renal and biochemical findings:*
  - Renal involvement is rare in children and adults, and may be asymptomatic. Renal involvement is usually 2° to hypercalcaemia and/or hypercalciuria (occurring in ~30% of paediatric sarcoid cases) rather than renal infiltration with granulomata.
  - Polyuria, enuresis (2° nephrogenic diabetes insipidus 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 also reported.
- *Pulmonary disease*—is the most commonly involved organ.
  - Chronic cough with or without dyspnoea.
  - 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 50% of all children with sarcoidosis demonstrate restrictive lung disease on pulmonary function tests.
  - An obstructive pattern 2° 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 children:
  - 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 hypopigmented 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 described in sarcoid:
  - Uveitis—general term used to describe inflammation of the uvea (comprising 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 teno-synovitis 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. 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, and 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).
  - Blau's syndrome.
  - sJIA.
  - 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 findings and useful investigations include:

- Leucopenia, thrombocytosis, eosinophilia relatively common, high ESR and CRP.

- Hypercalcaemia—varies from 2–60% 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:UC ratio, tubular function abnormalities.
- 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.
- Recent studies have suggested that serum chitotriosidase concentrations may be a useful marker for monitoring disease activity in sarcoidosis but this remains a research tool at present.
- 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.
- ↑ sensitivity of detection of pulmonary involvement with high-resolution CT of chest.
- Pulmonary function tests including transfer factor.
- MRI of brain for suspected neurosarcoid.
- FDG-PET scanning may be useful in assessing the extent of organ involvement and planning diagnostic biopsy.
- Tissue biopsy—skin, lung, salivary glands, muscle. 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: MTX, or AZA.
  - An RCT of MTX in 24 adults with sarcoid demonstrated steroid sparing efficacy.
- Occasionally cyclophosphamide or ciclosporin have been used for more aggressive disease.
- Biologic therapy including anti-TNFα has been used in some severe cases.
- Ocular involvement usually responds to corticosteroid administered locally, or systemically.

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.
- A recurrence after >1yr of remission is uncommon, but can occur and may develop at any age and in any organ.
  - Long-term follow-up of 46 Caucasian Danish children reported 78% complete recovery; 11% still had chronic active disease with multiorgan involvement; 7% died; and 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 patients without persisting active disease, health-related QoL scores were similar to the reference population.
  - In another series of 19 children followed-up for a mean of 21yr: 37% had persistent abnormalities on CXR, 68% had impaired lung function, and 63% had abnormal findings on echocardiography.

Further reading

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Macrophage activation syndrome

Introduction

MAS is the term used for 2° haemophagocytic lymphohistiocytosis (HLH) occurring in rheumatological diseases. It is potentially fatal with reported mortality rates of 8–22%.

Pathophysiology

- The exact pathophysiology remains unknown.
- It includes dysregulation of T lymphocytes, natural killer (NK) cells, excessive cytokine production, abnormal proliferation of macrophages, cytopenias, and coagulopathy.
- Macrophages phagocytose haematopoietic cells in the bone marrow.
- Proposed triggers for MAS include infections (see following list) and in the context of sJIA some medications, e.g. NSAIDs, but importantly *MAS can also precipitated by persistently active inflammatory rheumatologic disease alone*.

Potential infective triggers of MAS

- Epstein–Barr virus
- Varicella zoster virus
- Coxsackie virus
- Parvovirus B19
- Hepatitis A virus
- *Salmonella enteritidis*
- *Enterococcus*.

Diagnosis

- Early recognition and treatment is important on account of the significant morbidity and mortality.
- Diagnosis is often difficult because the features of MAS are similar to the underlying active rheumatological inflammatory disease (Table 4.26).
- The diagnostic criteria of the Histiocyte Society (Box 4.9) are the most universally recognized but have multiple limitations. The criteria are not absolute and need to be interpreted in the context of the clinical case. For example, in sJIA relative reductions of blood counts are more important than the absolute degree of cytopenia.
- Diagnosis can be made in the absence of bone marrow haemophagocytosis, and in the absence of absolute cytopenia.

Rheumatological diseases which may be complicated by MAS

Commonly

- sJIA (most commonly)
- SLE
- Kawasaki disease.

Less commonly

- JDM
- Polyarticular JIA
- PAN

- SSc
- MCTD
- Sarcoidosis
- Sjögren's syndrome
- CINCA.

Characteristic clinical features

- Unremitting high fever
- Hepatosplenomegaly
- CNS dysfunction (irritability, disorientation, headache, seizures, coma)
- Purpuric rash or haemorrhages.

Other clinical features

- Renal involvement
- Lymphadenopathy.

Box 4.9 Diagnostic guideline for haemophagocytic lymphohistiocytosis: HLH 2004 protocol

Establish the diagnosis if either (1) or (2) is fulfilled:
(1) A molecular diagnosis consistent with HLH.
(2) Diagnostic criteria for HLH fulfilled (5 or more out of the 8 criteria):

- (a) Fever
- (b) Splenomegaly
- (c) Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood:
  - (i) Haemoglobin <9.0g/dL (in infants <4 weeks: haemoglobin <10.0 g/dL)
  - (ii) Platelets $<100 \times 10^9$/L
  - (iii) Neutrophils $<1.0 \times 10^9$/L
- (d) Hypertriglyceridaemia and/or hypofibrinogenaemia: fasting triglycerides ≥3.0mmol/L (>265mg/dL), fibrinogen ≤1.5g/L
- (e) Haemophagocytosis in bone marrow, spleen, lymph nodes or cerebrospinal fluid: no evidence of malignancy
- (f) Low or absent natural killer cell activity (according to local laboratory reference)
- (g) Elevated ferritin (≥500mcg/L)
- (h) Soluble CD25 (i.e. soluble interleukin-2 receptor) above normal limits for age.

Adapted with permission from Henter JI, Horne A, Aricó M, *et al.* HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; **48**:124–31.

Recognized haematological features

- Low haemoglobin
- Low WCC and neutrophil count
- Low platelets
- Normal or falling ESR
- Raised liver transaminases
- Prolonged PT and PTT
- Low fibrinogen
- Very high ferritin (>500 microgrammes/L possible HLH, and >10,000 microgrammes/L very likely HLH)
- High D-dimers
- Raised LDH
- Low albumin
- Raised triglycerides
- Raised sCD25 and CD163
- Low NK cell activity
- Bone marrow haemophagocytosis
- Abnormal perforin and MUNC expression—although usually associated with 1° HLH this may also be a feature of 2° HLH in sJIA.

Important: laboratory values recognized to be falling or to be incongruous with the level of inflammation clinically evident may allow earlier recognition of developing MAS.

Management

1st-line—successful alone in almost 50% of cases:

- Supportive treatment—very important in all cases.
- Corticosteroid is the essential 1st-line treatment and should be started immediately with pulse high-dose methylprednisolone (30mg/kg/day with a maximum dose of 1g). This may be required for several days and is followed by maintenance oral prednisolone at least 1mg/kg/day or the equivalent corticosteroid intravenously depending on the patient condition.

2nd-line—chosen depending on progress and extent of multiorgan involvement:

- Ciclosporin 3–5mg/kg/day PO or 1–2mg/kg/day IV.
- IVIg 1–2g/kg—also useful when diagnosis is unclear, i.e. whether this is true MAS or sepsis.
- Etoposide 150mg/m^2 twice weekly (day 1 and 4) for the first 2 weeks then once-weekly for another 6 weeks—effective, however concerns exist regarding reported risk of 2nd malignancies. In patients with refractory disease therapy based on protocols for 1° HLH might be required.

Alternative 2nd-line management options with biologics—some successful treatment has been reported with biologics including anakinra and etanercept however outcome data is currently limited:

- Etanercept 0.4mg/kg (maximum 25mg) twice-weekly SC injection
- Anakinra 2mg/kg (maximum 100mg) once daily SC injection. Higher doses have been used anecdotally, mainly for MAS 2° to sJIA—seek expert advice

Table 4.26 Comparison of clinical and laboratory features of sJIA and MAS

Feature	sJIA	MAS
Fever pattern	Quotidian	Unremitting
Rash	Evanescent, maculopapular	Petechial or purpuric
Hepatosplenomegaly	Yes	Yes
Lymphadenopathy	Yes	Yes
Arthritis	Yes	No
Serositis	Yes	No
Encephalopathy	No	Yes
White cells and neutrophil count	High	Low
Haemoglobin	Normal or low	Low
Platelets	High	Low
ESR	High	Normal or sudden fall
Bilirubin	Normal	Normal or high
ALT/AST	Normal or slightly high	High
PT	Normal	Prolonged
PTT	Normal	Prolonged
Fibrinogen	High	Low
Ferritin	Normal or high	High or very high
D-dimers	High	Very high

Primary immunodeficiency and rheumatological disease

1° immunodeficiency disorders (PID) are characterized by:

- Unusual susceptibility to (and recurrent) infections presenting from birth/early childhood.
- Deregulation of immune functions resulting in:
  - Autoimmunity (mediated by auto-reactive B or T lymphocytes) or as
  - 'Auto-inflammatory' disorders (see 📖 Periodic fever syndromes/ autoinflammatory disease, p 288) with episodes of seemingly unprovoked inflammation, without presence of auto-reactive B or T lymphocytes (Figure 4.19).
- Many of the conditions recognized are summarized in Box 4.10.

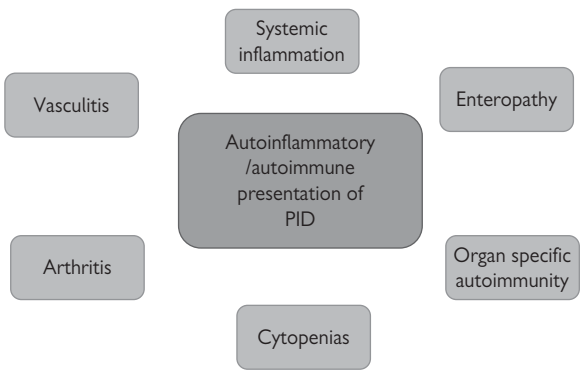

Fig. 4.19 Auto-immune/-inflammatory presentation of PID.

The most common clinical features (i.e. when to 'think of' PID)

- Chronic (non-septic) arthritis and features of systemic autoimmunity (fever, vasculitis, dermatomyositis, and SLE-like syndromes), as well as organ-specific autoimmunity, in particular cytopenias, are described in well-defined *PID syndromes* (e.g. Wiskott–Aldrich and DiGeorge syndromes, the (clinical and genetic), continuum of selective IgA deficiency and common variable immunodeficiency (CVID), hyper-IgM syndrome(s) due to class-switch recombination (CSR) process failures.
- Vasculitis, cytopenias, and features of Omenn syndrome are associated with 'leaky' mutations (less-severe mutations are called 'leaky' mutations because some function still 'leaks through' into the phenotype) in genes causing severe combined immunodeficiency (*SCID*).
- Different features of autoimmunity and/or immune dysregulation, including vasculitis, are increasingly reported in patients with other, less well-defined *'combined immunodeficiencies (CID)*', some of which have recently been characterized (e.g. Aicardi–Goutiere syndrome [AGS], spondyloenchondrodysplasia [SPENCD]).

- *Monogenic autoimmune diseases* presenting with autoimmunity as the main feature of the underlying 1° (monogenic) immunodeficiency:
  - Autoimmune lymphoproliferative syndrome (ALPS) is due to mutations of genes involved in the apoptosis (programmed cell death pathway), can present clinically with features of *systemic autoimmunity* such as SLE.
  - Autoimmune polyendocrinopathy, candidasis, ectodermal dystrophy (APECED) and immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndromes present with *organ-specific autoimmunity* (i.e. polyendocrinopathy, enteropathy, cytopaenias):
    - — APECED or APS-1 (autoimmune polyendocrinopathy syndrome type 1) are due to mutations in *AIRE* (autoimmune regulator) which plays a crucial role in central (thymic) tolerance.
    - — IPEX syndrome is due to mutations in *FOXP3* which plays a crucial role in peripheral tolerance.
- ***'Classical' disorders of the innate immunity'*** include disorders of phagocyte function (e.g. chronic granulomatous disease [CGD]) and/or the classical complement activation pathway (in particular deficiencies of C1q-r-s, C2, C1 esterase inhibitor) which may present with autoimmune features such as SLE-like or dermatomyositis-like syndromes.
- ***Newly defined innate immune system disorders:***
  - Mutations (causing loss of function) of genes coding for different molecules of innate immune system signalling pathways, normally leading to an effective inflammatory process by releasing pro-inflammatory cytokines (such as IL-1 and -6) are characterized by 'peculiar' absence of the inflammatory response (no fever or rise in CRP) in the light of an overwhelming, usually bacterial infection. (*NEMO, IRAK4, MyD88*).
  - In contrast, the 'gain-of-function' mutations of the genes involved in the same process of IL-1 production, but via intracellular 'inflammasomes' (such as *NLRP3*), cause unprovoked and ongoing inflammation and manifest with fevers, rashes, arthritis, vasculitis and bone lesions, the clinical hallmark of cryopyrin associated periodic fever syndrome *(CAPS)* and other *auto-inflammatory syndromes* (see 📖 Periodic fever syndromes/autoinflammatory disease, p 288).
  - Although not as often as expected, some of these patients do present with autoimmune features such as colitis in *NEMO* mutation(s) (otherwise presenting with ectodermal dysplasia [EDA-ID]).
  - Uncontrolled macrophage activation leading to *haemophagocytic lymphohistiocytosis (HLH)* results from mutations of several genes involved in perforin-related cytolysis, intracellular vesicle trafficking (*Chediak–Higashi, Griscelli and Hermansky–Pudlak syndrome*s) and/or signalling (*lymphoproliferative syndrome*s; X-linked and/or autosomal recessive). Whilst these 1° immunodeficiency disorders were recently re-classified as auto-inflammatory syndromes, some patients with clinically well defined rheumatological conditions such as sJIA and/or SLE can present with similar features of MAS (see 📖 MAS, p 305).
  - Current and future research into this area provides new insights in the underlying pathophysiology, and hopefully will result in successful targeted therapies such as the use of IL-1 blockade in CAPS (see 📖 Periodic fever syndromes/autoinflammatory disease, p 288), IL-1, IL-6 and TNFα blockade in JIA.

Further reading

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Box 4.10 PID with features of autoimmunity and/or rheumatic/connective tissue disorders

Well-defined PID syndromes

- Selective IgA deficiency—common variable immunodeficiency
- DiGeorge syndrome (Table 4.28)
- Wiskott–Aldrich syndrome
- Hyper-IgM syndromes (class-switch recombination (CSR) deficiencies)
- Severe combined immunodeficiency syndromes (SCID).

Innate immune system disorders

'Classical'

- Neutrophil disorders (chronic granulomatous disease—CGD)
- Complement disorders (classical activation pathway component deficiencies—C1-q-r,-s, C2, C4, C5-8, C1 esterase inhibitor).

'Newly defined'

- TLR/IL-1 receptor (TIR) signalling pathway (*IRAK4; MyD88; NEMO*).

Haemophagocytic syndromes ('macrophage activation')

- Perforin-related cytolysis (perforin, syntaxin-11, UNC 13-D, UNC 18–2)
- Intracellular vesicle trafficking (Chediak–Higashi, Griscelli, Hermansky–Pudlak syndromes)
- Intracellular signalling (lymphoproliferaive syndromes; X-linked (SH2DIA and XIAP) and/or autosomal recessive (ITK).

Monogenic autoimmune diseases

- Autoimmune lymphoproliferative syndrome (ALPS)
- Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX)
- Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy syndrome (APECED)/autoimmune polyendocrinopathy syndrome type I (APS I).

Auto-inflammatory disorders (see 🕮 Periodic fever syndromes/ autoinflammatory disease, p 288)

- Cryopyrin-associated periodic fever syndromes (CAPS):
  - Chronic infantile neurological cutaneous and articular syndrome (CINCA)/neonatal-onset multisystem inflammatory disease (NOMID)
- Mevalonic kinase deficiency (MKD)/hyper-IgD syndrome (HIDS)
- TNF receptor-associated periodic fever syndrome (TRAPS)
- Deficiency of IL-1 receptor antagonist (DIRA)
- Chronic recurrent multifocal osteomyelitis (CRMO)
- Majeed syndrome
- *NOD2*-associated granulomatous inflammatory syndromes (early onset sarcoidosis (EOS); Blau syndrome; Crohn's disease).

Newly defined (combined) immunodeficiencies

- Aicardi–Goutieres syndrome (AGS)
- Spondyloenchondrodysplasia (SPENCD).

Mucopolysaccharidoses (MPS) and mucolipidoses (ML)

- Rare progressive storage disorders with a spectrum of clinical features (Table 4.27) varying from facial dysmorphism, bone dysplasia, hepatosplenomegaly, neurological abnormalities, developmental regression, and a reduced life expectancy at the severe end of the clinical spectrum to an almost normal clinical phenotype and life span in patients with more attenuated disease.
- MPS is due to a reduction of activity in lysosomal enzymes which break down glycosaminoglycans (GAGs)—long chains of carbohydrates that help build bone, cartilage, tendons, corneas, skin, and connective tissue. Over time, GAGs in 3 different forms—dermatan sulfate (DS), heparan sulfate (HS), or keratan sulfate (KS)—accumulate in the cells, blood and connective tissues resulting in progressive skeletal dysplasia, dwarfism, marked coarsening of the facial features. In addition, deposition of GAG leads to corneal clouding and neurological deterioration.
- ML is due to multiple enzyme deficiencies 2° to failure of targeting of enzymes to lysosome.
- Phenotypic variability (heterogeneity) is very much a feature of MPS disease and within each specific enzyme deficiency there is a very wide spectrum of clinical effects.

Differential diagnosis

- Arthrogryposis
- Juvenile polymyositis and dermatomyositis
- Scleroderma and SSc
- JIA
- Skeletal dysplasia
- Osteogenesis imperfecta.

Investigations

- *Prenatal*—chorionic villus biopsy at around 12th week of pregnancy
  - Amniocentesis: measuring the enzyme activity in cultured amniotic cells in the 15–16th week of gestation or GAGs in cell-free fluid.
- *Postnatal*—urinary glycosaminoglycan as screening test (GAG):
  - White blood cell enzyme assay and cultured cells.
  - Urine oligos and blood gastrin in mucolipidoses.
  - Mutation analysis—possible for all disorders listed.
- *Imaging*—skeletal survey—dysostosis multiplex:
  - Large skull with thickened calvaria, premature suture closure, j-shaped sella turcica, and shallow orbits:
    - — Short, thickened, and irregular clavicles
    - — Short, wide, and trapezoid shaped phalanges
    - — Oar-shaped ribs
    - — Anterior hypoplasia of the lumbar vertebrae with kyphosis
    - — Poorly formed pelvis with small femoral heads and coxa valga
    - — Enlarged diaphyses of long bones and irregular metaphyses
    - — Abnormal spacing of teeth with dentigerous cysts.

  - MRI scan: hydrocephalus, white matter change, cerebral atrophy, arachnoid cysts
  - Echocardiogram: valvular heart disease, ventricular wall thickening
- *Neurophysiology:*
  - Electroretinography: retinal degeneration
  - Nerve conduction study: carpal tunnel syndrome.
- *Audiology*—conductive and neuro-sensory hearing loss.

Management

Apart from MPS I specific treatment is limited for MPS and ML that involve the CNS. In such patients, management has been limited to a supportive one in improving QoL for the child.

Early identification and diagnosis (Fig. 4.20) of the condition is essential and follow-up will require the involvement of multi-agency expertise in specialties including: paediatrician specialized in metabolic disorder, orthopaedic surgeon, ENT surgeon, neurologist, physiotherapist, occupational therapist, cardiologist, and rheumatologist.

Enzyme replacement therapy (ERT)

- *Laronidase* therapy ↑ catabolism of GAGs, which accumulate with MPS I. Laronidase therapy has shown to improve walking capacity and pulmonary function.
- *Idursulfase* is a purified form of human iduronate-2-sulfatase, a lysosomal enzyme. It is used to replace insufficient levels of the lysosomal enzyme iduronate-2-sulfatase in MPS II, Hunter syndrome.
- *Galsulfase* is a recombinant form of galactosamine 4 sulphate sulphatase. It is used as replacement therapy in MPS VI (Maroteaux–Lamy syndrome).

All ERTs are administered by weekly IV infusions. ERT for MPS IVA is at an advanced stage of development and intra thecal ERT for MPS IIIA is in early phase II/III clinical trials.

Haematopoietic stem cell transplantation

Offered to severely affected patients, usually Hurler disease, and is shown to improve life span. Skeletal manifestations, cardiac valve lesions, and corneal clouding do not improve with stem cell transplantation.

Hearing and vision

- Hearing aids, grommet placement, and visual aids are beneficial.
- Corneal grafting.

Respiratory

- Sleep apnoea may necessitate treatment with high-pressure CPAP with supplementary oxygen.
- Tracheostomy.

Central nervous system

- Ventriculoperitoneal(VP) shunting is indicated in moderate to severe hydrocephalus.
- Carpal tunnel syndrome with surgical decompression of median nerve.

Table 4.27 Classification and clinical features

Types	Name	Inheritance	Enzyme defect	Clinical manifestations
MPS				
IH	Hurler	AR	Alpha-L iduronidase	Corneal clouding, coarse facies, dysostosis multiplex, hernia, kyphosis, hepatomegaly, severe mental retardation
IS	Scheie	AR	Alpha-L iduronidase	Joint contractures, corneal clouding, valvular abnormalities, carpel tunnel syndrome, hernia
IHS	Hurler/ Scheie	AR	Alpha-L iduronidase	Mild learning disability, mild organ and skeletal involvement
II	Hunter	XR	Iduronate sulfatase	Coarse facial features, skeletal deformities (such as claw hand), joint stiffness, retinal degeneration, hydrocephalus, mental retardation
IIIA	Sanfilippo	AR	Heparan N-sulfatase	Subtypes are not distinguishable clinically, hyperactivity, mental deterioration, developmental delay, coarse hair, hirsutism, mild hepatosplenomegaly, and enlarged head. Severely disturbed social behaviour occurred later in life (e.g. uncontrollable hyperactivity, destructive physical aggression)
IIIB	Sanfilippo	AR	Alpha-N-acetylglucosaminidase	
IIIC	Sanfilippo	AR	Acetyl CoA:alpha-glucosaminide acetyltransferase	
IIID	Sanfilippo	AR	N-acetylglucosamine 6-sulfatase	
IVA	Morquio	AR	N-acetylgalactosamine-6-sulfate sulfatase	Skeletal involvement with spondyloepiphyseal dysplasia, genu valgum, short stature, spinal curvature, odontoid hypoplasia, ligamentous laxity and atlantoaxial instability. Normal intelligence.
IVB	Morquio	AR	Beta-galactosidase	Mild skeletal involvement, normal life span

VI	Maroteaux-Lamy	AR	N-acetylgalactosamine-4-sulfatase	Corneal clouding, coarse facies, joint stiffness, skeletal deformities, heart valvular disease and normal intelligence
VII	Sly	AR	Beta-glucuronidase	Severe form with hydrops fetalis and hepatosplenomegaly in the neonatal period. Corneal clouding, coarse facies, macrocephaly, metatarsus adductus, prominent sternum, pelvic hypoplasia, hepatosplenomegaly, and hernias.
IX		AR	Hyaluronidase	Mild short stature and multiple periarticular soft-tissue masses
Mucolipidoses				
ML I	Sialidosis I	AR	Neuraminidase	Myoclonus and ataxia associated with a macular cherry-red spot, dementia in later life
ML II	I cell	AR	*Phosphotransferase (mutation in *GNTAB* gene alpha sub unit)	Course facies, hepatomegaly, skeletal dysplasia and severe learning difficulties
ML III	Pseudo-Hurler polydystrophy ML III alpha/beta	AR	*Phosphotransferase (mutation in *GNTAB* gene either alpha or beta subunits)	Hepatosplenomegaly, dysostosis multiplex, cardiac valve lesion
ML III	Pseudo-Hurler polydystrophy ML III gamma	AR	*Phosphotransferase (mutation in *GNPTG* gene)	Learning impairment, cardiac valvular lesion, skeletal disease
ML IV		AR	Unknown	Motor impairment, severe mental retardation, retinal degeneration, corneal clouding, iron deficiency anaemia and achlorhydria with elevated blood gastrin levels

*UDP-N-acetylglucosamine: lysosomal hydrolase N-acetylglucosamine-1-phosphotransferase (GNPTAB) enzyme deficiency—enzyme requires the action of 2 genes *GNTAB* and *GNPTG*. Mutations in *GNTAB* are associated with ML II and ML III alpha/beta and mutations in *GNPTG* cause ML III gamma.

Cardiovascular

- Valve replacement surgery. Bacterial endocarditis prophylaxis may be necessary
- Routine evaluation of ventricular function, wall thickness.

Orthopaedic

- Soft tissue surgery with release of contractures
- Corrective osteotomy: valgus deformity
- Posterior spinal decompression and fusion: kyphosis or atlantoaxial subluxation.

Further reading

Manger B. Rheumatological manifestations are the key in early diagnosis of mucopolysaccharidosis type I. *Eur Musculoskeletal Rev* 2008; 1–6.

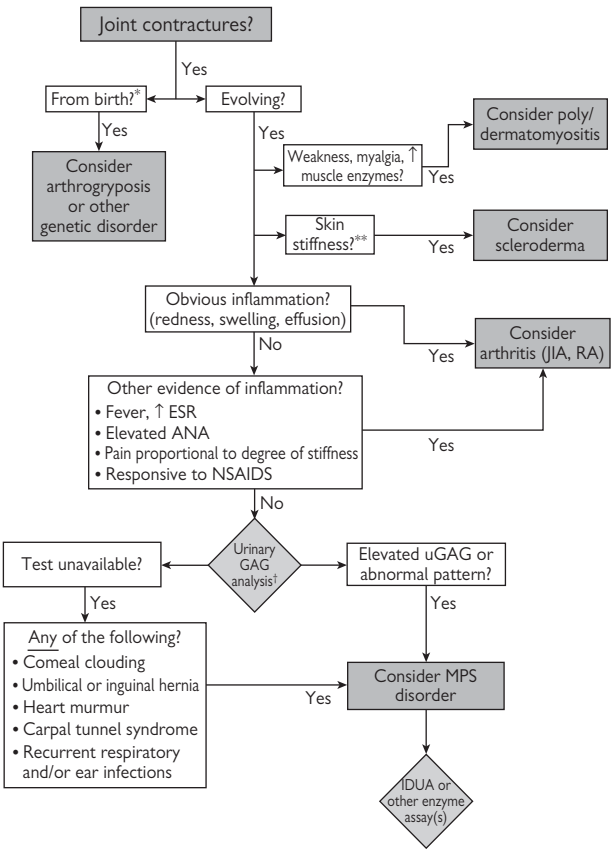

Fig. 4.20 Diagnostic algorithm for attenuated mucopolysaccharidoses. *Newborn infants with the most severe form of MPS I (Hurler syndrome), although normal appearing, often have radiological evidence of bone and joint abnormalities. **Note that overall skin texture in patients with MPS I can be thickened and rough. MPS II and rarely MPS I can be associated with a distinctive skin lesion consisting of white 'pebbly' papules 2–10mm in diameter, sometimes coalescing in ridges. †Authors recommend both quantitative and qualitative (GAG profile) analysis in a reputable laboratory. False negatives can occur with spot screening. IDUA: α-L-iduronidase; uGAG: urinary glycosaminoglycan; JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis. Reproduced from Cimaz R, Coppa GV, Koné-Paut I, et al. Joint contractures in the absence of inflammation may indicate mucopolysaccharidosis *Paediatr Rheumatol* 2009; **7**:18.

Chromosomal abnormalities and associated musculoskeletal morbidity

- Children with chromosomal problems may have significant musculoskeletal (MSK) problems.
- These are often overlooked, especially in the presence of learning difficulties, developmental delay, and other complex needs where the child cannot communicate symptoms and observed motor problems may be ascribed to neurological or other cause.
- Examples of the most common conditions and associated MSK morbidity are given in Table 4.28. The frequency of MSK abnormalities in these conditions is often poorly defined.
- It is important to consider other differentials including metabolic disorders and skeletal dysplasias (see 📖 p 333) especially in the presence of contractures.
  - Most chromosomal problems are also associated with hypermobility, dysmorphism, and short stature.
- Inflammatory arthritis in these children is managed in a similar way to JIA (see 📖 p 155, p 159, and Table 4.29) and require input from an experienced MDT.
  - The use of MTX and biologics in this patient group requires caution as some conditions are prone to malignancy (e.g. Down's syndrome) and anecdotally, these children appear less tolerant of MTX. However, most patients derive benefit from these agents where indicated, and the presence of a chromosomal abnormality per se is not a contraindication to the use of DMARDS or biologics for inflammatory arthritis in this context.

Table 4.28 Chromosomal conditions and musculoskeletal (MSK) problems

Chromosomal condition	MSK abnormalities	MSK presentations and clinical features
Down's syndrome (Trisomy 21) Learning difficulties, upslanting palpebral fissures, epicanthic folds, brachycephaly, cardiac abnormalities	Inflammatory arthritis • Poly or oligo articular • Psoriatic • Small and large joints Cervical spine instability: • Atlanto axial • Occipital cervical Hip dislocation/ subluxation General hypotonia: • Joint hypermobility • Pes planus (flat feet) • Patella dislocation • Scoliosis Other: • Short stature • Metatarsus primus varus • Brachydactyly	Limp, leg-length discrepancy, motor delay. May express no pain, instead behavioural changes, e.g. reluctance to hold hands, reversion to earlier stage of development, morning stiffness.Joint swelling, ↓ or 'normal' range of movement *(remember these children are normally markedly hypermobile therefore an observed 'normal' range of joint movement, especially if symmetrical, may actually signify loss of movement)* Associated psoriatic rash ±nail pitting Asymptomatic, neck pain, limited neck mobility/torticollis, sensory deficit, hyper-reflexia, spasticity Limp, antalgic gait, motor delay Clumsiness, poor-coordination, generalized hypotonia, front of feet pointing away from each other, may be asymptomatic Big toe bending inwards Short fingers
DiGeorge syndrome (22q11 deletion) Immunodeficiency T-cell dysfunction, IgA deficiency hypocalcaemia, facial, pharyngeal and cardiac abnormalities	Inflammatory arthritis Micrognathia and retrognathia Scoliosis, short stature	Limp, leg-length discrepancy, motor delay. Pain, joint swelling, ↓ range of movement Malocclusion, difficulty brushing teeth Feeding difficulties, dentist recognizes problem. Postural shift, altered function, back pain
Turner's syndrome **(X0)** Webbed neck, low hair line, horseshoe kidney, lymphoedema	Inflammatory arthritis: poly or oligo Cubitus valgus Clinodactyly, brachydactyly Blunt fingertips Micrognathia Short stature	Limp, leg-length discrepancy. Pain, joint swelling, ↓ range of movement Wide carrying angle at elbows Curved 5th fingers Short fingers Small jaw, malocclusion

(*continued*)

Table 4.28 (*Contd.*)

Chromosomal condition	MSK abnormalities	MSK presentations and clinical features
Trisomy 8 Learning difficulties thick lips, deep-set and prominent ears, pectus excavatum (mild clinical features often associated with mosacism)	Joint contractures—camptodactyly, clinodactyly Scoliosis Absent patella Micrognathia	Restricted joints—e.g. fixed flexion deformity of interphalangeal joint of little fingers Curved 5th fingers Postural shift Small jaw, malocclusion
18p syndrome Learning difficulties, IgA deficiency	Inflammatory or non-inflammatory arthritis of large joints Short stature	Limp, leg-length discrepancy, pain, morning stiffness, joint swelling, ↓ range of movement
Cystic fibrosis (CF)—see 📖 p 323 Mutations for CF transmembrane conductance transporter, chromosome 7 Detected on screening, failure to thrive, chronic respiratory symptoms, malabsorption	Arthralgia Inflammatory arthritis: • Oligo or polyarticular • Relapsing Hypertrophic pulmonary osteoarthropathy	Troublesome joint pain, occasionally related to ciprofloxacin use Limp, pain, joint swelling, ↓ range of movement Can be associated with erythema nodosum Joint pain and swelling. Consider in long-standing CF and marked finger clubbing.
Neurofibromatosis (NF) *NF1* gene—chromosome 17 2 or more of the following: ≥6 café au lait spots, ≥2 neurofibromata, axillary or inguinal freckling, optic glioma, ≥2 Leish nodules, osseous dysplasia on the sphenoid bone or cortex of a long bone, 1st-degree relative with NF	Scoliosis & kyphosis Short stature Pseudoarthrosis of the tibia or forearm Bone/soft tissue hypertrophy	Usually presents before 10yr of age, May be an incidental clinical finding, back pain, postural shift Bowing of leg or arm Asymmetrical limb length/ macrodactyly

Table 4.28 (*Contd.*)

Chromosomal condition	MSK abnormalities	MSK presentations and clinical features
***NF2* gene**—long arm chromosome 22 Usually presents in adults but childhood cases are reported. May present with VIII nerve masses, family history *NF2*, presence of ≥2 neurofibroma, meningioma, glioma, schwannoma, juvenile posterior capsular lenticular opacity	Spinal tumour	Difficulty walking, pain, postural shift, loss or altered function, neurological signs

Table 4.29 Chromosomal conditions and MSK problems: an overview approach to management

MSK problem	MSK radiological investigations & features	Management
Inflammatory arthritis	If clinical uncertainty, US or contrast-enhanced MRI to identify joint effusions & synovial enhancement. Plain films are of limited use until long-standing arthritis has caused significant joint damage such as joint space narrowing and erosions	Referral to a paediatric rheumatology MDT for confirmation of diagnosis, medical treatment and access to ophthalmology for uveitis screening. Consider broad spectrum of autoimmune disorders
Cervical spine Instability	Cervical spine plain radiograph—as showing ↑ atlanto-dental interval on lateral flexion/extension view (normal <8yr <4mm, >8yr <3mm) MRI may show ligamentous swelling suggestive of instability. CT may show malalignment of vertebrae in the neutral position	Close surveillance, neurosurgical referral Advice to avoid contact sports and to wear a neck collar when travelling in a car.
Hip dislocation/ subluxation	Hip plain radiograph—flared iliac wings, hip dysplasia and or dislocation Hip US may be useful in younger children	Referral to orthopaedics

(*continued*)

Table 4.29 (*Contd.*)

MSK problem	MSK radiological investigations & features	Management
Abnormal foot positioning	Radiology of limited use	Referral to orthotics/podiatry or orthopaedics.
Scoliosis	Spinal plain radiograph	Referral to orthopaedics or spinal surgeon
Hypermobilty	Radiology of limited use	Referral to hypermobility MDT —physiotherapy and occupational therapy
Joint contractures	Radiology of limited use	Referral to physiotherapy & occupational therapy Consider orthopaedic referral to improve function if severe
Abnormal finger positions e.g. camptodactyly/ clinodactyly	Radiology of limited use	Referral for occupational therapy for hand function assessment and aids
Micrognathia Jaw malocclusion	Orthopantomogram may show malalignment of the teeth and small mandible	Referral to orthodontics or maxillary facial surgeons depending on severity
Short stature		Ensure plotted on appropriate growth chart (e.g. Turner's and Down's syndromes). Referral to endocrinologist for growth hormone consideration (e.g. in Turner's syndrome)

Arthritis and other musculoskeletal features associated with cystic fibrosis

Many patients (reported as 13%) with cystic fibrosis (CF) will have musculoskeletal complaints; with increasing prevalence of rheumatic symptoms with age, CF lung disease severity, and infection with *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. CF arthropathy is reported in 2–8.5% of patients and hypertrophic osteoarthropathy in 2–7% of patients. Undoubtedly patients with chronic lung disease are more likely to be physically deconditioned and this tends to associate with generalized musculoskeletal pain and being prone to mechanical/non-inflammatory musculoskeletal complaints.

Musculoskeletal manifestations in CF tend to be one of the following categories:

- Cystic fibrosis-related inflammatory arthritis:
  - Transient recurrent arthritis: with rash/without rash.
  - Persistent/chronic inflammatory arthritis.
- Hypertrophic osteoarthropathy (HOA).
- Metabolic bone disease (osteopenia/osteoporosis/osteomalacia/renal osteodystrophy)
- Cystic fibrosis associated with sarcoidosis
- Non-inflammatory musculoskeletal pain (often due to physical deconditioning).

Transient recurrent arthritis (most common)

Transient recurrent arthritis does not seem to be related to the severity of lung involvement as it can occur in mild to severe lung disease. The pathogenesis of this arthritis has not been well established. It is suspected that the presence of immune complexes may play a role in joint and skin involvement in CF.

Clinical features

- Painless/painful joint swelling with restricted movement:
  - Joints affected (in order of reducing frequency)—knees, ankles, wrists, PIPJs of hands, shoulders, elbows, and hips.
- Episodes lasting 1–10 days.
- Recurrent at intervals of weeks to months.
- Mostly monoarticular but can be oligo- or polyarticular.
- Unrelated to severity of lung disease.
- With our without rash (often vasculitic), which if present can be (in reducing order of frequency):
  - Pruritic ± painful erythematosus nodules, commonest over anterior tibia
  - Purpura (more commonly over legs)
  - General erythematous macular-papular rash
  - Erythema nodosum.

Investigations

- Acute phase reactants may be raised.
- ANA usually negative, RF negative.

- No HLA association.
- Hypergammaglobulinaemia/raised complement in patients with vasculitis-associated arthritis.
- Amylase is useful to measure as there is a rare association of pancreatitis, panniculitis, and arthritis.
- Biopsy of rash may demonstrate vasculitis.

Management

- Shared care with paediatric respiratory team.
- Symptom relief:
  - NSAID (caution may induce bronchoconstriction and supervised trial may be necessary). If not suitable for NSAIDS, then regular paracetamol.
  - Physical therapy (physiotherapy and occupational therapy).

Pending severity and nature of arthropathy (inflammatory versus non-inflammatory), consider short course of oral corticosteroids or intra-articular corticosteroids (see 📖 p 390).

Persistent chronic inflammatory arthritis

Clinical features

- Usually in patients with progressive lung disease and clubbing.
- Similar to clinical features of JIA, typically polyarthritis (may be RF+ve), and often affecting small joints of hands and feet.
- May have tenderness of distal long bones (HOA—see following section).
- Lethargy, joint pain and stiffness, functional limitation.

Management

- Shared care with paediatric respiratory team.
- Screening joint assessment (pGALS) as a minimum followed by full joint examination for pattern of joint involvement.
- Investigations:
  - Assessment of severity of lung disease and possible infective flare.
  - FBC and acute phase reactants may show evidence of inflammation.
  - RF (titre may rise with progressive lung disease).
- Treat infective flares of lung disease first.
- Symptom control.
- Consider systemic corticosteroids and DMARDs similar to JIA (see 📖 p 415) with persistent severe joint involvement, with early physiotherapy in addition.

Hypertrophic osteoarthropathy

Clinical features

- Excessive proliferation of skin and bone at distal ends and digital clubbing.
- Symptoms worse at time of acute infective exacerbations.
- Can be mild to severe, and usually in older children.
- Variable relation to severity of lung disease:
  - Bone pain and burning sensation in distal extremities, which can be severe.

  - May be associated joint disease (most likely knees, ankles, wrists, and metacarpals).
- Clubbing in all cases and tenderness along distal long bones (tibia and radius); radiographs of long bones:
  - Acute changes—periosteal reaction of tubular bone separated from underlying cortex by thin radiolucent line at ends of long bones.
  - Chronic changes—mid shafts of long bones with new bone formation fused with cortex of shaft and no intermediate band of radiolucency.
- May have acne, hyperhydrosis, coarse facial features (2° to hypertrophy of soft tissue).
- Differential diagnosis: thyroid acropathy, acromegaly.

Management

- Shared care with paediatric respiratory team.
- Treat underlying infective exacerbations of lung disease.
- Symptom control and active physiotherapy.
- Pending severity of symptoms, consider:
  - Oral corticosteroids or
  - Pamidronate (see 📖 p 427) has been used in isolated, refractory cases and proven to be effective. If used, a preceding full bone profile and DEXA scan should be performed.

Metabolic bone disease

- Multiple risk factors include malabsorption of vitamin D, corticosteroid use, diet and reduced physical activity, chronic ill health, and chronic renal impairment in some patients.
- May be asymptomatic (most cases) or may present with musculoskeletal pain (often without joint swelling), muscle pain and fatigue, low trauma fractures.
- Assessment and management—see 📖 Metabolic bone disease, p 330.

Cystic fibrosis and vasculitis

- 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.
- Arthritis may be a feature.

Further reading

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Inflammatory bowel disease and musculoskeletal features

Introduction

- Musculoskeletal symptoms in inflammatory bowel disease (IBD) are common and include arthralgia, myalgia, peripheral arthropathy, enthesitis, sacroiliitis, and spondylitis.
- Non-inflammatory MSK pain can be the result of deconditioning and general debilitation in IBD.
- Glucocorticoid and chronic disease-related osteopenia and 2° hypertrophic osteoarthropathy may also result in MSK pain.
- Inflammatory arthropathy is uncommon.
- Features of arthropathy may occur before, during or after the presentation of clinical features suggestive of IBD.

Definitions

- *Ulcerative colitis (UC)*—diffuse mucosal inflammation limited to the colon.
- *Crohn's disease (CD)*—patchy transmural inflammation affecting any part of the GI tract.
- *Indeterminate colitis (IC)*—10% of children with IBD affecting the colon cannot be classified as there are some features of both conditions.
- *Arthropathy of inflammatory bowel disease*—any non-infectious arthropathy occurring before or during the course of UC, IC, or CD.
- Clinical features, see Table 4.30.

Epidemiology

- Collective incidence of IBD <16yr olds in UK is 5.2 per 100,000 (60% CD, 28% UC and 12% IC). Mean age at presentation: 11.9yr (58% are boys, 4% are <5yr). 25% of all IBD presents in children and young people.
- Family history—29% have a ≥1 relative with IBD (greatest in those presenting before 3yr old).
- Arthralgia and myalgia are common (1/3 of patients and often coincide with disease activity)—this may reflect the incidence of MSK pain in healthy adolescents.
- Incidence of arthropathy in IBD variable (2.4–21%) and there is no observed difference between UC and CD.

Physical features that may also be present/occur

Anal fistula/anal abscess (CD), growth failure/delayed puberty (CD), erythema nodosum/rash (CD), liver disease, appendicitis, toxic megacolon (UC), uveitis.

Table 4.30 Clinical features of IBD at presentation

Symptoms or sign	CD (%)	IC (%)	UC (%)
Common symptoms			
Abdominal pain	72	75	62
Diarrhoea	56	78	74
Bleeding	22	68	84
Weight loss	58	35	31
Lethargy	27	14	12
Anorexia	25	13	6
Arthropathy	7	4	6
Other symptoms			
Nausea/vomiting, constipation/soiling, psychiatric symptoms, 2° amenorrhea			

Peripheral arthritis

- Oligoarthritis affecting knees and ankles most common. Occasionally affects multiple joints, including small joints of hands and TMJs.
- Episodes of arthritis tend to be short (1–2 weeks).
- Onset of arthritis does not correlate with activity of IBD and may occur before, during, or unrelated to flare of bowel disease.
- Persistent arthritis is more likely to reflect poor control of bowel disease.
- Arthritis is rarely persistent, progressive, or erosive.

Sacroiliitis and spondyloarthropathy (axial skeletal involvement)

MSK symptoms with back pain and generalized idiopathic (non-inflammatory) pain are common in IBD and important to distinguish from inflammatory back pain.

- May begin as a peripheral inflammatory arthritis and progress to involve sacroiliac joints, hips, and lumbosacral spine.
- Disease does not reflect activity of IBD, and may be progressive despite good control of IBD.
- Associated with the presence of HLA B27.
- May progress to ankylosing spondylitis (3–7%) albeit with no difference between UC and CD for the prevalence of axial spine involvement.

Diagnosis and investigation

See: Guideline for the investigation and management of IBD in children in the United Kingdom (http://bspghan.org.uk/). A high level of suspicion from a history suggestive of arthritis accompanied by any of the listed presenting clinical features of IBD. Consider IBD in the child who is intolerant of NSAIDs.

- Presence of anaemia, raised acute phase reactants, and low albumin.

- Perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA), may help distinguish between UC and CD (pANCA 68% of UC; ASCA 81% of CD).
- MRI of sacroiliac joints and spine help distinguish non-specific MSK pain from true sacroiliitis and spondylitis—x-rays are not helpful in the adolescent patient as the epiphyses do not fuse until mid-20s.

Management

- Control of IBD usually results in resolution of peripheral arthritis.
- If persistent peripheral arthritis, then intra-articular steroids are effective.
- Axial disease may (or may not) benefit from sulfasalazine or MTX.
- Persistent arthritis, axial disease, or resistant IBD may respond to parenteral MTX, AZA, or anti-TNF such as infliximab (there are reports that IBD has developed whilst on treatment with etanercept).

Chapter 5

Bone diseases, skeletal dysplasias, disorders of collagen

Metabolic bone diseases

Primary osteoporosis

Osteogenesis imperfecta (OI)

- Principal features are bone fragility and low bone mass leading to fractures and bone deformity with growth retardation.
- Ligamentous laxity, dentinogenesis imperfecta, and blue scleral hue are variable features. 90% of OI dominantly inherited due to defects in the type I collagen genes *COL1A1* and *COL1A2*.

Idiopathic juvenile osteoporosis

15–20% due to heterozygous mutations in low-density lipoprotein receptor related protein 5 (*LRP5*) gene, rest unknown. Typically presents pre/early puberty with metaphyseal and vertebral crush fractures.

Rare disorders presenting in the neonatal period with fractures

All have other features that help distinguish them from OI. These disorders include:

- Akinesia
- Spinal muscular atrophy with arthrogryposis
- Neurofibromatosis
- Cytomegalovirus inclusion disease
- Caffey's disease
- I-cell disease (mucolipidosis II).

Bone active treatment is with bisphosphonates to ↑ bone mass, reduce bone pain, and improve vertebral size and shape:

- Infants and those with more severe disease, or where growth will soon cease more often receive IV therapy—pamidronate 9–12mg/kg/yr (see 🕮 Guidelines, p 431).
- Oral therapy in milder cases with risedronate (1–2mg/kg/week) is safe and effective. Other bisphosphonates are used but the evidence base is less clear.

Secondary osteoporosis

Inflammatory conditions (e.g.)

- *Inflammatory bowel disease*—bone loss and fractures more common in Crohn's disease than in ulcerative colitis, before and after starting glucocorticoids.
- *Juvenile arthritis*—up to 7% of children with inflammatory joint disease have vertebral crush fracture prior to use of glucocorticoids. Main clinical feature is back pain.
- *Cystic fibrosis*—bone mass loss after 1st decade with concomitant ↑ in fracture risk.

Use of glucocorticoids

- ↑ fracture risk when taking oral glucocorticoids irrespective of underlying condition.
- Complex actions on skeleton—reduce cortical bone turnover leading to retention of older, more heavily mineralized bone that ↑ DXA-measured

bone mass; loss of trabecular bone, leading to ↑ risk of fractures in vertebrae.
- Resolution of risk 3–6 months after steroid cessation.

Disuse
- *Cerebral palsy*—long bone fractures occur in major bones during handling; bones are narrow with thin cortices.
- *Duchenne muscular dystrophy*—low bone mass 2° to disuse and corticosteroids; fractures occur whilst still mobile, but ↑ in frequency once boy becomes immobile. Bone loss ↑ when steroid dose higher.
- *Epidermolysis bullosa*—bone loss due to immobility.

Endocrine disturbance
- *Anorexia nervosa*—low bone mass may not be apparent in childhood/adolescence—low bone mass consistently reported in adult women who were anorexic as teenagers.
- *Cushing's syndrome*—low bone mass and fractures reported, vertebral crush fractures resolve on treatment of underlying disorder.
- *Turner's syndrome*—no evidence of low bone mass or fractures until young adulthood.

Haematology/oncology
- Acute leukaemia—↑ fracture risk and bone loss both at diagnosis and during treatment.
- Post chemotherapy for childhood cancer. Studies suggest that chemotherapy alone does not lead to ↑ later fracture risk—risk is ↑ in those receiving radiotherapy.
- Thalassaemia.
- Post-transplantation.

Osteomalacia/rickets

- Clinical features—bowed limbs, metaphyseal swelling, bossed forehead, pain.
- Vast majority are due to lack of vitamin D, resulting from poor sunlight exposure or dietary inadequacy; more common in darker-skinned individuals living in colder climates.
- Vitamin D deficiency results in myopathy and musculoskeletal aches and pains; infants are usually miserable. Investigations: serum Ca, PO_4, ALP, PTH, and 25OH vitamin D.
- The threshold for deficiency in asymptomatic individuals is debated widely; a typical cut-off is 25mmol/L 25OH vitamin D. Above this, either treatment or supplementation (200–400U/d) is given. Sufficiency is generally accepted as being >75mmol/L.
- Treatment is with ergo/cholecalciferol daily for 2 months. <2yr 3000U/day; 2–10yr 6000U/day; 10+y 10,000U/day.
- Inherited forms of rickets often associated with ↑ circulating FGF-23, which promotes phosphaturia and inhibits renal production of the vitamin D metabolite 1,25 dihydroxyvitamin D; this group includes X-linked hypophosphataemic rickets, and children with McCune–Albright syndrome/polyostotic fibrous dysplasia. Replacement with oral phosphate in divided doses (40–50mg/kg) and 1,25 dihydroxyvitamin D or 1-α calcidol (30–50ng/kg).

Osteopetrosis

- ↑ bone mass due to failure to resorb bone.
- Severe cases present with bone marrow failure and incipient blindness at 3–6 months—urgent decompression of optic nerves may be required.
- Some respond well to bone marrow transplantation.
- Milder forms present later in life—nerve compression and poor fracture healing are significant problems.

Avascular necrosis

- Commonest site affected is the femoral head (other sites described in 📖 The osteochondroses, p 343).
- Thought to be due to interruption to blood supply to the femoral head.
- Affects approximately 1in 1000 children, ♂ more than ♀ (4:1), usually between 3–12yr. 5–10% of cases are bilateral.
- Presenting features—deep hip or referred pain to the knee especially with exercise, may present with limp.
- Diagnosis is by radiograph; however MRI results in earlier detection.
- Treatment—conservative in early disease. Surgical intervention may be required.
- Prognosis—relatively good in the very young and with early detection. Older children and those with significant deformities of the femoral head develop premature osteoarthritis.

Bone densitometry

- DXA is most commonly used to assess bone density, but cannot measure tissue depth; hence adjustment procedures are often applied to account for body size.
- No simple algorithm is available that fully corrects this problem.
- Small children will have lower values than large children; hence adjusting for body size seems logical, but may be confounded when the underlying disease affects growth. Sequential measurements (usually 2-yearly) assessed alongside a growth chart are helpful in assessing bone mass trajectory in response to therapy.
- Indications for the use of DXA in 1° and 2° osteoporosis in children, along with comprehensive supporting evidence, are given on the International Society for Clinical Densitometry (ISCD) website: 🖱 http://www.iscd.org/visitors/pdfs/ISCD2007OfficialPositions-Pediatric.pdf.

Skeletal dysplasias

Background

A group of several hundred clinically and genetically heterogeneous disorders causing generalized abnormalities of bone growth and/or bone modelling. The majority are rare with one of a small number (~10) conditions present in most affected individuals. Usually present with 1 or more of:

- Short stature (usually disproportionate)
- Bone deformity/joint malalignment
- Joint (or generalized bone) pain or limitation of movement
- Abnormal gait
- Recurrent fractures
- Significant family history.

Healthcare needs, associated features, prognosis, and recurrence risks in other family members are dependant on specific diagnosis.

Assessment

History

- Pre- and postnatal growth pattern—age at which abnormalities first noted.
- Age of onset and progression of symptoms.
- Associated features including abnormalities of vision, hearing, teeth, palate, development, neurological function.
- Effect on physical and psychosocial functioning.
- Three-generation family history including, parental heights, evidence of short stature, early onset 'arthritis', joint replacement at young age, and consanguinity.

Examination

- Height, weight, head circumference.
- Skeletal proportion—span, where possible sitting height (subischial leg length = height − sitting height) or upper and lower segments (US, LS) and US/LS.
  - (LS measured from symphysis pubis to floor, US = height − LS).
  - (Centile charts are available for sitting height and subischial leg length. US/LS normally >1.0 until age 10yr, 1.0 at 10yr, <1.0 after 10yr (see http://www.castlemeadpublications.com).
  - If limbs are short it is important to note which segment(s) are affected: i.e. if the proximal segment (shoulder to elbow, or hip to knee) is short, e.g. in achondroplasia—*rhizomelic* shortening, middle segment (elbow to wrist, knee to ankle); *mesomelic*, distal segment (hands, feet); *acromelic*; or all segments *micromelic*.
- Hands and feet—brachydactyly, polydactyly, talipes, joint limitation/deformity.
- Joint function, spine (assess for kyphosis, scoliosis, ↑ lumbar lordosis), gait.
- General examination—including particularly vision, hearing, palate, teeth, heart, abdominal organomegaly, dysmorphic facial features and development.

Investigation

- Radiological skeletal survey—discuss exact composition with local radiologist but likely to include:
  - Anterior–posterior (AP) and lateral skull.
  - PA chest.
  - AP and lateral spine.
  - AP pelvis and bilateral hips.
  - AP 1 upper limb and 1 lower limb.
  - AP of left hand and wrist (both if hands affected).
  - Other views as clinically indicated—consider views of cervical spine in flexion and extension where there is significant spine involvement.
- Biochemical assessment including vitamin D levels if abnormal bone density or metaphyseal abnormalities (nutritional rickets is frequently misdiagnosed as a metaphyseal dysplasia).
- Metabolic investigation if features of storage disorder (coarse facies, organomegaly, dysostosis multiplex, developmental delay.
- Chromosome analysis—if associated malformations and/or cognitive developmental delay.
- DNA analysis—rarely indicated. May be helpful in specific circumstances or where prenatal diagnosis in future pregnancies is requested. Discuss with clinical genetics.

Differential diagnosis

- Most skeletal dysplasias result in disproportionate short stature with specific clinical and radiographic features:
  - Expert assessment of x-rays may be required (discuss with radiology or European Skeletal Dysplasia Network: http:www.esdn.org).
  - Radiographic changes may not be present in infancy and may disappear after puberty—previous x-rays may be helpful.
- Consider other causes of short stature—endocrine, chronic illness, syndromic, constitutional delay of growth and puberty particularly if short stature is proportionate ± delayed bone age ± non-skeletal features (including cognitive delay).
- Consider overall diagnostic group (Table 5.1). Common diagnoses only are described for full classification of skeletal dysplasias (for more information see Further reading, p 342).

Management

- Multidisciplinary team including rheumatology, orthopaedics, radiology, clinical genetics, physiotherapy, occupational therapy, ENT, paediatrics, neurosurgery.
- Diagnosis will help identify likely natural history and healthcare needs. Anticipatory management important—e.g. kyphosis in achondroplasia, retinal detachment in spondyloepiphyseal dysplasia congenita (SEDc).
- Surgical intervention is not always required.
- Pain is a major feature of many bone dysplasias and is often poorly controlled:
  - Pain may be 1° presenting feature, e.g. joint pain in multiple epiphyseal dysplasia (MED), generalized bone pain in Engelmann disease:
    - May not respond to usual analgesics.

— Appropriate physiotherapy may be more helpful.
  - Steroid treatment can be very effective in, e.g. Engelmann disease.
- Most bone dysplasias are heritable—discuss with family and offer referral to clinical genetics.
- Support available for family from several organizations (see 📖 Useful contacts, p 342).

Table 5.1 Skeletal dysplasias

Clinical/ radiographic group	Clinical features	Radiological features	Inheritance/ molecular genetics	Other features
Short limbs/'normal' trunk				
Achondroplasia/ hypochondroplasia	• Short limbs (rhizomelic) • Macrocephaly • Thoraco-lumbar kyphosis in infancy, lordosis later • Trident hand • ↓elbow extension • Tibial bowing	• Large calvaria, ↓size foramen magnum • ↓interpediculate distance, short pedicles • Flat, round iliac bones, notch-like sacroiliac groove • Short tubular bones • Brachydactyly	AD—mostly new dominant with unaffected parents Mutations in *FGFR3*	Risk of hydrocephalus and foramen magnum stenosis in early years. Lumbar stenosis in adulthood Obstructive sleep apnoea common Achondroplasia/ hypochondroplasia may be difficult to differentiate clinically
Pseudoachondroplasia	• Short limbs (micromelic) • Brachydactyly • Extreme joint hypermobility • Normal head size/shape • Kyphoscoliosis • Waddling gait • Knee deformity (wind swept)	• Delayed epiphyseal ossification, flat irregular epiphyses • Biconcave vertebrae, later platyspondyly, anterior vertebral tongue • Brachydactyly	AD—many new dominant Mutations in *COMP*	***Not*** related to achondroplasia Present with waddling gait and later hip and knee pain. At risk of cervical spine instability Overlaps with severe multiple epiphyseal dysplasia
Dyschondrosteosis	• Madelung deformity of upper limbs with limitation of pronation supination • Mesomelic shortening • Radial, tibial bowing • May present as 'isolated' familial short stature	• Madelung deformity • Bowing of forearm and lower leg bones	AD Deletion or mutations in *SHOX*	Very variable phenotype Growth velocity may increase on treatment with hGH Important to differentiate from familial short stature

Short trunk with 'normal' limbs				
Spondyloepiphyseal dysplasia congenita (SEDc)	• Short spine and neck, barrel chest, pectus carinatum, genu valgum • Hands and feet clinically normal • Flattened midface • ± myopia, cleft palate, club feet	• Delayed ossification of skeleton, absence of various ossification centres (e.g. pelvis, vertebral bodies, femoral head and neck) • Odontoid hypoplasia, kyphoscoliosis • Coxa vara	AD Mutations/deletion/ duplication of *COL2A1* Spectrum of allelic disorders includes Kniest dysplasia, AD spondyloarthropathy, stickler syndrome COL2 type, achondrogenesis II, hypochondrogenesis	Motor development may be delayed, but cognitive development normal Small thorax may cause respiratory complications Risk of atlanto-axial dislocation and spinal cord compression High myopia associated with retinal detachment
Progressive pseudorheumatoid arthropathy of childhood (spondyloepiphyseal dysplasia tarda with progressive arthropathy)	• Short trunk • Progressive large joint contracture • Contracture of small joints of hands and feet with soft tissue swelling	• Platyspondyly, ± scoliosis • Enlarged epiphyses initially. Later develop cystic lesions with flattening • Enlarged epiphyses and metaphyses of bones of hands and feet with osteoporosis but no periostitis	AR Mutations in *WISP3*	An important differential for JIA especially where there is a family history Differentiating factors include platyspondyly and the absence of erosions and periostitis Progressive joint contracture and osteoarthrosis may lead to decreased mobility and the need for joint replacement

(*continued*)

Table 5.1 (*Contd.*)

Clinical/ radiographic group	Clinical features	Radiological features	Inheritance/ molecular genetics	Other features
Brachyolmia	• Short trunk, scoliosis, mild short stature • Clinically and genetically heterogeneous • Types 1–3	• Platyspondyly • Short ilia • ± longitudinal striations of metaphyses of large long bones (e.g. femur)	Heterogeneous Both AR and AD forms documented Type 1: AR Type 2: AR Type 3: AD, *TRPV4*	Type 1: corneal opacities Type 2: calcification of falx cerebri Type 3: severe kyphoscoliosis
Short trunk with short limbs				
Kniest dysplasia	• Short limbs, joint enlargement, ↓joint mobility • Dorsal kyphosis, ↑lumbar lordosis, thoracic scoliosis • Flattened midface, depressed nasal bridge, • ± cleft palate, myopia, deafness, clubfeet	• Platyspondyly, anterior wedging of vertebral bodies • Broad, hypoplastic ilia • Broad, short femoral necks • Delayed ossification of capital femoral epiphyses • Short tubular bones, broad metaphyses, deformed epiphyses	AD, mutations in *COL2A1* (most are deletions resulting in truncated type II collagen)	Complications include chronic otitis media, retinal detachment, cataracts, joint contractures, early arthrosis

Diastrophic dysplasia	• Wide phenotypic variability • Short limbs • Multiple joint contractures • Proximal hypermobile thumbs ('hitchhiker thumb', deformity of 1st metacarpal) • Clubfeet • Cysts of external ear (in first 12 weeks of life), subsequently cauliflower deformity of pinnae • Progressive kyphoscoliosis • ± cleft palate	• Flat dysplastic epiphysis with wide metaphyses • Delta shaped distal femoral/ radial metaphyses • Short, wide, long bones • Deformities of metacarpals, metatarsals, and phalanges • Progressive thoraco-lumbar kyphoscoliosis, cervical kyphosis	AR Mutations in *DTDST*	Perinatal and infant mortality ↑ Risk of medullary compression from cervical kyphosis (present at birth but usually resolves by ~7y) Clubfeet often difficult to manage and resistant to surgical correction Joint contracture is progressive and may recur after surgical release
Epiphyseal disorders				
Multiple epiphyseal dysplasia (MED)	• Very variable phenotype • Joint pain • Hypermobile joints, especially in hands • ↓mobility, waddling gait	• Delayed epiphyseal ossification • Flattened irregular epiphyses • Mild irregularity and flattening of vertebrae in severe cases	Mostly AD Mutations in: *COMP* *MATN3* *Col9A1/A2/A3* Rare AR form Mutations in: *DTDST*	Poor correlation between phenotype and genotype. Very variable even within families Overlaps with mild pseudoachondroplasia severe end of MED spectrum

(*continued*)

Table 5.1 (*Contd.*)

Clinical/ radiographic group	Clinical features	Radiological features	Inheritance/ molecular genetics	Other features
Metaphyseal dysplasias				
Metaphyseal dysplasia, Schmid type	• Bowed legs, waddling gait • Normal epiphyseal development • Brachydactyly • Lordosis	• Short tubular bones • Broad irregular metaphyses hips worse than knees • Coxa vara, short femoral necks • Brachydactyly • ± mild platyspondyly	AD Mutations is *COL10A1*	May be difficult to differentiate clinically and radiographically from rickets. Always check biochemistry including vitamin D levels
Cartilage–hair hypoplasia	• ↓length at birth • Fine, sparse hair/eyebrows/lashes • Brachydactyly with hypermobile hands • ↓elbow extension • Ligamentous laxity • Recurrent infections (children) secondary to ↓*in vitro* T-cell function • Particularly at risk from varicella infection • Hirschsprung's disease	• Short tubular bones • Metaphyseal dysplasia of tubular bones knees more than hips • Mild platyspondyly • Brachydactyly with cone-shaped epiphyses	AR Mutations in *RMRP*	Risk of cervical spine instability All features variable including severity of immunodeficiency Probable ↑ risk of malignancy in adulthood, e.g. lymphoma.

Skeletal dysplasias with ↓bone density				
Osteogenesis imperfecta	• Recurrent low trauma fracture • Bone deformity • Blue sclerae and dentinogenesis imperfecta may be present • Back pain • Very variable phenotype with multiple types based on clinical features	• Generalized hypomineralization • Wormian bones in skull	Mostly AD Mutations in *COL1A1/A2* Very rare AR forms	Vital to differentiate from non accidental injury. Requires expert assessment. Both diagnoses may be present Management of severe OI revolutionized by use of IV bisphosphonates
Skeletal dysplasias with ↑bone density				
Osteopetrosis	• Very variable phenotype • Severe infantile • Intermediate childhood onset • Mild late onset • Low trauma fractures • Cranial nerve impingement • Bone marrow failure • Early dental decay and loss	• Generalized increase in bone density especially at skull base • 'Bone within a bone' • 'Rugger jersey' spine	AR—severe neonatal form Mutations in: *CLCN7* *TCIRG1* *OST* AD—later onset forms Mutations in: *CLCN7* *LRP5*	Mutation analysis is important in neonatal forms as it may determine suitability for definitive treatment by BMT. Urgent assessment is required Neurosurgical assessment required

AD, autosomal dominant; AR, autosomal recessive.

Further reading

Superti-Furga A, Unger S, the Nosology Group of the International Skeletal Dysplasia Society. Nosology and classification of genetic skeletal disorders. *Am J Med Genet* 2006; **143A**:1–18.
Trotter TL, Hall JG. Health supervision for children with achondroplasia. *Pediatrics* 2005; **116**:771–83.

Useful contacts

European Skeletal Dysplasia Network—online diagnostic resource: http://www.esdn.org.
Little People of America—support organization: http://www.lpaonline.org.
Restricted Growth Association—support organization: http://www.restrictedgrowth.co.uk.

The osteochondroses

Definition

Historically, the term 'osteochondrosis' or 'osteochondritidis' has been applied to a heterogeneous group of conditions characterized by a disturbance in endochondral ossification in an area in which previously growth had been normal; such changes have been observed in almost every growth centre (epiphysis or apophysis) in the body and the different sites are often associated with eponyms. The degree of articular cartilage involvement varies and in some localized cases the term osteochondritis dissecans (OCD) is used (Table 5.2). Also see 🕮 Metabolic bone disease, p 330.

Aetiology

The initial event or combination of events that leads to the disorder in endochondral ossification is unknown and hence these conditions are considered idiopathic in origin:

- Both a vascular and a traumatic aetiology have been proposed.
- The vascular theory is certainly part of the process in Legg–Perthes *and*
- Repetitive microtrauma is implicated in OCD and Osgood–Schlatter's amongst others.

Pathology

Histologically, the affected area shows many of the features of ischaemic necrosis affecting both bone and cartilage:

- Necrosis.
- Revascularization.
- Invasion with granulation tissue.
- Osteoclastic resorption of dead bone.
- Osteoid replacement along necrotic trabeculae.
- Formation of mature lamellar bone

In OCD, the process is more localized:

- Segmental epiphyseal necrosis may lead to physical separation of an osteoarticular fragment in which the bony fragment may be very small.
- Once separated this fragment may continue to grow as the articular cartilage is nourished by the synovial fluid.

When the history, clinical examination, and imaging are typical then bone biopsy is not required.

Clinical features

Overall, the natural history for the osteochondroses (as distinct from OCD) is well defined and generally the outcomes are predictable and often good. The specific symptoms vary from site to site and with age of onset of the condition. Symptoms and signs may include:

- Local or referred pain.
- Swelling and symptoms of inflammation such as tenderness and warmth.
- Joint stiffness, with or without a limp.

Table 5.2 The osteochrondroses

	Eponym	Site
Lower limb	Kohler	Navicular
	Freiberg	2nd metatarsal head (or 3rd/4th)
	Sever	Calcaneal apophysis
	Osgood–Schlatter	Tibial apophysis
Upper limb	Panner	Capitellum
	Keinboch	Lunate
Spine	Schuermann	Vertebral end plates
Others	*Blount	Proximal tibial physis
	*Legg–Calve–Perthes	Proximal (capital) femoral epiphysis
	Osteochondritis dissecans	Knee (distal femoral condyle and patella), talus, capitellum

* Most paediatric orthopaedic surgeons consider these two conditions as separate entities—the natural history of these two conditions is more severe and the management strategies significantly more aggressive.

Features on imaging

The exact features vary with the anatomical site involved but some plain radiographic changes are common:

- Early signs include a ↓ in size, change in shape, ↑ in density or irregularity of the bony epiphysis/apophysis. Often the whole bony area is involved.
- Later bone resorption is seen as fragmentation.
- With continued re-ossification the radiographic appearances may return to normal.
- With delay in revascularization, non-union may lead to separation of an osteochondral fragment as seen in OCD (where the process is localized so that the rest of the epiphysis appears normal).

The MRI features vary depending on the stage of the disease process and the site of involvement but bone oedema is common. Small subchondral fractures might be identified and early identification of fragment separation for OCD lesions may be helpful. MRI and/or bone scans can be useful in diagnosing other pathologies (see 📖 Pitfalls, p 345).

Natural history and treatment recommendations

Most osteochondroses are benign, self-limiting processes; treatment is usually symptomatic and conservative. Symptoms may take some time to resolve and with apophyseal lesions this may not occur until after physeal fusion. Beware of 'over-treatment'. Management includes the following:

- Family/patient education.
- Relative rest from exercise—encourage sporting 'warm up and cool down'.
- Analgesic and/or anti-inflammatory medication as required.

In selected cases:

- Physiotherapy, support bandaging, bracing (perhaps in Scheuermann's disease) may help.
- Treatment of Blount's and Legg–Perthes requires referral to an orthopaedic surgeon.

The management of OCD lesions can be more complex: symptoms such as locking, sharp pain, and 'giving way' of the joint with signs of an effusion warrant an orthopaedic opinion. Surgical options include:

- Pinning *in situ* for the lesion that is not separated.
- Drilling to enhance revascularization.
- Replacement of the loose fragment (or removal).
- Debridement of craters/ulcers if the fragment has been 'lost'.
- Consideration of techniques such as ACI or MACI (autologous chondrocyte implantation or matrix-induced ACI).

Pitfalls

- Children are not used to 'chronic' pain and parents do not like to see their child limping. For both it can be a depressing/frustrating time.
- If the child has a 'disease' label, then parents expect treatment for it. It is unfortunate that most of the eponyms imply that OCD is a disease state rather than a usually benign condition that disrupts normal growth temporarily.
- Remember that some of the radiological features described such as fragmentation of the calcaneal apophysis (in Sever's disease) and the tibial tubercle (in Osgood–Schlatter's) may also be seen in normal, asymptomatic children.
- Thus it is important to determine whether or not the radiographic features are a 'red herring': does the clinical history and examination match the imaging results?
- For localized pain and swelling in a child the ***differential diagnosis*** must always include:
  - Tumour.
  - Bone and joint infection.

Heritable disorders of connective tissue

A number of inherited disorders of connective tissue may present to paediatric rheumatology services with biomechanical pain related to musculoskeletal features.

- The majority of these conditions are recognizable by their clinical features.
- It is important to identify those patients with conditions that may predispose to potentially preventable causes of morbidity and mortality.
- A physiotherapy-led multidisciplinary approach with attention to strengthening areas of weakness and pacing activities is effective for patients with significant musculoskeletal symptoms.
- Emerging new therapeutic drug approaches are being used in Marfan syndrome to limit cardiovascular complications.

Marfan syndrome

Background

- Inherited disorder of fibrillin transmitted as an autosomal dominant trait.
- Incidence 1:5000, panethnic, no sex predilection.
- Marfan syndrome is fully penetrant with variable expression.

Pathophysiology

- Caused by mutations in Fibrillin-1 gene (*FBN1*), located on chromosome 15.
- Fibrillin-1 is a glycoprotein which aggregates to form complex extracellular structures called microfibrils which are essential for elastic fibre maintenance in postnatal life.
- Abnormal microfibrils weaken the aortic wall and other structures such as the suspensory ligament of the lens, ligaments, lung airways, and spinal dura.
- Recent studies suggest that abnormalities in *FBN1* lead to dysregulation of transforming growth factor-beta (TGF-β) and that many of the multisystem manifestations including cardiovascular complications relate to excess TGF-β signalling.
- Severe neonatal Marfan syndrome is associated with a cluster of mutations between exons 24–32 of *FBN1* but there are no other established correlations between genotype and phenotype.

Clinical features

A diagnosis of Marfan syndrome is based on the revised Ghent nosology.

- Systemic features and differential diagnosis are shown in Tables 5.3 and 5.4.
- In the absence of family history, Marfan syndrome is diagnosed when there is:
  - Aortic root dilatation or dissection (z score >2) *and* ectopia lentis.
  - Aortic root dilatation or dissection *and FBN1* mutation.
  - Aortic root dilatation or dissection *and* ≥7 points on systemic features score.
  - Ectopia lentis *and FBN1* mutation known to be associated with aortic root dilatation or dissection.

- In the presence of family history Marfan syndrome is diagnosed when there is ectopia lentis *or* ≥7 points on systemic features score *or* aortic root dilatation/dissection.
- *Caveat*: when the diagnosis of Marfan syndrome is made without a known mutation in *FBN1*, discriminating features of vEDS, SGS, or LDS must not be present (Table 5.3) *and* appropriate diagnostic tests performed if indicated.
- Patients <20yr with borderline aortic root measurements and a family history of Marfan syndrome or a known *FBN1* mutation are defined as having potential Marfan syndrome and require close cardiology follow-up to detect progressive aortic root dilatation.
- Patients with musculoskeletal features typical of Marfan syndrome without further organ involvement are classified as having a Marfanoid habitus.
- Neonatal Marfan syndrome is not a separate entity but represents the most severe end of the Marfan syndrome spectrum.

Investigations

- A high rate of new mutations means a clinically useful genetic screening test has not been developed.
- ECG and echocardiogram are indicated in patients with Marfanoid habitus to identify potential cardiac involvement.

Management

- Antihypertensive treatment with β-blockers to delay or prevent aortic root dilatation and dissection is the current standard of medical care.
- Elective aortic graft surgery is recommended for patients with an aortic diameter of ≥5cm or rapidly progressive dilatation.
- Losartan is an angiotensin II receptor blocker which has also been shown to block TGF-β signalling. Recent animal studies and one case series of 18 children with progressive aortic root dilatation unresponsive to standard therapy suggest that Losartan may reduce or halt progression of aortic root dilatation in these patients.

Table 5.3 Scoring system for systemic features of Marfan syndrome (Revised Ghent nosology)

Feature	Points	Feature	Points
Wrist **or** thumb sign*	1	Pneumothorax	2
Wrist **and** thumb sign	3	Dural ectasia	2
Pectus carinatum	2	Protrusio acetabuli	2
Pectus excavatum or chest asymmetry	1	Reduced upper:lower segment ratio **and** increased armspan:height ratio **and** no severe scoliosis	1
Hindfoot deformity	2	Scoliosis or thoracolumbar kyphosis	1
Pes planus	1	Reduced elbow extension	1
Facial features 3/5 from: dolichocephaly, enopthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia	1	Skin striae	1
Myopia >3 dioptres	1	Mitral valve prolapse	1

Maximum score = 20 points. ≥7 points indicates systemic involvement.
*The thumb sign is positive if the thumb, when completely opposed within the clenched hand, projects beyond the ulnar border.
The wrist sign is positive if the distal phalanges of the 1st and 5th digits of 1 hand overlap when wrapped around the opposite wrist.

Table 5.4 Differential diagnosis of Marfan syndrome

Differential diagnosis	Gene	Discriminating features
Loeys–Dietz syndrome (LDS)	*TGFBR1/2*	Bifid uvula/cleft palate, arterial tortuosity, hypertelorism, diffuse aortic and arterial aneurysms, craniosynostosis, clubfoot, cervical spine instability, thin and velvety skin, easy bruising
Shprintzen–Goldberg syndrome (SGS)	*FBN1* and others	Craniosynostosis, mental retardation
Congenital contractural arachnodactyly (CCA)	*FBN2*	Crumpled ears, contractures
Weill–Marchesani syndrome (WMS)	*FBN1* and *ADAMTS10*	Microspherophakia, brachydactyly, joint stiffness
Ectopia lentis syndrome (ELS)	*FBN1* *LTBP2* *ADAMTSL4*	Lack of aortic root dilatation
Homocystinuria	*CBS*	Thrombosis, mental retardation
Familial thoracic aortic aneurysm syndrome (FTAA)	*TGFBR1/2, ACTA2, MYH11*	Lack of Marfanoid skeletal features, livedo reticularis, iris flocculi
Arterial tortuosity syndrome (ATS)	*SLC2A10*	Generalized arterial tortuosity, arterial stenosis, facial dysmorphism
Ehlers–Danlos syndromes (vascular, valvular, kyphoscoliotic)	*COL3A1, COL1A2, PLOD1*	Middle-sized artery aneurysm, severe valvular insufficiency, translucent skin, dystrophic scars, facial characteristics

Ehlers–Danlos syndromes (EDS)

- The EDS are a heterogeneous group of disorders characterized by hyperextensible skin, hypermobility, dislocations, poor wound healing, wide thin scars, tissue fragility and easy bruising.
- Diagnostic criteria and clinical features for EDS are shown in Table 5.5.
- Patients who present with biomechanical pain and are found to have joint hypermobility and soft, mildly extensible skin have previously been classified as EDS type III or 'hypermobile type EDS'; the label may cause unnecessary anxiety for patients and families and current UK practice is to describe these patients as having joint hypermobility and biomechanical pain.

Osteogenesis imperfecta

- Children with mild subtypes of osteogenesis imperfecta (OI) are usually of average stature and have a history of minimal trauma fractures.
- Family members with OI type 1 have been identified who have never sustained a fracture and these patients may present with hypermobility and musculoskeletal symptoms.
- Clinical and laboratory discriminating features are shown in Table 5.6.

Table 5.5 Diagnostic criteria for Ehlers–Danlos syndromes

Type and inheritance	Major features	Minor features	Laboratory
Classical AD	Skin hyperextensibility **Widened atrophic scars** Joint hypermobility	Smooth velvety skin Molluscoid pseudotumors Subcutaneous spheroids Complications of joint hypermobility (sprains, subluxations/dislocations, pes planus) Muscle hypotonia Delayed gross motor development Easy bruising Manifestations of tissue extensibility and fragility Postoperative hernia Positive family history	Abnormalities in skin collagen under electron microscopy Abnormal collagen type V **30% due to mutation in tenascin**
Vascular AD	Thin, translucent skin **Arterial/intestinal/uterine fragility or rupture** Extensive bruising Characteristic facial appearance	Acrogeria Hypermobility of small joints Tendon and muscle rupture Talipes equinovarus Early onset varicose veins Arteriovenous, carotid-cavernous sinus fistula	Abnormal type 3 collagen *COL3A1* mutation

(*continued*)

Table 5.5 (*Contd.*)

Type and inheritance	Major features	Minor features	Laboratory
		Pneumothorax	
		Gingival recession	
		Positive family history or sudden death in close relatives	
Hypermobility	Generalized joint hypermobility	Recurring joint dislocations	
AD	Hyperextensible or smooth, velvety skin	Chronic joint or limb pain	
		Positive family history	
Kyphoscoliotic	Generalized joint laxity	Tissue fragility, including atrophic scars	Urinalysis for lysylpyridinoline and hydroxylysylpyridinoline
AR	Severe muscle hypotonia at birth	Easy bruising	
	Scoliosis at birth, progressive	Arterial rupture	
	Scleral fragility and rupture of the ocular globe	Marfan-like habitus	
		Microcornea	
		Osteopenia	
		Family history	

Arthrochalasia AD	Severe generalised joint hypermobility with recurrent subluxations **Congenital hip dislocation**	Skin hyperextensibility Tissue fragility, including atrophic scars Easy bruising Muscle hypotonia Kyphoscoliosis Radiologically demonstrated mild osteopenia	Skin biopsy and demonstration of abnormal collagen type 1
Dermatosparaxis AR	Severe skin fragility Sagging, redundant skin	Soft doughy skin texture Easy bruising **Premature rupture of fetal membranes** **Large hernias (inguinal and umbilical)**	Demonstration of abnormal collagen 1 chains in skin

For a diagnosis to be made a patient must have one or more of the major criteria. Presence of minor criteria is 'suggestive' of a diagnosis. Items in bold are distinguishing features of that particular subtype of Ehlers–Danlos syndrome.

Table 5.6 Disorders predisposing to bone fragility which can be associated with joint hypermobility (see 📖 Metabolic bone diseases, p 330)

Type and inheritance	Discriminatory features	Other features	Laboratory
Osteogenesis imperfecta type I AD	**Blue sclera** Hypermobility, especially of small joints **Wormian bones in 70%** Generalized osteopenia on DEXA	Kyphoscoliosis Arcus cornea Hearing impairment Metatarsus varus Easy bruising Fractures from minimal trauma Opalescent dentine	**Reduction in synthesis of type I procollagen** **Abnormalities in *COL1A1***
Osteogenesis imperfecta type IV AD	**White sclera** Fractures from minimal trauma Short stature **Wormian bones in 50–70%**	Progressive long bone deformity Joint hypermobility Opalescent dentine	***COL1A1* or *COL1A2* mutations which reduce collagen stability**

Further reading

Loeys BL, Dietz HC, Braverman AC, *et al*. The Revised Ghent Nosology for the Marfan syndrome. *J Med Genet* 2010; **47**:476–85.

Infection and immunization

Tuberculosis and mycobacterial disease

There are 3 main scenarios to consider:
- Latent TB infection (LTBI).
- 1° musculoskeletal TB and reactivation of LTBI as a result of drug-induced immune-suppression.
- Reactive immunological phenomena associated with *Mycobacterium tuberculosis* (MTB) and/or antimycobacterial therapy.

LTBI

- Following infection with MTB, 95% of individuals will develop LTBI, hosting live MTB in the absence of clinical manifestations (Fig. 6.1). In LTBI, MTB is deemed a state of non-replicating persistence or low replication contained by a highly organized infiltrate called a granuloma constituted by mycobacteria-containing macrophages surrounded by activated lymphocytes.
- Tumor necrosis factor (TNF) plays multiple roles in the host's ability to respond against the infection with MTB including responsibility for granuloma formation and maintenance.
- MTB are kept at bay long term in most immunocompetent individuals. However, MTB remains viable and a change of host's immune response such as immune-suppression with TNF antagonists may lead to granuloma disintegration and uncontrolled replication of MTB to produce TB disease.
- A review of the current knowledge of the risk of TB in relationship to TNF antagonists published by the Tuberculosis Network European Trials Group (℔ http://www.ncbi.nlm.nih.gov/pubmed/20530046) can be summarized as follows:
  - The risk of TB in adults with RA treated with TNF antagonists is ↑ ≤25x with risk likely ↑ from the disease itself and the use of non-biological immunosuppressants.
  - The risk of TB may be ↑ in children exposed to TNF antagonists although data (8 years to date) reports very few cases. This may be because children treated with biologics have so far been in countries with a very low risk of TB.
  - TNF antagonists efficacious against granulomatous conditions (Crohn's disease and sarcoidosis) such as infliximab and adalimumab are more likely to cause TB reactivation than etanercept.
- Screening for LTBI is currently recommended for all candidates prior to starting anti-TNF therapies (see 🕮 p 393). Consequently paediatric rheumatologists have to manage ***children with positive immunodiagnostic tests for TB*** in absence of clinical symptoms.

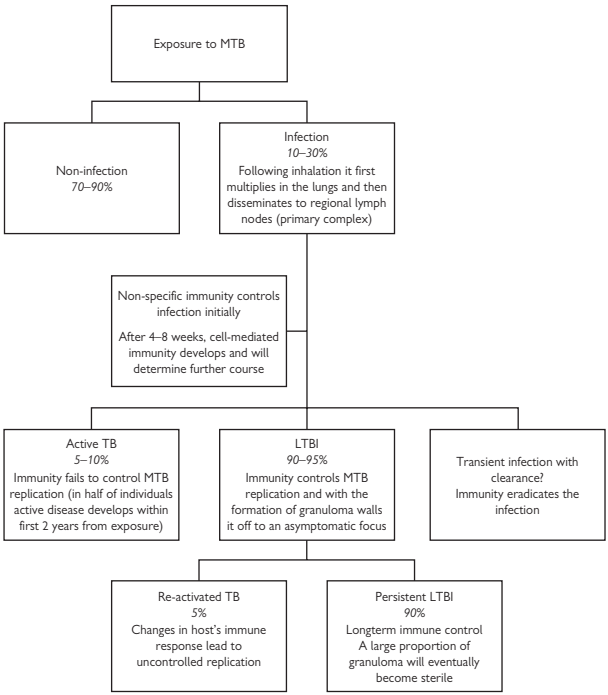

Fig. 6.1 Pathogenesis of TB following exposure to MTB in immunocompetent individuals.

Diagnosis

- Immunodiagnostic tests for TB, either tuberculin skin tests (TSTs) such as Mantoux and/or the newest T-cell based interferon-γ release assays (IGRAs), measure adaptive immune response to MTB infection and neither of them distinguish active TB disease from LTBI. In the absence of a gold standard for the detection of LTBI these immunodiagnostic tests are used as 'proxy measures' for LTBI.
  - A positive TST (i.e. Mantoux) indicates a cellular immune response to MTB antigens.
  - TST induration >5mm indicates infection in individuals without BCG vaccination and ≥15mm with BCG. Variable 'cut-offs' between >5 to >10 exist (e.g. World Health Organization).
  - IGRAs measure interferon γ released by T cells (QuantiFERON-TB Gold) or T cells releasing interferon γ (T-SPOT.TB) in response to MTB-specific antigens. Both include a positive control and a negative control to helps differentiate a true negative response from anergy (i.e. in children or immune-suppressed patients). IGRAs compared to TSTs are more specific (i.e. do not cross-react with BCG strains and environmental mycobacteria), are more reliable to test immunosuppressed patients, and are likely to be more accurate in diagnosing LTBI in children than TSTs.
- There are current no published guidelines on how to best screen children prior starting anti-TNFα.
  - Most paediatric rheumatology local guidelines are modelled on adult recommendations.
  - Expert opinion support simultaneous TST, IGRAs, CXR and offering treatment if any test is positive.

Treatment

- Preventive chemotherapy should be offered to all individuals receiving TNFα antagonists in the presence of evidence of LTBI. Recommended prophylactic treatments for LTBI (all ages) in the UK include 3 months of rifampicin and isoniazid or 6 months of isoniazid.
- TNFα antagonist treatment can be initiated after 4 weeks of treatment for LTBI has been completed.

Primary musculoskeletal TB and reactivation of LTBI as a result of drug-induced immune-suppression

- There are an estimated 1.3 million cases of TB annually in children resulting in 450,000 deaths.
- Overall notification rates for TB in children have been rising in Europe over the last decade, mostly due to a significant rise in Eastern Europe and some specific areas such as London, whilst notification rates for Western Europe including the UK in general have been declining.
- Musculoskeletal TB is rare in developed countries and epidemiological data is scarce especially in the paediatric population. 2–5% of children with TB have musculoskeletal involvement.
- In untreated 1° MTB infection the average risk of developing bone lesions for all children under the age of 5yr is ~1–2% in 2yr.
- TB is caused by MTB, rarely by *M. bovis* (see Fig. 6.1).

- During the formation of the 1° complex and for some months after, in many individuals bacilli escape intermittently into the bloodstream and may lodge anywhere in the body, but particularly in the CNS, bones, or the kidneys.
- If circumstances favour the organism rather than the host (i.e. young age or poor nutrition), then the cells of the reticular endothelial system do not control the disease and haematogenous spread lead to a localized lesion or multiple lesions (***miliary disease***).
- Bone or joint disease is usually the result of lymphohaematogenous spread from a 1° focus, usually pulmonary. Rarely, direct invasion by extension from adjacent lymph nodes or lung may cause spinal disease. Lesions can be found <3 months but usually occur within 1–3yr of the 1° infection and hence evidence of concomitant pulmonary involvement is not always found.
- Infection develops in the metaphyses, bone may be destroyed eroding through into the adjacent joint space and epiphyseal growth plates are at risk of damage.
- In spinal TB, 3 different patterns of vertebral body infection have been described—anterior, paradiscal, and central. Subsequent spread involves intervertebral discs and narrowing of the disc space.
- Abscesses frequently develop in advanced disease, following tissue planes from vertebrae into the retropharyngeal space, lung, psoas sheath, perineum, or gluteal region or may extend posteriorly into the spinal canal.
- Healing is by formation of fibrous tissue and calcification may be seen.

Clinical presentation

- Often indolent and non-specific often leading to significant diagnostic delay.
- Manifestations of musculoskeletal TB include spondylitis, osteomyelitis, and septic arthritis.
- *TB spondylitis* ('Pott's disease') accounts for 50% of TB involvement of the musculoskeletal system in adults although data is unclear in children.
- Thoracic and lumbar lesions are most common. Pain is the presenting symptom producing alteration of gait or posture 2° to muscle spasm. Young children unable to localize the pain may cry when moved or picked up, or refuse to sit or walk. Vertebral collapse may results in kyphosis. Paraplegia is usually due to spinal cord compression either by oedema, abscess, granulation tissue or sequestra.
- *Extra-axial osteomyelitis* is responsible for 20% of musculoskeletal TB, in children commonly involving the metaphysis of femur, tibia, skull, and small bones of hands and feet (i.e. dactylitis). Osteomyelitis can be associated with septic arthritis and overlying soft tissue abscess or can occur without joint involvement in any bone but more often in the long bones or in dactylitis. Soft tissue swelling is seen, followed by a non-tender mass attached to bone. Dactylitis usually presents as painless or mildly painful swelling mostly involving the proximal phalanges or the metacarpal bones. TB osteomyelitis is most commonly a single focus process in the immune-competent host.

- *Septic arthritis*, although rare, is particularly relevant due to the frequent monoarticular nature (90% of cases), common involvement of large weight-bearing joints, and insidious manifestations rendering it difficult to differentiate from oligoarticular JIA. Involvement of the small joints of hands and fingers are often described in children and immune-suppressed patients. Onset is gradual with joints initially becoming swollen, then limitation of movement, followed by pain, stiffness, and alteration of gait.
- Because of the rarity of musculoskeletal TB in Western countries, there are no current recommendations to rule out TB in children presenting with mono-arthritis. However unusual features such as proliferative synovitis with subtle signs of inflammation, peri-articular abscesses and draining sinuses and/or lack of response to intra-articular steroids should prompt investigations to rule out TB.
- *Other musculoskeletal manifestations* including tenosynovitis, bursitis, and muscle abscesses are rarer and often a result of continuous spreading from adjacent bony and articular lesions.
- For children on TNF antagonists, due to the ↑ risk of reactivation of LTBI, paediatric rheumatologists need to be aware of presentations of TB in the immune-suppressed host which are similar to those of 1° TB albeit with an ↑ frequency of multifocal articular and bone lesions.

Diagnosis (Fig. 6.2)

- The triad of a history of TB contact, positive Mantoux test, and suggestive CXR changes is highly suggestive for a diagnosis of TB. Plain x-ray skeletal survey is often abnormal and therefore essential and cost-effective. Typical x-ray features include:
  - Lytic lesions with poorly defined edge.
  - Absent or minimal reactive sclerosis.
  - Juxta-articular osteopenia, narrowing of joint space and adjacent soft tissue involvement.
  - In dactylitis there is usually enlargement of the bone with periosteal thickening and destruction of the spongiosa giving a cystic appearance ('spina ventosa').
  - Plain x-ray of the spine may show disc space narrowing, anterior vertebral scalloping or variable degrees of destruction with kyphosis.
- Definitive diagnosis relies on culture of the organism. Open biopsy or fine needle aspiration of bone, or synovial fluid aspiration and synovial biopsy obtain specimens. The differential diagnosis is broad but includes bacterial and fungal infection, syphilis, and bone tumours including sarcomas and sarcoidosis.

Assess likelihood of MT infection	• Local prevalence rate? • History of contact (in non/low endemic regions and young children a household contact is more likely)?
Ask for systemic manifestations *	• Cough >2–3 weeks not improving after 1 course of antibiotics, fever, weight loss, night sweat
Look for concurrent pulmonary TB **	• CXR • Chest CT if equivocal findings on CXR
Look for radiological evidence of musculo-skeletal TB and identify site for biopsy	• Radiographic skeletal survey • CT scan (better for defining bone involvement) • MRI (better for defining articular and soft tissue involvement)
Assess supporting immunological evidence ***	• Tuberculin skin test • Interferon γ release assay
Look for hystological evidence if tissue specimen possible	• Granulomatous inflammatory changes (multinucleated giant cells, histiocytes and chronic inflammatory cells)
Attempt bacteriological confirmation	• Acid fast bacilli in direct smear microscopy (synovial fluid) • Culture of tissue specimen

Fig. 6.2 Diagnosis of musculoskeletal TB.
*Systemic manifestations will be absent unless disseminated TB or concurrent pulmonary involvement.
** The coexistence of pulmonary TB is reported in 30–50% of cases. If a pulmonary lesion is identified, attempt specimen collection (sputum in older children, gastric aspiration and/or nasopharyngeal aspirate in young children) and detection of acid fast bacilli in direct smear microscopy and culture; these yield a positive result in only 20–50% of cases.
*** Both TSTs and IGRAs lack sensitivity to reliably distinguish between TB and LTBI in a patient with TB-like illness. Either test is therefore an adjunct to other tests for diagnosing TB disease. A recent UK study failed to show that IGRA are more sensitive than TST>15 mm in diagnosing active TB but confirmed that combining both tests identified more than 90% of culture-confirmed cases.

Treatment

- Due to the difficulty in bacteriological confirmation of TB disease in children, treatment should be started if the histology and clinical picture are consistent without waiting for the results of the cultures, and should be completed even if the culture results are negative if an alternative aetiology is not identified.
- The standard regimen recommended from NICE to treat active musculoskeletal TB in all ages is 6 months of isoniazid and rifampicin initially plus pyrazinamide and ethambutol for the first 2 months.
- Reactivated TB disease in association with immunosuppression is treated as 1° TB.
- If TNF antagonists required in children with active TB, a full course of anti-tuberculous treatment should be completed before initiation.
- The role of surgery in spinal TB is debatable; it is indicated to establish a diagnosis and in those with active disease and neurological deficit requiring decompression. Drainage may be useful in joint involvement

to relieve pressure. Radical resection/bone grafting may be considered if there is destruction of ≥2 vertebral bodies.
- Bed rest and immobilization are no longer recommended.

Prognosis

MTB does not produce proteolytic enzymes that easily destroy cartilage (contrast to bacterial infection). Therefore a good response to treatment and return to normal function is expected if the diagnosis is made early.

Reactive immunological conditions (in association with MTB infections and anti-mycobacterial therapy)

- Erythema nodosum is a not uncommon hypersensitivity reaction to MTB.
- Poncet's disease, a rare aseptic reactive polyarthritis usually seen in the context of active pulmonary TB, has been described. Other hypersensitivity reactions to MTB include ocular manifestations such as conjunctivitis and phlyctenular keratoconjunctivitis (redness, tearing and foreign body sensation) and interstitial keratitis.
- Drug-induced lupus has been described in association with isoniazid and rifampin therapy. Reactive phenomena tend to resolve with discontinuation of the offending drug.

Rheumatic fever

Introduction

- Acute rheumatic fever (ARF) is an auto-immune consequence 2° to infection with group A *Streptococcus* (GAS), causing a sub-acute generalized inflammatory response and an illness that affects mainly the heart, joints, brain, and skin.
- ARF results from a complex interplay between susceptible hosts, virulence of GAS strain, and environmental features (Fig. 6.3).
- The prognosis of rheumatic fever is almost solely determined by its cardiac sequelae. Cardiac involvement leads to rheumatic heart disease (RHD). People who have had ARF previously are at higher risk of subsequent episodes which may cause further cardiac valve damage.
- Arthritis occurs early and more frequently in large joints. Lower extremities are generally affected initially followed by upper extremities. It is often, but not always, transient and self limiting.

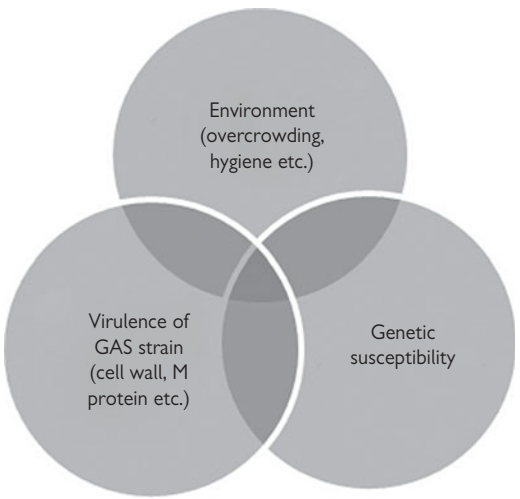

Fig. 6.3 ARF pathogenesis.

Epidemiology

- The mean annual incidence is 19/100,000; a higher incidence of >10/100,000 was reported in Eastern Europe, the Middle East, Asia, and Australasia and a far lesser incidence of ≤10/100,000 was found in Western Europe and North America; the difference is probably due to improved hygiene standards. In Western Europe and North America, periodic outbreaks occur rather than an endemic form.
- RHD is the most common form of acquired paediatric heart disease in the world and thus is the leading cause of cardiac death in the first 5 decades of life. Notably, Kawasaki disease is now the commonest cause of acquired paediatric heart disease in developed countries including the UK and North America (see 📖 chapter on Kawasaki disease, p 183).
- Worldwide, an estimated 5–30 million children and young adults have chronic RHD, and 90,000 patients die from this disease each year.

Clinical features (Table 6.1)

Table 6.1 Clinical features

Musculoskeletal	Non- musculoskeletal
• Polyarthritis • Arthralgia-migratory • Fatigue • Malaise • Motor dysfunction	• Antecedent sore throat • Fever, pallor, weight loss • Erythema marginatum, SC nodules • Neurological involvement—Sydenham's chorea • Irritability and personality change—PANDAS • Headache • Epistaxis • Abdominal pain, vomiting • Rheumatic pneumonia • Chest pain (valvulitis, carditis), orthopnoea • Microscopic haematuria, pyuria

Modified Jones criteria

The Duckett Jones criteria (revised by the American Heart Association, and now referred to as the modified Jones criteria: the latest updated revised criteria were published in 1992) are *guidelines* to assist the physician to diagnose ARF:

- If evidence of a preceding GAS infection (positive throat culture for GAS, positive rapid streptococcal antigen test, elevated or rising streptococcal antibody titre, most often antistreptolysin O) *plus*
- Presence of 2 major criteria; or 1 major and 2 minor criteria (Table 6.2) is suggestive of ARF.

Table 6.2 Modified Jones criteria in diagnosing ARF

Major manifestations	Minor manifestations
1. Carditis*	1. Arthralgia
2. Polyarthritis	2. Fever
3. Chorea	3. Elevated acute phase reactants (ESR, CRP)
4. Erythema marginatum	4. Prolonged PR interval
5. Subcutaneous nodules	

*Data were insufficient to allow echocardiographic documentation of mitral or aortic regurgitation in the absence of auscultatory findings as the sole criterion for valvulitis.

Investigations

- White blood cell count.
- ESR (repeat weekly once diagnosis confirmed).
- CRP.
- Blood cultures if febrile.
- ECG.
- CXR.
- Echocardiogram (repeat as necessary in 2–4 weeks if equivocal or if serious carditis).
- Throat swab (preferably before giving antibiotics)—culture for group A *Streptococcus*.
- Anti-streptococcal serology: both anti-streptolysin O and anti-DNase B titres, if available (repeat 10–14 days later if 1st test not confirmatory).

Management

Antibiotics

- Oral penicillin V (1–6yr: 125mg qds; 6–12yr: 250mg qds; 12–18yr: 500mg qds) should be commenced in all cases while the diagnosis is being established.
- Oral erythromycin (2–8yr: 250mg qds; 8–18yr: 500mg qds) used in cases with reliably documented penicillin allergy.
- To reliably eradicate GAS, antibiotics should be given for the full 10 days.

Arthritis/arthralgia

Controlled trials show response with salicylates or NSAIDS often within hours and almost always within 3 days (Level II). Mild arthralgia and fever may respond to paracetamol alone.

Carditis/heart failure
- Diuretics/fluid restriction for mild-moderate failure.
- ACE inhibitors for more severe failure, particularly if aortic regurgitation present.
- Glucocorticoids optional for severe carditis.
- Digoxin if atrial fibrillation present.
- There is little experience with β-blockers in heart failure due to acute carditis, and their use is not recommended (Grade D evidence).
- Bed rest.

Chorea
- Sydenham's chorea is self-limited.
- Carbamazepine can be used initially for severe chorea and valproic acid be considered for refractory cases (Level III 2, Grade B).
- Medication should be continued for 2–4 weeks after chorea has subsided and then withdrawn.
- Remember that antiphospholipid syndrome (APS) can cause cardiac valve pathology (including the mitral valve) and chorea and thus may mimic rheumatic fever (see 🕮 APS, p 279).

Valve surgery
- Usually deferred until active inflammation has subsided.
- Rarely, valve leaflet or chordae tendinae rupture leads to severe regurgitation which requires emergency surgery.
- Valve replacement, rather than repair, is usually performed during the acute episode, because of the technical difficulties of repairing friable, inflamed tissue.

Prevention
- 1° prophylaxis: ARF episodes can be prevented by antibiotic treatment of GAS throat infections.
- 2° prophylaxis: to prevent recurrent episodes of ARF in patients with credible history of ARF or RHD, 2° prophylaxis is recommended.
  - Register based co-coordinated control programs with regular (3-weekly) IM benzathine penicillin G (1.2 MU or 600,000 U if <20kg) in association with education is effective.
  - Alternatives include oral phenoxymethylpenicillin (1 month–6yr: 125mg bd; 6–18yr: 250mg bd.), or erythromycin (1 month–2yr: 125mg bd; 2–18yr: 250mg bd.).
- A vaccine for GAS is in development.

Differentiation from post streptococcal reactive arthritis (PSRA)
- PSRA is a term coined in 1980s to differentiate a group of patients from ARF with no/less incidence of carditis and where modified Jones criteria are usually not met.
- The incidence of ARF in the USA and Western Europe is ↓, and PSRA is more prevalent.

- PSRA patients are generally older, have a longer interval between group A *Streptococcus* infection and symptom onset, and respond less dramatically to salicylates than ARF patients.
- The course of PSRA is characterized by arthritis that, in contrast to ARF, is additive, non-migratory and is frequently chronic.
- Extra-articular manifestations including renal involvement can be present with PSRA.

Further reading

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Lyme disease

Lyme disease is caused by infection from the spirochaete *Borrelia burgdorferi,* transmitted by the bite of the *Ixodes* tick, and can affect the skin, joints, nervous system, and heart.

For the rheumatologist the task is to distinguish the arthritis caused by Lyme disease (most commonly a monoarthritis affecting the knee) from that due to other diseases such as JIA, septic arthritis, or TB (Table 6.3). If this distinction is correctly made, and appropriate treatment delivered, Lyme disease in children usually has an excellent prognosis. However, the rheumatologist also needs to be aware of the ongoing controversy surrounding the phenomenon of 'chronic Lyme disease' and the evidence base behind it.

Aetiology and epidemiology

- *Borrelia burgdorferi* is transmitted by a bite from a tick of the *Ixodes* genus, after the tick has been attached for more than 24h. The patient is often unaware of having been bitten.
- The tick is mainly found in temperate regions of Europe, NE USA, Asia, most commonly in or near densely forested areas. The incidence of Lyme disease is approximately 69 per 100,000 but may be as high as 1:100 in hyperendemic areas.

Clinical presentation

Early localized—erythema chronicum migrans

- First presentation in 89% of children.
- Days to weeks after tick bite.
- Expanding over days to weeks, 8–50cm in diameter.
- May be associated with flu-like symptoms.

Early disseminated

- Weeks after infection.
- Neurological: facial nerve palsy, lymphocytic meningitis, rarely meningoencephalitis.
- Cardiac: conduction defects.
- Articular: arthralgia.

Late disease

- Predominantly articular; chronic cutaneous and neurological features can occur but are uncommon, especially in children, who are more likely to have arthritis as the sole presenting problem.
- Occurs weeks to months after initial infection.
- Arthritis—most commonly single knee with intermittent, relatively painless large effusions lasting days/weeks, remitting and recurring course.
- Small joints not affected.

Table 6.3 Clinical features of Lyme arthritis compared with septic arthritis and JIA

Lyme arthritis	Septic arthritis	JIA
History of tick bite/travel to forested area exposure to ticks		May be associated with rash, uveitis, autoantibodies
Monoarthritis, large joints Small joints not affected	Monoarthritis, any joint	Any joints may be affected, any number
Intermittent/recurrent symptoms	Persistent symptoms	Persistent symptoms >6 weeks
WBC, ESR, CRP may be normal or raised. Not febrile in late disease	WBC, ESR, CRP raised. May be febrile	WBC, ESR, CRP may be normal or raised. May be febrile
May be relatively painless, not usually stiff	Extremely painful, often unable to weight-bear	May be relatively painless, commonly stiff
High synovial fluid WBC	Very high synovial fluid white blood cell count. Organisms cultured	Moderately raised synovial fluid WBC

NB Always consider TB in cases of monoarthritis (see 📖 TB, p 356).

Diagnosis

Need clinical features *plus* history of exposure *plus* positive serology.

Serology

- Enzyme immunoassay for IgG is sensitive but not specific—if positive, do Western blot (immunoblot is highly specific as well as sensitive). Arthritis is a late stage finding, so by the time this occurs IgG levels are high on Western blot, and serology is therefore reliable.
- If Western-blot negative, then a positive/indeterminate enzyme immunoassay is a false positive.

Joint fluid assessment

- Helpful in excluding septic arthritis.
- PCR for *Borrelia burgdorferi* DNA is very useful in previously untreated patients, with higher positivity on synovial tissue than fluid. Culture of *B. burgdorferi* rarely successful from joint fluid/synovial biopsy.

Treatment (Box 6.1)

Box 6.1 Summary of IDSA treatment guidelines*

- 4 weeks of:
  - Oral doxycycline 1–2mg/kg bd if >12yr.
  - Oral amoxycillin 50mg/kg/day in 3 doses if <12yr.
- For meningitis/peripheral nerve involvement 2 weeks of IV antibiotics** (ceftriaxone).
- For meningoencephalitis 3 weeks of IV antibiotics** (ceftrioxone or cefotaxime).

* Based on Infectious Diseases Society of America guidelines (2006): http://www.idsociety.org/lymedisease.htm.
** Ceftriaxone 75–100mg/kg od or IV cefotaxime 50mg/kg tds.

- If persistent symptoms after 3 months try a second 4-week course of oral or IV antibiotics.
- Thereafter, if persistent symptoms try NSAIDs, IA steroid injections, or DMARD.

Prognosis

- Children treated according to the IDSA guidelines summarized in Box 6.1 have an excellent prognosis, and do not go on to develop chronic arthritis, joint deformities, or recurrence of infection.
- Some patient groups and practitioners advocate that Lyme disease can manifest as a chronic illness, able to evade conventional medical tests and treatments.
- There is no evidence to support this view, or to show that persistent arthritis is due to continuing or refractory infection, and therefore amenable to prolonged courses of antibiotics.
  - The paediatric rheumatologist needs to be aware that non-accredited laboratories/clinics sometimes incorrectly make a diagnosis of chronic Lyme disease in patients with medically unexplained symptoms based on substandard or inherently unreliable tests.
  - In the UK the Department of Health have provided specific guidance on this difficult subject, found at: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/LymeDisease/GeneralInformation/lym020UnorthodoxPractices/.

Varicella zoster infections

1° infection with varicella zoster virus (VZV) causes varicella (chickenpox), while its reactivation from latency produces zoster (shingles). Cellular immunocompromise dramatically ↑ the risk of severe and disseminated varicella, including potentially fatal pneumonitis, encephalitis, and hepatitis. In children who have already acquired VZV, immunosuppression ↑ both the rate and severity of zoster; 2nd episodes of varicella are also well-described. VZV disease therefore requires active management in children with present or anticipated immunosuppression. Children may be immunosuppressed due to their underlying diagnosis (e.g. JSLE with lymphopenia) or more commonly due to therapy. Relevant immunosuppressive drugs include systemic corticosteroids (equivalent to prednisolone 1mg/kg/day for 1 month or 2mg/kg/day for 1 week within the previous 3 months), azathioprine, ciclosporin, methotrexate, cyclophosphamide and biologics e.g. anti-TNF therapy, anakinra, tocilizumab etc.

Assessment of VZV immunity

- At diagnosis, assess VZV susceptibility in the patient and family members by eliciting a history of varicella and/or zoster.
- Check VZV serology at diagnosis/prior to commencing immunosuppressive therapy.
- Young children with no history of varicella (or receipt of varicella vaccine—unusual in the UK) are very likely to be seronegative.

Counselling/education

- Families should be warned of the dangers of VZV in immunosuppressed children (see 🕮 Biologics, p 393).
- The need to avoid exposure should be reinforced; varicella vaccination of any other susceptible family members should be advised.
- Families should be advised to contact their medical team immediately in the event of known exposure or suspected VZV disease.

Active vaccination

- The live attenuated varicella vaccine is safe and effective in healthy children above 1yr of age. For optimal protection, 2 doses are advised at least 4 weeks apart.
- Consider vaccinating currently immunocompetent but VZV-susceptible patients who are likely to require immunosuppression later in the disease course (but not for at least 3 weeks). In recently diagnosed oligo-JIA—suggest varicella vaccination at time of joint injection (and can be done at the time of the general anaesthetic). The 2nd dose can be considered 4 weeks later.
- Vaccination is contraindicated in the immunocompromised but not in their healthy varicella-susceptible household contacts—preventing varicella in healthy sibs is an important step towards protecting the immunosuppressed child. *Pre- and post- serology are not required in healthy children; the lack of a history of chicken pox in the young child is a good surrogate for being non immune and vaccination is advised.* Should vaccine-associated rash develop (<5%), there is a small risk of transmission which should be managed as for wild type exposure of the immunocompromised individual.

Post-exposure prophylaxis

- If significant exposure to VZV is recognized, post-exposure prophylaxis should be given to all immunosuppressed patients who are seronegative. (Significant exposure is defined as any household or nosocomial contact with VZV; any face to face contact or 15min in same room as index case of varicella from 48h before rash until all spots crusted over; and contact with exposed dermatomal zoster or any zoster in the immunocompromised.)
- Good evidence supports the use of VZIG as prophylaxis when administered early (<72h) after exposure; in the UK, stocks are held by HPA laboratories or their equivalent who will advise on its appropriate use. See Fig. 6.4 and 'The Green Book' (see 📖 Further reading, p 373).
- High-dose oral aciclovir from <7 to 21 days post-exposure is currently used as an alternative or adjunct to VZIG in some UK centres and should be offered if no VZIG has been given within 72h of exposure; however the evidence base for its use as single agent, post-exposure prophylaxis in the immunocompromised is poor.
- Consider post-exposure prophylaxis using aciclovir in VZV-seropositives who are severely immunosuppressed, e.g. patients on a combination of steroids and biologics or cyclophosphamide.
- Neither VZIG nor aciclovir is completely effective in preventing varicella; clinical infection may follow after a prolonged incubation period (21–28 days post-exposure) and although usually mild, may occasionally be severe.
- Irrespective of serostatus and prophylaxis after exposure, families should be advised to examine the patient daily for spots and report any suspicion of illness immediately (including non-specific symptoms such as fever, back/abdominal pain as well as rash).

Treatment

- Prompt initiation of antiviral therapy contains viral replication and reduces the risk of dissemination in both varicella and zoster.
- Immunosuppressed children with suspected VZV disease should be admitted without delay to an isolation cubicle for IV aciclovir and general supportive care.
- Suggested laboratory work-up includes FBC, liver and renal function; consider baseline CXR.
- IV aciclovir dose is 500mg/m^2 8-hourly (3 months–12yr), 10mg/kg 8-hourly (12–18yr). Recommended duration of therapy is at least 7 days; persist with IV therapy until fever and constitutional symptoms have resolved and no new spots have appeared for 48h.
- Remember to consider the possible need for post-exposure prophylaxis among susceptible nosocomial contacts.

Further advice

Paeditric infectious disease specialists, virologists, public health agencies (in the UK see: http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1287147556958).

Further reading

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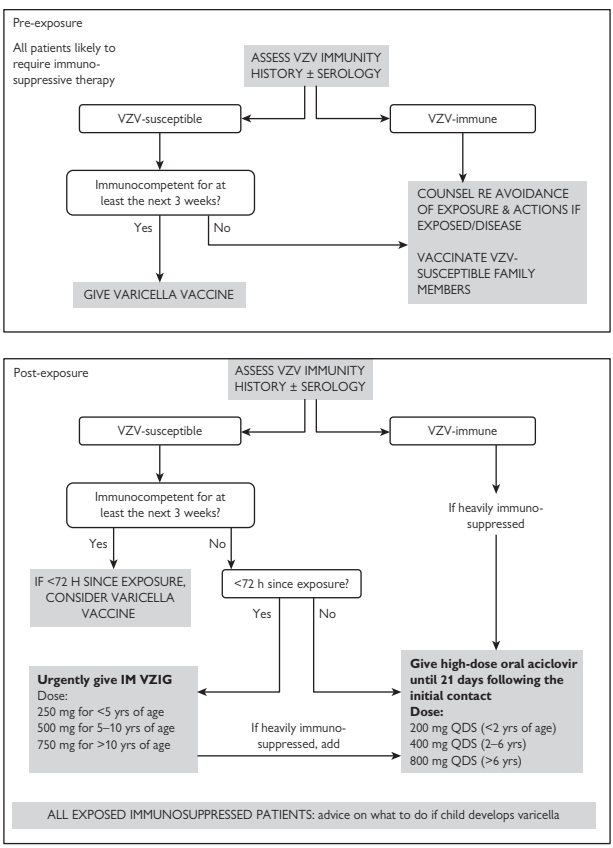

Fig. 6.4 Guidelines for the prevention of severe VZV infection in the immunocompromised child.

Immunization schedules and the immunocompromised

General principles which guide immunization of children who are taking immunosuppressive treatments (such as MTX, MMF, azathioprine, cyclophosphamide, biological agents, and systemic corticosteroids) include the following:

- The routine childhood immunization schedule should be followed with the exception (in general) of live vaccines.
- Live vaccines may be given once the child has been off systemic corticosteroid treatment for >3 months, and off other or combination immunosuppressive treatment for >6 months.
- The dose and duration of systemic corticosteroid treatment that results in significant immunosuppression is usually considered to be prednisolone 2mg/kg/day for >1 week, or 1mg/kg/day for >1month.
- Influenza vaccine should be given annually each autumn.
- If circumstances permit, varicella zoster antibody status should be checked prior to starting immunosuppressive treatment; where appropriate, varicella zoster vaccine should be given at this time (see 🕮 Varicella, p 371).
- Consider giving varicella zoster vaccine to seronegative family members to provide indirect protection for susceptible patients.
- Administration of live vaccines (except MMR and BCG) to siblings of immunocompromised patients, especially live oral polio vaccine (OPV), should be avoided. Patients should also avoid close physical contact with children vaccinated with OPV for approximately 4–6 weeks following administration.

Table 6.4 includes a list of vaccines recommended in the UK national schedule for healthy individuals, and states their suitability in the patient taking immunosuppressive treatment. Table 6.5 lists other vaccines that are available and their suitability for the immunosuppressed patient.

Live vaccines may be given to immunocompromised children in exceptional circumstances (e.g. a child returning to a home country where yellow fever is endemic). However it is strongly advised to seek specialist advice before taking such a decision. In children taking immunosuppressive treatment there is evidence of good efficacy and safety for the use of inactivated vaccines. Transient flares of disease have been reported.

Table 6.4 Vaccines recommended in the UK national schedule for healthy individuals

Age	Immunization (vaccine given)	Type *Live/ inactivated*	Suitability for the child who is taking immunosuppression
2 months	**DTP/polio/Hib** (diphtheria, tetanus, pertussis (whooping cough), polio, and *Haemophilus influenzae* type b)—all-in-one injection	Inactivated	Can be given
	PCV (pneumococcal conjugate vaccine)—in a separate injection	Inactivated	Can be given
3 months	**DTP/polio/Hib** (2nd dose)	Inactivated	Can be given
	MenC (meningitis C)—in a separate injection	Inactivated	Can be given
4 months	**DTP/polio/Hib** (3rd dose)	Inactivated	Can be given
	MenC (2nd dose)—in a separate injection	Inactivated	Can be given
	PCV (2nd dose)—in a separate injection	Inactivated	Can be given
Around 12 months	**Hib/MenC** (combined as one injection—4th dose of Hib and 3rd dose of MenC)	Inactivated	Can be given
Around 13 months	**MMR** (measles, mumps and rubella—combined as one injection)	Live	Contraindicated
	PCV (3rd dose)—in a separate injection	Inactivated	Can be given
Around 3yr and 4 months	'Pre-school' booster of: **DTP/polio** (diphtheria, tetanus, pertussis and polio)	Inactivated	Can be given
	MMR (2nd dose)—in a separate injection	Live	Contraindicated
Around 12–13yr (girls)	**HPV** (human papillomavirus)—**three injections** The 2nd injection is given 1–2 months after the 1st one. The 3rd is given about 6 months after the 1st one	Inactivated	Can be given
Around 13–18yr	**Td/Polio booster** (a combined injection of tetanus, low-dose diphtheria, and polio)	Inactivated	Can be given
Adults	***H. influenzae* and PCV** if aged 65 or over or in a high-risk group **Td/polio**—at any age if you were not fully immunized as a child	Inactivated	Can be given

Table 6.5 Other vaccines that are available and their suitability in the immunocompromised

Vaccine	Targeted population	Type (Live/ inactivated)	Suitability for the child who is taking immunosuppression
BCG	Susceptible population	Live	Contraindicated
Varicella	Varicella non-immune patients with high risk or their close contacts	Live	Contraindicated
Hepatitis B	Children at high risk of exposure to virus or complications of disease/ babies born to infected mothers	Inactivated	Can be given
Influenza vaccine (currently available as combination with pandemic H1N1 strain)	Children at ↑ risk of morbidity and mortality from influenza infection	Inactivated	Strongly recommended
Measles	Those who decline MMR	Live	Contraindicated
Mumps		Live	Contraindicated
Rabies	Exposure to animals suspected to be infected	Inactivated	Can be given
Yellow fever	Children >9 months of age travelling to Yellow fever endemic zones	Live	Contraindicated
Typhoid	Children >1yr travelling to areas endemic to typhoid	Inactivated Vi vaccine	Can be given
		Live Ty21a oral vaccine	Contraindicated

Further reading

Royal College of Paediatrics and Child Health. *Immunisation of the Immunocompromised Child: Best Practice Statement*. London: Royal College of Paediatrics and Child Health, 2002. Available on BSPAR website: http://www.bspar.org.uk/pages/clinical_guidelines.asp.

Salisbury D, Ramsay M, Noakes K (eds) *Immunisation against infectious disease – 'The Green Book'* http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_079917.

Heijstek MW, Ott de Bruir LM, Bijl M, *et al*. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis* 2011; **70**(10):1704–12.

Chapter 7

The multidisciplinary approach to management

The multidisciplinary team

- The experienced MDT is integral to the holistic management of children and young people with rheumatic disease with the patient and family at the centre (Fig. 7.1) with input from specialist consultant, specialist nurse, paediatric physiotherapist and paediatric occupational therapist.
- In the context of JIA the role of the MDT is paramount with children and emphasized in the BSPAR Standards of Care (see 🕮 Chapter 9, p 409).

The composition of the paediatric rheumatology MDT may vary from centre to centre and may often involve a managed clinical network with colleagues in primary, community, and hospital care. The roles of the members of the MDT may overlap and are often complementary. The BSPAR position statement outlines the requirements for training and expertise for the MDT. The clinical roles of the nurse specialist, physiotherapist, occupational therapist, and podiatrist are detailed in the rest of this chapter and reference to the important other members of the MDT are given in other chapters in the handbook (see 🕮 Pain, p 87) for the role of the clinical psychologist in the context of chronic pain management). The roles of the parent and child/young person in research are also given.

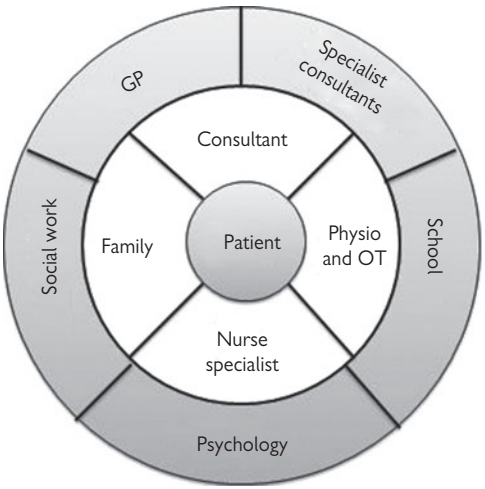

Fig. 7.1 Patient-centred MDT management.

The paediatric rheumatology MDT

Core members

Access to named member required by every child or young person with JIA:

- Paediatric rheumatologist
- Ophthalmologist
- GP
- Paediatric rheumatology clinical nurse specialist
- Paediatric physiotherapist
- Paediatric clinical psychologist
- Paediatric occupational therapist
- Podiatrist
- Health visitor or school nurse
- The child and parent/carer.

The extended team

Access to named member required if clinically indicated:

- Shared care delivery (paediatrician with an interest in rheumatology or adult rheumatologist)
- Adult rheumatologist for transitional care
- Children's community nursing team
- Play therapist/youth worker
- Special educational needs coordinator
- Orthodontist/dentist/maxillofacial surgeon
- Orthopaedic surgeon
- Endocrinologist.

NB The extended team may work in conjunction with a paediatrician with an interest in paediatric rheumatology or an adult rheumatologist with an interest in paediatric rheumatology (operating within a formal paediatric rheumatology clinical network).

Further reading

Baildam EM, Davidson JE. BSPAR Position Statement on Professional working in Paediatric Rheumatology. *Rheumatology (Oxford)* 2008; **47**(6):743–4. http://www.bspar.org.uk/downloads/clinical_guidelines/Final_BSPAR_Position_Statement_on_Professionals_working_in_Paediatric_Rheumatology_Teams.pdf.

Davies K, Cleary G, Foster HE, *et al.* on behalf of the British Society of Paediatric and Adolescent Rheumatology: BSPAR Standards of Care for children and young people with Juvenile Idiopathic Arthritis. *Rheumatology* 2010; **49**(7):1406–8. http://www.bspar.org.uk/downloads/clinical_guidelines/Standards_of_Care.pdf.

The role of the clinical nurse specialist

The specialist nursing team is integral to the clinical service in paediatric rheumatology and such nurses will be qualified as children's nurses with varied training background and experiences. The role of the specialist nurse has evolved rapidly largely as a result of the era of potent immunosuppression such as biologics and the more pro-active pharmacological approach to management of paediatric rheumatic diseases. The role of the clinical nurse specialist (CNS) is described in the British Society for Paediatric and Adolescent Rheumatology (BSPAR) Position Statement (see 📖 Further reading, p 381) albeit details of the roles and responsibilities may vary between local services.

Such roles may include:

Clinical coordination

- Holistic care for the child and young person with chronic illness, acting as patient and family advocate in clinical decision-making.
- Clinical care for children with complex illness and often involving other specialist services including child protection as necessary.
- Clinical networks and regional shared care services.
- MDT meetings and their documentation.
- Day-case administration of infusions such as biologics, cyclophosphamide pamidronate.
- DMARDs and biologic therapy monitoring and liaising with home delivery services.
- Telephone helpline and triage of queries.
- Transitional care and transfer to adult services.

Other clinical roles

- Nurse-led review clinics.
- Joint injections and delivery of Entonox®.

Clinical governance

- Clinical guideline development and audit to deliver high-quality care.
- Patient information leaflets and educational resources.
- Development of proformas and checklists for use of biologics in accordance with national guidance (see 📖 Approvals for use of biologics therapies, p 393 and p 399).

Training and education

- Disease and treatment education for patients and their families, medical and allied health colleagues involved in shared care (community, general paediatric and primary care).
- Disease and treatment education to school and educational services.
- Training and support for patients and families regarding immunosuppressive treatments and home administration where appropriate.

Service development

- National guidance on clinical services development through national bodies (such as BSPAR in the UK) and links with other professional bodies (e.g. Royal College of Nursing—see 🕮 Further reading, below).
- Development of training programmes for parenteral methotrexate for nurses to train patients and families.
- Liaising with pharmaceutical companies to develop information packs and devices that are appropriate for use in children and young people.

Research

- Contribution to clinical research priority setting within national professional bodies (such as BSPAR and CSG).
- Participation in obtaining informed consent and data collection for clinical trials, registries, and clinical research activities.
- Support for children and families taking part in clinical trials.

Further reading

Baildam EM, Davidson, JE. BSPAR Position Statement on Professional working in Paediatric Rheumatology. *Rheumatology (Oxford)* 2008; **47**(6):743–4.

The following documents are available on the BSPAR website (🖱 http://www.bspar.org.uk).

Department of Health (2004) *National Service Framework for Children, Young People and Maternity Services.* London: DoH.

Royal College of Nursing. *Adolescent transition care – Guidance for nursing staff.* London: RCN, 2004.

Royal College of Nursing. *Administering subcutaneous methotrexate for inflammatory arthritis: Guidance for nurses.* London: RCN, 2007.

Royal College of Nursing. *Assessing, managing and monitoring biologic therapies for inflammatory arthritis.* London: RCN, 2009.

Royal College of Paediatrics and Child Health. *Bridging the Gaps: Health care for Adolescents.* London: RCPCH, 2003.

The role of the physiotherapist

Generic roles of the physiotherapist

- Assessment of musculoskeletal system:
  - Joints—active disease, range of movement, abnormal biomechanics.
  - Muscles—strength, stamina, length, and biomechanics and normal patterns of movement.
  - Generalized stamina and fitness.
  - Balance, proprioception, and gait.
- Physiotherapy treatment can:
  - Reduce pain, reduce fatigue, and ↑ energy.
  - Improve or maintain joint range of movement, minimize joint deformity.
  - ↑ or maximize muscle strength and function, ↑ generalized fitness.
  - Improve balance and proprioception, restore normal gait patterns.
- Family and patient education:
  - Pain management, disease management, goal setting and pacing.
  - Ensure full participation with school, family and friends, advice re sport and physical activity.

Condition-specific focus

Juvenile idiopathic arthritis

- Combined with medical management aim to maintain full range of movement in all joints.
- Maintain full muscle strength for all muscle groups.
- Re-education balance and proprioception, re-educate gait.
- Regain full fitness to ensure full participation with all sport and physical activities.

Juvenile dermatomyositis

- Physiotherapy combined with medical management and ideally started at the time of diagnosis:
  - Muscle function assessments (see 🕮 JDMS, p 266).
  - Maintenance of full muscle length/joint range (splinting, stretching, active movement).
  - Encouraging muscle function immediately; advice on safe handling and mobility.
- Graduated and progressive, resisted specific muscle strengthening programme with re-education balance, proprioception, and gait with aim to regain to full fitness to ensure optimal participation.

Juvenile systemic lupus erythematosus

- ↑ general fitness to reduce fatigue.

Juvenile scleroderma

- Assessment and monitoring of progression combined with medical management:
  - Stretches to maintain joint range, muscle length, skin mobility.
  - Deep tissue massage, wax treatment, and specific muscle strength training.

Non-inflammatory musculoskeletal pain syndromes

- Hypermobility/anterior knee pain/back pain—please see appropriate other 📖 chapters for details of the conditions, p 117 and p 124.
  - Assessment of biomechanical changes, specifically muscle function.
  - Explanation for young person and family about pain and treatment goals and objectives—regain full specific muscle strength/stamina with progressive/resisted specific muscle training, high reps and low weights emphasized.
  - Pain management techniques, restore balance and proprioception, re-educate gait.
- Complex regional pain syndrome:
  - Family education about disease and treatment; function despite pain approach.
  - Regain normal movement of affected limb immediately to reduce pain—desensitization is most effective through regaining normal movement and muscle strength.
  - Regain all physical, social, and psychological function.
- Chronic fatigue:
  - Education about paced approach to life, specific strength training, global fitness training.
  - Training to be 'fit for life'.

The role of the occupational therapist

The occupational therapist (OT) works within the MDT to encourage, motivate, and support patients and their families through periods of change to promote functional independence appropriate to their developmental age and stage, encompassing their life roles within their environments to lead full, satisfying lives. The therapeutic relationship forged with the family is likely to be long term and the success of that relationship is central to promoting the functional independence, social inclusion, and sense of well-being an individual associates with their self-actualization. The OT is functionally not diagnostically led, and uses a holistic assessment using a bio-psychosocial approach. The roles of the OT may be summarized as follows:

Clinical role

- To encourage, motivate, and support the young person and their family, especially at the point of diagnosis or transition to enable functional independence and self-advocacy.
- Provide specific disease education for the young person and their family at the correct level for their understanding/needs.
- To carry out a holistic standardized assessment (such as that defined by BSPAR), with regular monitoring of individual function, appropriate to the young person's developmental level—see http://www.bspar.org.uk/pages/bspar_home.asp.
- To help the young person manage pain, fatigue, anxiety, and psychosocial difficulties, through educative coping strategies.
- To act as an advocate, upon the young person's behalf and support development of self-esteem and self-confidence in activities of daily living.
- To provide advice to schools and other educational establishments, in order to promote inclusion, participation, and fulfilment of the young person's potential.
- To promote joint protection strategies during activities of daily living.
- To encourage ↑ physical functioning during periods of acute and chronic disease activity, utilizing pacing and energy conservation techniques.
- To carry out a transitional assessment/review prior to transfer to adult services.
- To provide appropriate upper limb splinting, albeit this is required less with current treatment approaches.
- Promote evidence based practice, implementing Standards of Care (e.g. BSPAR Standards of Care in JIA, see Chapter 9, p 409) and audit to promote high-quality clinical care.
- Training and education of colleagues working within clinical networks.
- Contribute to the development of evidence-based practice through research activity and promote the evolving role of the OT within paediatric rheumatology.

Further reading

Melvin J, Jensen G. *Rheumatologic Rehabilitation Series Volume 1: Assessment and Management.* Bethesda, MD: The American Occupational Therapy Association, 1998; p. 308.

The role of the podiatrist

The podiatrist has a specialized role to treat structural and functional problems in the feet, although there is some overlap with physiotherapists and orthotists depending on provision of services in the primary and hospital care settings. The podiatrist's 1° role is to improve the child's foot position and function, thus increasing the efficiency of gait and reduce soft tissue strain and fatigue. The podiatrist can also advise on and treat skin and nail pathologies that may occur with many of the paediatric rheumatological conditions. *A child should be referred to the podiatrist if the foot is in a poor position leading to an inefficient gait or the foot position is causing discomfort in the foot or is exacerbating problems in other lower limb joints.*

Podiatry therapeutic approaches

- Functional orthosis, footwear advice, and adaptations.
- Gait re-education, exercises, shoe raises, and orthodigital splinting:
  - Orthoses modify the foot position and alter the timing of the foot joint motions during gait and prefabricated orthoses or custom orthoses can be used.

The healthy paediatric foot (see 🕮 Normal variants, p 9)

The healthy child (<6y) will typically have a low-arch profile, bulging talonavicular joint medially, and a valgus heel position. This is called the *pronated*, *pes planus*, or *valgus foot*. The healthy foot is fully mobile and pain-free.

Changes in the foot caused by JIA

- Although possessing individual joint capsules, many of the joints appear to interconnect and synovitis affecting a single foot joint is the exception rather than the rule. Synovitis and stiffness in 1 joint is often accompanied by either reduced movement or a compensatory movement in a neighbouring joint and thus a good overview of foot mechanics and function is essential when treating the foot in inflammatory joint disease.
- With rearfoot and midfoot synovitis in JIA, the bony integrity of the arch is lost and ↑ foot pronation is seen, resulting in an ↑ in soft tissue strain in the foot, including the anti-pronatory muscles which are overused in an effort to stabilize the foot. The foot becomes painful and the gait changes as compensatory movements occur in an effort to off-load painful areas. The affected joints have reduced range of motion and fixed deformities may develop.
- Although the pronated foot type is common when rearfoot and midfoot synovitis is present, many other foot deformities are seen and may be related to the combination of joints affected, to local tenosynovitis, to muscle weakness, or be related to the impact of the more proximal joints on the foot (such as genu valgum and fixed flexion deformities at the hip which influence the foot position).
- Inflammatory joint disease can affect other synovial structures in the foot:
  - Tenosynovitis often occurs in conditions such as JIA.
  - Swelling in the rearfoot needs careful examination to differentiate ankle or subtalar synovitis from tenosynovitis of tibialis anterior, tibialis posterior, or peroneal involvement.

- Although not common, bursitis can occur in the forefoot with RF+ve JIA.
- Enthesitis of the Achilles and plantar fascia insertion is frequently seen in enthesitis-related arthritis and responds well to shock absorbing, custom orthoses.

Leg-length discrepancy in JIA

- This is much less observed with prompt access to appropriate care.
- The asymmetry created by the leg-length discrepancy can have a large impact on the musculoskeletal system with initial compensation mechanisms occurring in the feet and impacting on the knee, pelvis, and spinal positions.
- As a rule of thumb, when a leg-length discrepancy is seen to create asymmetry in gait or joint positions, it should be treated by a full length raise within or placed externally on the sole of the shoe. Such asymmetry is usually observed when a leg-length difference exceeds 1cm.

Compensatory gait change from pain

- Changes in gait occur as the child attempts to reduce the pain and discomfort of walking. These changes may become habitual and remain even when the joint disease has improved.
- It is the role of the podiatrist to assess the child's gait and use re-education or shoe adaptations to improve gait efficiency.

The foot in other rheumatological conditions

- Conditions such as JDM and SLE can affect the feet and require assessment and treatment by a podiatrist
- Muscle weakness associated with JDM may affect the feet by causing an ↑ in the degree of subtalar joint pronation, and 2° contracture (tendoachilles) can cause gait changes and again, excessive foot pronation.

Choice of footwear for children with inflammatory foot disease

- A podiatrist will not prescribe orthoses until the footwear is suitable for the child.
- Good footwear is important for all children to wear, particularly in the presence of joint inflammation or where the foot position requires supporting to reduce soft tissue strain.
- There is no single make of shoe that can be recommended for children therefore it is important to direct the child and parents towards local shoe shops where the staff have a good knowledge of fitting 'difficult' feet, are familiar with fitting a shoe with or without orthoses, and have a range of shoes that they can try.
- A supportive shoe will have a deep heel counter so that the shoe fits snugly up to the malleoli. The heel counter should be strong when squeezed. A fastening mechanism is needed to hold the foot into the strong heel counter and the sole should have some shock absorbing properties.
- A boot is sometimes recommended when extra support is needed as they often have stronger support, higher into the heel counter.

Transitional care

Definitions

- Transition is a multifaceted active process that attends to the medical, psychosocial, and educational/vocational needs of adolescents as they move from child into adult care.
- Transfer to adult services is a single event within this process.

Transition (key principles)

- Is an active, future-focused process with the aim to maximize life-long functioning and potential of young people.
- Is young person-centred and inclusive of parents/care-givers.
- Involves paediatric and adult hospital services as well as primary care, education, social and youth services, and voluntary agencies.
- Is age and developmentally appropriate recognizing the 3 phases of adolescent development: early (11–13yr), mid (14–16yr) and late (17–19yr) as well as emerging adulthood (20–25yr).
- Includes knowledge and skills training for the young person in health and disease education, communication, decision-making, assertiveness, self-care, and self-management.
- Is based on a resilience framework to enhance sense of control and interdependence in healthcare.

Interdependence of adolescent healthcare and transitional care

Transitional care is only one part of adolescent rheumatology care and core principles of adolescent medicine should underpin transitional care including:

- Acknowledgement of the reciprocal influences of adolescent development and the rheumatic condition in question.
- The importance of routine psychosocial screening of all adolescents (e.g. the HEEADS screening tool - Home, Exercise, Education, Activities, Drugs, Sexual health).
- Giving young people the opportunity to be seen independently.
- Respecting and assuring their rights to confidentiality.
- Effective use of strategies including motivational interviewing (see http://www.motivationalinterview.org).
- Adolescent rheumatology services should meet the 'You're Welcome' quality criteria of accessibility, publicity, confidentiality and consent, environment, staff training, joined-up working, monitoring/evaluation involving young people, and adolescent health issues for young person-friendly health services (see http://www.dh.gov.uk).

Core components of transitional care in rheumatology

- Written departmental transition policy agreed with all key stakeholders including young people and parents/care-givers.
- Transition lead professional.
- Transition care coordinator.
- MDT.
- Individualized transition plans—examples given at http://www.bspar.org.uk/pages/adolescentrheum.asp.
- Education, skills training, and informational resources for young people, parents, and professionals.

- Informed adult rheumatology/ophthalmology/orthopaedic/renal services, and primary health care.
- Links with education/vocational/youth/social services and voluntary agencies.
- Administrative support including transfer summaries, tracking mechanisms to confirm attendance at first 2 adult clinic appointments.
- Monitoring, evaluation, and audit of services involving young people.

Individualized transition plans

Individualized transition plans should consider the following issues in a developmentally appropriate context and through education, assessment of understanding, skills-training, and sign-posting to young people:

- Health issues:
  - Specific to rheumatic disease: disease knowledge, treatment, outcome, pain and fatigue management, independent healthcare utilization, self-medication and adherence, procedural pain management etc.
  - Generic health: exercise, healthy eating, sleep, sexual health, smoking, alcohol, recreational/illegal drug use, emotional well-being.
- Psychosocial issues—household chores, independence, self-care, mobility, benefits, driving, leisure activities, social and peer support, self-esteem, body image, bullying, coping strategies.
- Educational/vocational issues:
  - Impact of condition, disclosure, rights, Disability Discrimination Act.
  - Career plan, work experience, career counselling.
- Family issues—concept of transition, knowledge of condition and impact on adolescent development, transitional care needs.

Transition models

- Different models of transition exist depending on the local health services and resources.
  - A developmental transition model includes an adolescent clinic (11–16yr) and young adult clinic (16–25yr).
  - Evidence suggests an early start, ideally in early adolescence.
- The timing of transfer should be flexible, acknowledging disease status, readiness and maturity of the young person, and completion of growth and development.
- An evidence-based transitional care programme showed short-term benefits in rheumatology. Further research is needed to determine long-term outcomes and effectiveness of the young adult clinic model.

Futher reading

BSPAR website: http://www.bspar.org.uk/pages/adolescentrheum.asp for transitional care documents.

Department of Health. *You're welcome quality criteria. Making health services young people friendly*. London: DoH, 2007. http://www.dh.gov.uk.

Department of Health. *Transition: Getting it right for Young People. Improving the transition of young people with long-term conditions from childrens' to adult health services*. London: DoH, 2006. http://www.dh.gov.uk/transition.

DREAM Team website: http://www.dreamteam-uk.org.

e-Learning for Healthcare website: http://www.e-lfh.org.uk.

Goldenring JM, Rosen DS. Getting into adolescent heads: an essential update. *Contemp Pediatr* 2004; **21**(1):64–90.

HEEADSSS and Motivational Interviewing: http://www.motivationalinterview.webs.com/.

McDonagh JE. Young people first, juvenile idiopathic arthritis second: Transitional care in rheumatology. *Arthritis Rheum* 2008; **59**(8):1162–70.

Youthhealthtalk! Website: http://www.youthhealthtalk.org.

Chapter 8

Specialized therapeutic approaches

Corticosteroid intra-articular injections

Intra-articular corticosteroid injections are increasingly used as they allow rapid symptom control and allow time for other therapies, such as methotrexate (MTX) to have their effect. They often remove the need for the use of oral or IV corticosteroids and avoidance of side effects. There is no limit to the number of joints that can be injected at any one time or the total dose of corticosteroid.

Anaesthesia and analgesia

Various modalities are available:

- General anaesthetic is needed for multiple joints or in younger children.
- Inhaled nitrous oxide (Entonox®) is useful in older children and for 1–4 joints.
- 'Wide awake' is feasible in older children and adolescents—ethyl chloride topical spray gives local skin anaesthesia.
- Sedation is not recommended and difficult to achieve adequately—general anaesthetic is a much safer option.

Choice and dose of intra-articular corticosteroid

(see 🕮 Intra-articular corticosteroid use in JIA, p 445)

- Triamcinolone hexacetonide (TH) is the drug of choice with longer duration of remission, less systemic absorption, and without ↑ in local side effects compared to other more soluble corticosteroid preparations. TH is available from specialist suppliers (check with your pharmacy). Triamcinolone acetonide (TA; Kenolog®), is an acceptable alternative but produces many more systemic side effects due to ↑ systemic absorption. Other corticosteroid preparations are not recommended.
- Corticosteroid doses (given assuming TH is used) depends on body weight and the joint injected:
  - Large joints (knees, shoulders, hips): 1mg per kg per joint (max. 40mg/joint)—larger doses may be used in older larger patients albeit expert advice is recommended.
  - Medium joints (ankles, subtalars, elbows, wrists,) 0.5mg per kg per joint (max. 30mg/joint).
  - Temporomandibular joint 0.25mg per kg per joint.
  - Small joints (fingers and toes) 0.04–1mg total dose per joint.

These dosages can be safely rounded up or down and should be doubled when using TA—there is no maximum total dose that can be used at one time, but if TA is used, then there is a significant likelihood of systemic side effects with larger total doses.

Side effects of intra-articular corticosteroids

- Systemic:
  - Transient increases in BP, appetite and weight gain are described and more likely with TA. Striae from weight gain are uncommon.
- Local:
  - Subcutaneous atrophy—most likely with joints with a small intra-articular volume such as fingers, wrists, and subtalar joints.
  - Sepsis—very small risk (<1 in 10,000 with good aseptic technique).

- Peri-articular calcification—observed on x-ray but unlikely to cause clinical symptoms.
- Cartilage growth disturbance—may occur if corticosteroids are incorrectly placed into growing cartilage.
- Correct needle placement and appropriate dosage will reduce but not eradicate local side effects.

Procedure

- Informed consent/assent must be recorded in the patient's case notes and irrespective of the type of anaesthesia used.
- Aseptic technique—operator should have clean hands and wear sterile gloves. Gowns and masks are not necessary. Steroid preparation should be drawn up in a 2mL syringe (or 1mL syringe for PIPJs, MCPJs, and MTPJs).
- Needle size:
  - 21-gauge for shoulders, knees, ankles, and subtalars, 23-gauge for wrists and TMJs, 25-gauge for PIPJs, MCPJs, and MTPJs, Spinal needle should be used for the hips.
  - The needle should be placed into the joint capsule and attempts to aspirate the joint should be made—drawing back synovial fluid confirms needle placement, but the lack of fluid does not necessarily mean that the needle is not in the correct place. Once the operator is happy with the placement of the needle, 50% of the corticosteroid should be injected; the remaining corticosteroid should be injected after waiting a few seconds. The operator should then wait for a further 30sec before removing the needle and then pressing lightly on the injection site.
  - ***Never force an injection:*** if there is a need to use force then it is likely that the needle is incorrectly placed and the procedure should be abandoned and then restarted.
  - The use of an image intensifier or US can be used to aid correct needle placement.

Post-injection management

- Injected joints should be rested for 24h postoperatively—there is no need for bed rest but patients should defer from taking part in vigorous exercise for 48h postoperatively.
- Patients and carers should have clear instructions on who to call in the event of any postoperative complications developing.

Site of injection

- It is important to learn under the guidance of an experienced clinician with opportunities initially to observe and then perform under supervision.
- ***Knee***: the needle is inserted approximately 1cm medial (or lateral) to the patella, at the level of the junction of the upper 2/3 and lower 1/3. The needle is directed slightly caudally and at an angle to go under the patella.
- ***Ankle***: the needle is inserted anteriorly just lateral to the extensor hallucis longus tendon.

- ***Subtalar:*** the needle is inserted perpendicularly into the space just distal to the lateral malleolus.
- ***Hip:*** a line should be drawn between the anterior superior iliac crest (ASIC) and the pubic tubercle. A 2nd line should be drawn from the ASIC towards the medial border of the patella. A 3rd line should be drawn perpendicularly from the mid-point of the 1st line until it bisects the 2nd line. That bisection point is the site of needle entry. The needle is then directed towards the mid-point of the original line and at an angle of 60° to the skin. The needle should be slowly inserted until it hits bone. The needle should then be lying against the neck of the femur. The needle placement should be checked with fluoroscopy prior to injection of the drug.
- ***TMJ:*** the needle is placed a few millimetres anterior to the tragus and advanced until it hits the joint just distal to the head of the mandible.
- ***Shoulder:*** the needle is inserted anteriorly just lateral to the corocoid process and superior to the head of the humerus.
- ***Elbow:*** with the elbow flexed to 90° the needle is inserted between the epicondyles and above the olecranon process.
- ***Wrist:*** the needle is inserted just distal to the end of the radius angled at 60° to the dorsal forearm with the wrist slightly palmar flexed.
- ***Small joints of fingers and toes:*** these joints should only be injected by experienced clinicians. Needle placement should be confirmed by image intensifier or US.

Further reading

Ryder CAJ, Southwood TR, Malleson PN. Intra-articular corticosteroid injections. In Szer I, Kimura Y, Malleson PN, *et al.* (eds.) *Arthritis in Children and Adolescents*. Oxford: Oxford University Press, 2006; pp. 442–7.

Biologic therapies for paediatric rheumatological diseases

Biologic agents are genetically engineered drugs designed to target specific areas of the immune system which are implicated in disease aetiology by selectively blocking inflammatory pathways. They include monoclonal antibodies, soluble cytokine receptors and recombinant receptor antagonists (Table 8.1).

It is recognized that early aggressive management of paediatric rheumatological disease is needed to improve short-term and long-term outcomes and this has been much aided by the advent of biologics, particularly in patients who fail conventional treatment with DMARDs. However, a proportion of children do not respond to initial biologic, flare after period of quiescence, or suffer adverse events necessitating cessation of drug.

In JIA the efficacy of biologics has been shown in recent landmark clinical trials made possible by international multicentre collaboration. There are many reports of efficacy and safety in off-label use of biologics for a range of paediatric rheumatological diseases. There is concern about rare adverse events and long-term safety of biologics with emerging cases of infection, autoimmune disease, malignancy, and demyelination, which highlights the important role of Registries to document efficacy and long-term safety as adverse events may not be identified in short-term clinical trials.

NICE guidance on biologic therapies for JIA in the UK (see 📖 p 399)

- Use of etanercept approved (2002) for children aged 4–17yr with active polyarticular-course JIA who fail to respond adequately to, or who have proved intolerant of, MTX (see 🖱 http://www.nice.org.uk/nicemedia/pdf/JIA-PDF.pdf). Initiation of treatment should be in accordance with relevant sections of the British Paediatric Rheumatology Group (BPRG) protocol (now BSPAR) (see Appendix D in NICE guidelines), undertaken by an experienced consultant together with a nurse specialist who is able to teach families injection techniques.
- Infliximab not currently licensed for JIA in the UK and NICE have withdrawn infliximab from appraisal at this time.
- Abatacept, tocilizumab, and adalimumab have been licensed but not yet appraised by NICE for use in JIA.
- Use of biologics for treatment of JDM, JSLE, CAPs, and vasculitis is currently off-label and not under NICE guidance: see relevant chapters.

Table 8.1 Current use of biologics in paediatric rheumatological diseases (see p 📖 Guidelines and protocols, p 415)

Biologic agent	Mode of action	Administration	Commonly used doses	Current indications	Licensed indications
Abatacept	Humanized selective T cell co-stimulatory modulator	IV infusion	10mg/kg at 0,2,4 weeks then 4-weekly afterwards	#Polyarticular JIA (excluding ERA and PsA; not included in RCT). †JIA-associated uveitis	In USA and EU for refractory polyarticular JIA >6yr
Adalimumab	Humanized soluble anti-TNF monoclonal antibody	SC	24mg/m^2 up to 40mg fortnightly	#Polyarticular JIA. †JIA-associated uveitis. †Systemic vasculitis. †CRMO/SAPHO	EMEA*licence for refractory polyarticular JIA in 4–17yr age.
Anakinra	Humanized anti-IL1 receptor antagonist	SC	2mg/kg daily (max. 100mg)	#Systemic JIA. † Cryopyrin-associated periodic syndromes (CAPS)** †CRMO/SAPHO	Off label
Canakinumab	Human anti–IL-1β monoclonal antibody	SC	2–4mg/kg up to 150mg 8-weekly 4mg/kg, 4-weekly SJIA	# CAPS. #in progressSJIA	In adults and children with CAPS in EU
Etanercept	Soluble TNF p75 receptor fusion protein	SC	0.4mg/kg twice week (max. 25mg twice-weekly).	#Polyarticular JIA (reduced efficacy in SJIA) †ERA. †PsA †JIA <4yr of age. †Systemic vasculitis † CRMO/SAPHO	EMEA licence for refractory polyarticular JIA in age 4–17yr NICE approval. Licensed >2yr in USA

Infliximab	Chimeric human murine anti-TNF monoclonal antibody	IV infusion	6mg/kg. Initially at 0, 2, & 6 weeks; then at intervals of 4–8-weekly depending on clinical response	#Refractory polyarticular JIA. †JIA-associated uveitis. †Refractory JDM. Sarcoid †Systemic vasculitis. †PSA, ERA †Behçet's #Refractory Kawasaki's disease †CRMO/SAPHO	Off label
Rilonacept	Soluble fusion protein of IL-1 receptor and IgG Fc	SC	Initial dose 4.4 mg/kg (max. 320mg) then once-weekly at 2.2 mg/kg (max. 160mg)	#CAPS †SJIA	In adults and children with CAPS in EU & USA (≥12yr age); not yet available in UK.
Rituximab	Anti-CD20 antibody (B cell depletor)	IV infusion (often used synergistically with cyclophosphamide & methylprednisolone	750mg/m^2 (max. 1g) on day 0 and day 14	†JSLE. †SJIA Refractory polyarticular JIA †Refractory JDM †Systemic vasculitis	Off label
Tocilizumab	Humanized anti-IL-6 receptor monoclonal antibody	IV infusion	8mg/kg 2–4-weekly >30Kg 12mg/kg <30Kg (fortnightly initially)	#Systemic JIA	Off label

* EMEA, European Medicines Agency (℞ http://www.ema.europa.eu).

** Cryopyrin-associated periodic syndromes (CAPS) includes familial cold-induced autoinflammatory syndrome, Muckle–Wells syndrome, and chronic infantile neurologic, cutaneous, articular (CINCA) syndrome (also known as neonatal-onset multisystem inflammatory disease [NOMID]).

Level of evidence for efficacy and safety: # indicated clinical trial performed, † indicates case series or observational studies, no symbol indicates clinical use but no paediatric data published.

NB Within clinical trials polyarticular refers to any subtype of JIA that involves ≥4 joints including EOJIA, SJIA, ERA, as well as RF+ve and R|F−ve polyarthritis.

Assessment checklist prior to commencing biologic therapy

- ***Education (verbal and written; ideally provided by rheumatology CNS):***
  - Age appropriate, in format that family understand, with time for reflection to make informed decision.
  - Include knowledge of medication/side effects, dose needed (mg/mL), appropriate storage of medication (if keeping at home) and safe disposal of medication/equipment.
  - A frank and honest discussion is required to maintain trust between child and healthcare workers (e.g. adalimumab and anakinra injections may hurt).
- ***Blood screen:***
  - FBC, ESR, U&E, LFT, CRP, antibody screen (ANA, anti dsDNA, anti ENA, anticardiolipin), hepatitis serology, immunity status (measles, varicella IgG).
- ***Measurements:***
  - Accurate height, weight, and surface area to calculate dose of medication.
  - Plot growth chart.
- ***Risk assessment for tuberculosis (see 📖 TB, p 356):***
  - History—recent visits or previous residence in high-risk countries/close family/friend contact/past history of TB.
  - Baseline CXR for all patients ± Mantoux (if not on immunosuppressant/steroid therapy).
  - Consider immunological testing (T spot or Quantiferon), particularly if high index of suspicion. If positive, treat TB before starting biologic therapy—seek expert advice.
- ***Sexual health and contraception:***
  - Effects of biologic therapy on developing foetus unknown and pregnancy should be avoided. Education needed for all young people with potential of being sexually active (best provided by rheumatology CNS).
  - Meaning of confidentiality should be explained to young person and practiced by health professionals.
- ***Training on SC injections if applicable:***
  - The CNS/nurse teaching the patient/family must have experience and training in giving SC injections and be confident in ability to teach the patient/family, ensuring competence and safety.
  - Important to review injection technique especially if apparent waning of clinical response.
- ***Dealing with needle phobia where applicable:***
  - Suitable environment, allowing element of control with help of play specialist ± psychologist.
- ***Arrange delivery/pick up of medication/equipment:***
  - Homecare delivery services are available to regularly supply. medication direct to the patient's home and collect waste/sharps bins.
  - Some companies provide a teaching/assessing service for home administration.
- ***Safety checks:***
  - Families must understand the importance of safe handling and disposal of medication and equipment.

- ***Vaccinations:***
  - Consider varicella vaccination for non-immune patients if able to delay start of biologic treatment and vaccination not contra-indicated by other immunosuppressive therapy (see 🕮 Varicella, p 371).
  - Families need explicit and written instruction if child is non-immune (e.g. varicella or measles).
  - Live vaccinations (including MMR, varicella, BCG, yellow fever) should ***not*** be given to patients on biologic therapy or for 6 months after treatment has finished (see 🕮 Immunizations, p 355).
  - Killed vaccinations can be administered safely and are recommended (annual flu vaccine, 5-yearly pneumococcal vaccine, human papillomavirus vaccine).
- ***Counselling regarding infection:***
  - Essential that patient and family understand importance of seeking medical advice quickly in event of infection. Biologic treatment may predispose to serious manifestations of common bacterial infections and a low threshold for antibiotics is prudent. Consider opportunistic and atypical infections (see 🕮 Infection and the immunocompromised, p 374).
  - Withhold biologic treatment if child has an infection with raised temperature, but remember that serious infection may be present in the absence of pyrexia in a child receiving immunosuppression.
  - Varicella infection and varicella exposure in the non-immune (see 🕮 Varicella, p 371). In the event of infection, biologic therapy should be stopped until the child is well and the chicken pox lesions have crusted over. If the patient is varicella non-immune and there has been close (family) contacts with chicken pox, give prophylactic VZIG or acyclovir (see 🕮 Varicella, p 371) but the biologic therapy can be continued if the child does not develop lesions beyond the incubation period. It is advisable for a child's school/nursery to inform the family if there is a chicken pox outbreak. Consider vaccination of healthy siblings.
  - Exclude TB prior to starting biologic treatment and have low threshold for investigating for TB if symptomatic on treatment. See 🕮 TB, p 356.
- ***Baseline 'core set criteria' (see 🕮 Outcome measures, p 41 and p 165)***
  - Clearly documented before starting biologic treatment and monitor regularly throughout (recommended 3-monthly for first year).
- ***Supply contact details:***
  - Patient/family should need contact details for the hospital/local services including who to contact at weekends/bank holidays if necessary.
- ***Follow-up appointments and blood monitoring:***
  - Recommended to be at least every 3 months for the first year.
  - Families to be of clinic dates and plans for blood monitoring before discharge.
  - Families to have CNS helpline number.
  - Families to have written instructions when to seek healthcare if child unwell (e.g. febrile) and have open access to day units as necessary.

- ***Monitoring and reporting treatment response adverse events:***
  - For etanercept the BSPAR Biologics and New Drugs Registry: http://www.bspar.org.uk.
  - Other agents used in JIA (and in the future, other diseases) the Biologics for Children with Rheumatic Diseases Registry: http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology/bcrd.
  - In the UK suspected adverse reactions are reported through the 'Yellow card scheme': http://yellowcard.mhra.gov.uk.

Further reading

Beresford MW, Baildam EM. New advances in the management of juvenile idiopathic arthritis – 2: The era of biologicals. *Arch Dis Child Educ Pract Ed* 2009; **94**:151–6.

Gartlehner G, Hansen RA, Jonas BL, *et al*. Biologics for the treatment of juvenile idiopathic arthritis: A systematic review and critical analysis of the evidence. *Clin Rheumatol* 2008; **27**:67–76.

Woo P. Theoretical and practical basis for early aggressive therapy in paediatric autoimmune disorders. *Curr Opin Rheumatol* 2009; **21**:552–7.

Approvals for use of biologic therapies

Etanercept and adalimumab in juvenile idiopathic arthritis (JIA): NICE guidelines (🖰 www.nice.org.uk)

- NICE is funded by the Department of Health (UK) to provide independent appraisal of licensed therapies based on efficacy and cost effectiveness.
- Amongst the biologics, to date only etanercept (Enbrel®) has been fully appraised by NICE (2002: 🖰 http://guidance.nice.org.uk/TA35/Guidance/pdf/English)—see Tables 8.2 and 8.3.
- Adalimumab (Humira®) gained its licence for use in JIA in September 2008, is on the NICE portfolio but has yet to be appraised—see Tables 8.2 and 8.3.
- NICE advocates that patients on these biologics undergo long-term monitoring and surveillance (see 📖 Biologics and guidelines, p 415):
  - For etanercept, the BSPAR Biologics and New Drug Registry: 🖰 http://www.bspar.org.uk/pages/home.asp
  - All other biologics, the Extended Biologics Registry: 🖰 http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology/bcrd.

Table 8.2 Indications for etanercept and adalimumab as per NICE guidance

Etanercept	Children aged 4 to 17 years who have active JIA in ≥5 joints and whose condition has not responded adequately to MTX (3 months at a dosage of parenteral MTX = 20mg per m^2 once-weekly unless toxicity occurs) or those who have been unable to tolerate treatment with MTX. Etanercept is also licensed for use in psoriasis in children over 8yr
Adalimumab	Albeit licensed for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 4 to 17 years, NICE guidance stipulates that Adalimumab may be used in young people aged 13 to 17 years who have active polyarticular JIA, in combination with MTX. Adalimumab can be given as a mono-therapy where there is intolerance to MTX or when continued treatment with MTX is inappropriate. Adalimumab is licensed for the treatment of uveitis in adults in the USA

Table 8.3 Preparations available

Etanercept	• 25mg paediatric vial and solvent—multi-dose (x2) • 25mg vial and solvent—single use • 50mg pre-filled syringe • 50mg pre-filled pen device (MYCLIC)
Adalimumab	• 40mg pre-filled syringe • 40mg pre-filled pen device

Further reading

Royal College of Nursing. Assessing, managing and monitoring biologic therapies for inflammatory arthritis: guidance for rheumatology practitioners. London: RCN, 2009. http://www.rcn.org.uk.

Medicines for children and paediatric rheumatology

- Many drugs prescribed for children are used outside the terms of their product licence ('off-label') or are not licensed for any use in the applicable country.
- It is the responsibility of the prescriber to ensure an appropriate evidence base for safety and efficacy exists for an unlicensed use and specific guidance is provided by the General Medical Council (http://www.gmc.org.uk).
- The Summary of Product Characteristics (SmPC) for the drug product in question (http://www.medicines.org.uk/emc) should be consulted to ascertain the licensed indications, dosages, precautions, and possible side effects.

Paediatric pharmacokinetics

Growth and development influence the absorption, distribution, metabolism, and excretion (ADME) of drugs requiring constant adjustment of dosage regimens from birth to adolescence. In addition, it should be noted that:

- Absorption and bioavailability are influenced by the choice of formulation, route, fed/fasted state, and concomitant medication for the oral route and by the need for manipulation of the dosage form, which will additionally affect dose accuracy.
- Metabolism and excretion can be affected by the complexity of some multi-system auto-immune, auto-inflammatory disorders where renal and hepatic involvement may be part of the underlying disease process (e.g. SLE, sJIA, systemic vasculitides) and by concomitant medications that induce or inhibit drug metabolizing enzymes or affect renal function, thus impacting upon efficacy and toxicity which may necessitate dose adjustment or monitoring.
- Drugs with a narrow therapeutic index require close monitoring and dose adjustment (e.g. MTX, ciclosporin). Conditions such as nephrotic syndrome can affect drug excretion.

Safety issues

- Manual handling and inadvertent exposure to cytotoxic drugs (MTX, azathioprine, cyclophosphamide) must be avoided. Cytotoxic injectables should be prepared in the pharmacy in accordance with national guidance and local management policy on safe preparation and administration.
  - If manipulation (e.g. opening capsules or breaking tablets) is required, it should be referred to the pharmacy.
- Be aware of different product strengths available (e.g. MTX tablets and unlicensed MTX oral liquids) that can lead to dosing errors. Patients and carers should be educated to check every new prescription, dispensed product, and dosing instructions. Recommendations in safety alerts issued for MTX should be complied with. For primary care transfer, discharge letters should specify the strength to prescribe (plus manufacturer if difficult to source) and relevant monitoring.

- Monoclonal antibody (mAb) products should be treated as biohazardous—insufficient data exists on low-level long-term exposure to mAbs. Safe preparation and handling guidelines should be followed to minimize staff contamination and patient cross-contamination.

Dose calculation

Children's doses are usually calculated based on body weight (mg/kg) or body surface area (BSA) (mg/m^2) and should be obtained from appropriate paediatric formularies (e.g. BNFC). Several formulae of variable accuracy for estimation of BSA are available. The 2 commonly used equations are the Mosteller equation that provides a simple calculation for BSA based on height and weight and the Boyd equation (used in the BNFC tables) based on weight alone. Points to note:

- For overweight patients (e.g. those exposed to high doses/long-term corticosteroids): consider whether actual body weight or ideal body weight is appropriate to use.
- For NSAIDS, use body weight. Round doses if appropriate to avoid manipulation of dosage forms which leads to dose inaccuracies.
- For drugs with a narrow therapeutic index (NTI) (e.g. cytotoxics), use BSA.
- Consider when dose capping is required—the total daily dose should not exceed the maximum adult daily dose.
- When both body weight and BSA are used for dose calculation, ensure consistency. Check local guidelines on which measure is to be used.
- MTX often causes nausea and vomiting when given orally at higher doses. Consider switching from the oral to SC route to improve tolerability and bioavailability. Currently, the corresponding oral dose is used for the SC route.
- Due to differences in bioavailability between brands, certain oral drug products are not interchangeable (e.g. ciclosporin). Where brand switching is necessary blood levels should be monitored. Such status is usually stated in the BNFC. In general, switching oral formulations, e.g. tablets to liquid (even within the same brand), can affect bioavailability. Check for information on bioequivalence of different formulations of a specific brand in its SmPC.

Considerations for the drug classes used: see 🕮 Guidelines, p 415

- NSAIDs—the choice of NSAID depends on its side effect profile, individual efficacy and tolerance, and availability of age-appropriate formulations.
- Analgesics—step-up protocols from paracetamol, codeine, co-codamol to opioid analgesics must be followed and used as an adjunct to NSAIDs.
- Steroids—for oral therapy the minimum effective dose should be used. Long-term steroid use has osteoporotic side effects, calcium and vitamin D supplementation and the use of bisphosphonates for prevention and treatment should be considered.

- Cytotoxic immunosuppressants
  - Cyclophosphamide: toxic effects such as malignancy and infertility are related to cumulative doses therefore update the cumulative dose sheet in patient notes after each dose and dose cap as appropriate; consider fluid tolerance issues.
  - MTX: always prescribe the same strength formulation (i.e. 2.5mg tablets) and pay attention to the dosing interval (weekly doses). Homecare providers can greatly improve patient and parent convenience by reducing hospital visits. However, training must be provided and the suitability and competence of the patient/carer to administer medication must be assessed in advance.
- Immunoglobulin: for IgG replacement therapy be aware that infusion rates vary for the different brands available. Access to immunoglobulin is restricted due to availability/supply issues. Refer to the local/national guidance on clinical prioritization and managing supplies.
- Biologics: biosimilars (similar biological medicinal products) must not be treated as generics since they cannot be proven to have identical clinical characteristics (differences in starting materials, manufacturing processes, and immunogenic reactions). Thus, biosimilars are not interchangeable and must not be substituted without appropriate patient monitoring. The brand intended must be made clear on prescriptions. SC as opposed to IV administration enables the child not to miss school.

Issues to consider when selecting oral dosage forms

See Table 8.4.

Table 8.4 Advantages and disadvantages of different dosage forms

Dosage form	Advantages	Disadvantages
Tablets and capsules	• Portable, more palatable than liquids especially for drugs where taste is an issue • Lower contamination risks (cytotoxics) than liquids (spills/breakages)	• Fixed dose • Swallowing difficulty • Unavailability of higher strength products may require several to be taken or a single unit to be manipulated for lower doses
Dispersible tablets	• Overcomes swallowing difficulty • More portable than liquids	• Fixed dose • Limited strengths available • Taking proportion of liquid leads to poor dose uniformity & reproducibility
Sustained release tablets & capsules	• Reduces number of daily doses, avoids school time doses, interference with activities or sleep • May improve compliance	• Fixed dose, lack of paediatric PK data in most cases • Dosage forms cannot be manipulated • Lack of efficacy may complicate dose escalation and add-on therapy (e.g. pain management)
Oral liquids	• Dose flexibility, usually flavoured, can be administered via feeding tubes • Overcomes swallowing difficulty • May provide better/more consistent absorption than solids for patients with GI problems	• Palatability, may contain unsuitable excipients such as alcohol, preservatives, colours • Inconvenient/bulky for travel
Effervescent products	• More convenient to carry than liquids • Forms a liquid: overcomes swallowing difficulty	• Palatability • Need to be fully dissolved in large volume of liquid • Compliance with ingesting large volume • Usually have high Na^+/K^+— unsuitable for certain groups (e.g. renal patients)

Haematopoietic stem cell transplantation

- In a small proportion of affected children, rheumatic disease is severe and/or resistant to conventional treatments—these children often develop significant side effects from the long-term treatment with multiple, and often combined disease-modifying agents (both immunosuppressive and anti-inflammatory) such as corticosteroids, MTX, cyclophosphamide, and whilst undergoing therapeutic trials of multiple new biologic agents.
- Even in the era of biologics, this small group of children may benefit from haematopoietic stem cell transplantation (HSCT) and national guidance is available. However, autologous HSCT is still regarded as 'experimental' treatment and as a rule offered as a 'last chance' option, whilst allogeneic HSCT is 'generally not recommended'.

Autologous T-cell depleted (TCD) HSCT

The hypothesis

Deletion of presumed auto-aggressive lymphocyte clones—immunosuppressive conditioning (usually anti-T lymphocyte globulin-ATG, and cyclophosphamide or fludarabine).

T-cell depletion (usually by CD34+cell selection)

Newly developing lymphocyte population leads to 're-setting' of the immune system, i.e. self-tolerance.

The evidence

TCD auto-HSCT for JIA induces complete remission (CR):

- Immediate improvement of acute inflammation, due to the immunosuppressive conditioning regimen.
- Subsequent improvement in disease activity (CR >50%), due to 'immunomodulation' (re-establishment of immune tolerance):
  - Albeit may be a transient effect.
  - Significant transplant-related mortality (TRM).

Emerging potential weakness of the hypothesis for sJIA

- Disease recurrence following long-term remission (7–9yr) post-autologous HSCT for sJIA.
- Many now regard sJIA as an autoinflammatory disease.
- Some patients with sJIA have a genetic predisposition to haemophagocytic lymphonistiocytosis (HLH) and there may be some overlap between sJIA/severe macrophage activation syndrome (MAS) with primary HLH patients.
- Induction of self-tolerance by autologous HSCT may thus only provide partial or temporary improvement in those patients.
- Allogeneic HSCT may arguably be a more logical approach in this subgroup—an area of ongoing debate in the rheumatological and transplant communities.

Inclusion criteria for autologous TCD HSCT for JIA

Severity of disease and persistent disease activity

- Any JIA subtype with a polyarticular course, with persisting active inflammatory disease, total disease duration >1yr, active disease >6 months.
- The persistence of active disease should be despite immunosuppressive medication or only controlled with unacceptable drug toxicity (see following section).
- The patient must be in a satisfactory general condition—significant end-organ disease (e.g. from amyloidosis, hypertension, other major organ involvement, immunosuppression-related, or other pathology) may or may not preclude autologous HSCT.
- Patients with sJIA should not have uncontrolled active systemic features due to ↑ risk of MAS at conditioning (see 🕮 Macrophage activation syndrome, p 305).
- There should be no evidence of active ongoing infection, including with opportunistic organisms.
- Consideration should be given to the potential for improvement in functional disability (previously established joint/bone damage cannot be restored).
- Psychosocial factors need to be considered by the referring team who are likely to know the child and family well, and are best placed to judge how they would cope with autologous HSCT.

Failure of immunosuppressive and anti-inflammatory therapy

- It is difficult to define 'failure of treatment' as treatment options are ever increasing. The key point is to think ahead for severe and 'refractory' cases as the process of auto-HSCT takes time.
- Conventional immunosuppressive treatment for JIA is MTX, and in the era of emerging novel therapies most patients, prior to consideration of auto-HSCT, will have failed >1 biological therapy and a trial of parenteral MTX, each for at least 3–6 months before being deemed 'failure'.
- The use of combination therapy, changing from one anti-TNF drug to another, or considering other biologics such as anti-IL-1 or anti-IL6 'blockade' should be considered before auto-HSCT. The downside is that if these approaches fail, disease and therapy-related damage may accrue.
- An informal discussion with the transplant team and referral for independent assessment may be helpful when dealing with a child with severe, persistently active JIA who has failed immunosuppressive and anti-inflammatory therapy—i.e. disease uncontrolled on:
  - Systemic corticosteroids (>0.3mg/kg/day) and/or repeated IV pulses of methylprednisolone (30mg/kg/day) *or*
  - High-dose MTX (≥15mg/m^2/week) given parenterally for >3 months *or*
  - Biologics such as etanercept or other novel/biologic drugs, given at appropriate doses for >3–6 months.

Drug toxicity or intolerance to medication as defined by any of the following:

- Evidence of corticosteroid toxicity.
- Intolerance of MTX (e.g. unacceptable nausea/vomiting despite anti-emetic medication, psychological intervention, and trial of parenteral route; alopecia; severe mucosal ulceration).
- Unacceptable elevation in liver enzymes related to MTX or drug induced cytopenia or other toxicity, e.g. renal toxicity or hypertension related to ciclosporin.

Allogeneic HSCT for severe childhood autoimmune disorders)

- Benefit—potentially curative procedure, based on very few case reports:
  - Initially procedures were intended for treatment of coincidental malignancy.
  - Subsequently, procedures undertaken for intentional treatment of severe and recalcitrant autoimmune disorders.
- Retrospective survey of 35 patients (EBMT Working Party for Autoimmune Disorders):
  - Complete response in 55%; partial response in further 24%.
  - Transplant-related mortality (TRM) ~20%.
  - Risk of acute/chronic graft-versus-host disease (GvHD) ~40%
- The risk:benefit ratio—may be further improved:
  - Reduced intensity conditioning (more immunosuppressive, less myeloablative) and
  - Better GvHD prophylaxis (cyclosporin A, mycophenolate mofetil).

Notes on HSCT for autoimmune disorders and clinical outcomes

- TRM associated with autologous TCD HSCT is higher (~10–15%) than for non-TCD (~3–5%), almost comparable to that of allogeneic HSCT.
  - The most likely reason for this is the combined effect of conditioning immunosuppression and T-cell depletion, leading to a severe and prolonged T-cell immunodeficiency state (6–12 months).
- Autologous TCD HSCT for autoimmune disorders should not be regarded any longer as 'experimental treatment' and should be offered earlier in the course of the disease:
  - If this approach is still considered a treatment option, it should be brought forward to avoid ↑ risks of TRM from infectious complications (occurring as a cumulative result of long-term and combined immunosuppression).
- Experience with allogeneic HSCT for monogenic autoimmune disorders (IPEX—immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; ALPS—autoimmune lymphoproliferative syndrome) is good
  - 10 patients; 1% TRM; follow-up 1–6yr (Abinun M et al., unpublished data).
  - Until more evidence is available (from ongoing and planned clinical trials), allogeneic HSCT for autoimmune disorders should only be offered to selective patients in specialized centres.

Further reading

Foster HE, Davidson J, Baildam E, *et al.* Autologous haematopoeitic stem cell rescue (AHSCR) for severe rheumatic disease in children: guidance for BSPAR members-Executive summary. *Rheumatology* 2006; **45**:1570–1.

Ljungman P, Bregni M, Brune M, *et al.* Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. *Bone Marrow Transplant* 2010; **45**:219–34.

Milanetti F, Abinun M, Voltarelli JC, *et al.* Autologous hematopoietic stem cell transplantation for childhood autoimmune disease. *Pediatr Clin North Am* 2010; **57**:239–71.

Chapter 9

British Society of Paediatric and Adolescent Rheumatology clinical guidelines and protocols

BSPAR Standards of Care for children and young people with JIA

- The BSPAR Standards of Care (SOC) for JIA are based on the fundamental principle that all children and young people with JIA have the right to equitable access to the highest quality of integrated services (http://www.bspar.org.uk/downloads/clinical_guidelines/Standards_of_Care.pdf).
- The SOC are primarily aimed at professionals working in paediatric rheumatology, designed to support clinical service development, and delivery in conjunction with colleagues and funding bodies and by being in the public domain, promote awareness of good clinical practice to parents and families affected by JIA. Key standards include:

Standards to improve access, early diagnosis and treatment

- All healthcare practitioners likely to come into contact with a child with JIA should acquire the necessary clinical skills and knowledge to recognize the condition early.
- Musculoskeletal clinical examination should be included in education and training of medical students and hospital trainees.
- All children and young people with suspected JIA should be referred to a paediatric rheumatology team (PRT) ≤6 weeks of the onset of symptoms and should be seen by the PRT ≤4 weeks of referral, with 45min allocated for the first appointment.
- On diagnosis all children and young people with JIA should have prompt access to a multidisciplinary PRT who must have appropriate experience and training as defined by the appropriate professional bodies.
- On diagnosis all children/young people with JIA should have a full assessment of their disease, general health, psychosocial, educational, and pain management needs.
- On confirmation of the diagnosis:
  - Within 6 weeks all patients should have a slit lamp examination performed by an experienced paediatric ophthalmologist or optometrist.
  - Where required, IA corticosteroid injections should be performed by a member of the PRT in ≤6 weeks and SC MTX should be available within ≤4 weeks.

Standards to empower patients and their families by improving information, access to support, and knowledge

- Children and young people with JIA and their families will be encouraged to participate in disease management.
- Information for patients and families must be provided to inform decision-making, and optimize their physical, psychosocial, and emotional development. Information should be provided:
  - In a variety of formats, be developmentally appropriate, and presented in clear simple language avoiding jargon.
  - About JIA, treatment options, and general health issues.
  - About the members of the PRT and how to access them.

Standards to improve access to ongoing and responsive treatment and support

- Patients with active disease should be assessed at intervals not greater than 4 months apart.
- Patients should have regular ophthalmology reviews in accordance with BSPAR/Royal College Guidelines (see Chapter 9 and 📖 Uveitis screening in JIA, p 148).
- Each patient should have an individualized care plan (pathways for treatment, information on what to do in the event of worsening symptoms), details of national or local support groups, and provision of information for schools and employers.
- Patients and families should have:
  - Access to their named MDT members with direct and easy access during flares of disease.
  - A dedicated telephone helpline managed by the PR clinical nurse specialist.
  - The opportunity to participate in clinical research and clinical trials.
- Paediatric rheumatology clinical networks should have referral pathways, guidelines, and framework for clinical governance.
- Drugs used for the treatment of JIA must be prescribed and monitored in accordance with BSPAR/NICE guidelines (see 📖 Biologics, NICE, p 393 and p 399) and should be available without undue delay.
- Specialist surgery should be performed by a surgeon with training in the management of JIA and communicating with children and adolescents and who is linked to the paediatric rheumatology clinical network.

Standards to maximize independence, inclusion, and quality of life

- The psychosocial well-being of the child/young person with JIA and their family should be addressed by all professionals (health, education, and community).
- The PRT should encourage and facilitate age-appropriate participation in interests, sport, and community life.
- The educational setting (school and college) should ensure full inclusion of the child/young person with JIA.
- Young people with JIA should be supported to develop the skills to move into employment.
- The child/young person with JIA and their families should be provided with support/strategies to manage distressing aspects of their treatment.
- The child/young person with JIA should be given the skills to disclose their arthritis to others, should they choose to do so.
- Age- and developmentally-appropriate individualized transitional care for the child/young person with JIA, should take place reflecting early, mid, and late phases of adolescent development (see 📖 Transitional care, p 387).

Further reading

Davies K, Cleary G, Foster H, *et al.* on behalf of the British Society of Paediatric and Adolescent Rheumatology: BSPAR standards of care for children and young people with juvenile idiopathic arthritis. *Rheumatology* 2010 **49**(7):1406–8.

BSPAR drug information leaflets for parents and families

Medication is a major component in the treatment of rheumatic diseases and medicine taking is an area in which patients and carers should be enabled to make informed choices and decisions. A market research survey in 2003 (http://www.ipsos-mori.com/default.aspx) found that patients want more medicines information than they get and that they want it from a variety of sources.

The clinical nurse specialist (CNS) plays a major role in patient and family education about medicines. This is integral to optimizing adherence and it is important that both patients and carers understand why a drug is being prescribed, the risks and benefits, and the importance of monitoring. The CNS needs to have a good understanding of the medicine that is being prescribed including:

- Pre-screening that may be required prior to commencement of drug.
- How to report adverse events (e.g. yellow card system) and awareness of drug alerts (http://www.medicines.org.uk).
- How to access psychological support/counselling for non-adherence.
- Shared care guidelines with local and tertiary services.

Drug information should initially be given verbally and key messages reinforced with patient information leaflets (PILs) and where appropriate 'signposting' to relevant websites. Guidance for PILs is available (http://www.mhra.gov.uk) and should be:

- Fit for purpose, i.e. appropriate for the intended target group.
- Proof read by a pharmacist for content accuracy.
- Readability assessed (http://www.plainenglish.co.uk).
- Inclusive of public and patient involvement (http://www.dh.gov.uk).

A series of PILs are available on the BSPAR website (http://www.bspar.org.uk)—these are evidence-based where possible, and consensus-derived from the BSPAR paediatric rheumatology CNS group.

They highlight aspects of drug education that should be covered:

- Formulary and generic names of the drug.
- Drug interactions, contraindications, side effects, monitoring required (blood tests).
- Counselling as appropriate; sexual health, contraception and pregnancy (to both sexes, http://www.brook.org.uk, http://www.fpa.org.uk), alcohol, and smoking (http://www.units.nhs.uk).
- Potential risk of infection. 'Do's and don'ts', when to seek medical attention and travel information (taking medication abroad, insurance and contact if become unwell).
- Immunizations and impact on live vaccines.

Specific points relevant to paediatric rheumatology practice (see 🕮 Medicines for children, p 401)

NSAIDs

- Formulations available, e.g. liquid, tablet, melt, and its suitability for the patient and family.
- Consideration should be given to dose intervals, e.g. fitting around the school day.
- Gastric protection—NSAIDs should be administered with or after food. Gastroprotective drugs may be required, especially if symptoms occur or prophylactically if on combination therapies such as prednisolone.
- Sun protection against pseudoporphyria with naproxen.

Corticosteroids

- Gastric protection (as for NSAIDs).
- Weight gain—dietary advice for the whole family.
- Body image and risk of bullying—psychology/counselling support (🖰 http://www.bullyingonline.org).
- Changes in mood and behaviour.
- Acne—clindamycin ointment.
- Osteoporosis—activity levels, calcium and vitamin D intake.

DMARDs

- Blood monitoring (see 🕮 BSPAR drug guidelines, p 415).
- Sexual health and pregnancy (consult latest product literature).
- Infection risks.
- Avoidance of live vaccinations.
- Potential hair loss with cyclophosphamide, MTX, hydroxchloroquine sulphate, MMF.
- Safe handling and disposal as per local guidelines especially MTX and cyclophosphamide.
- Potential ↑ risk of certain cancers.

Methotrexate

- Use 2.5mg tablets where possible to minimize confusion and medication errors.
- Parenteral administration—RCN document: 🖰 http://www.rcn.org.uk.
- Nausea—the use of antiemetics, change time of dosing and/or split the dose over 24h.
- Liver toxicity—alcohol advice and counselling: 🖰 http://www.need2know.co.uk.

Biologics

(🖰 http://www.rcn.org.uk: assessing, managing, and monitoring biologic therapies).

- Need for pre-treament screening, e.g. TB.
- Long-term unknown side effects.
- Potential risks of malignancy.
- Risk of serious infections—when to seek medical advice.
- Avoidance of live vaccines.
- Regular blood monitoring.

- Sexual health and pregnancy.
- When to stop or omit—i.e. surgery, active infection—temperature >38°C.
- Injection site reactions for SC drugs—apply cold packs pre- and postinjection, antihistamine cream/oral antihistamines.
- IV infusion reactions including potential anaphylaxis.

Issues to consider for all DMARDs and biologic therapies (see 🕮 Biologics, p 393)

Blood monitoring

- Age of child.
- Difficulty with venous access.
- Capabilities of local services.
- Distance from home.
- Play therapy/psychology input.
- As infrequent as possible.
- Local anaesthetics, e.g. Ametop®, cold spray.
- Establish a monitoring agreement.

Travel

- Vaccinations required.
- Letter re: medications.
- Adequate supply of drug.
- Travel insurance.
- Clinic letter/carriage of medicines.

This section covers some of the issues that should be considered when giving information about treatments. It is important that patients and families feel empowered about their treatment and it is their right to be given a balanced view of all the information available so that they can make informed choices.

BSPAR guidelines for treatments used in paediatric rheumatology

A current list of available classes of treatments is provided: readers are directed to recommended drug formularies (http://www.cbnf.org.uk) for more details and current guidelines and patient information leaflets are available on the BSPAR website (http://www.bspar.org.uk).

- NSAIDs.
- Corticosteroids (oral, IV, IA and IM).
- Conventional DMARDs: MTX, sulphasalazine, hydroxychloroquine.
- Other immunosuppressive agents: azathioprine, ciclosporin, MMF, cyclophosphamide.
- Other agents: pamidronate, epoprostenol.
- Biologic agents:
  - Anti-TNF: etanercept, infliximab, adalimumab.
  - T-cell co-stimulatory blockers: abatacept.
  - IL-1 blockade: anakinra, rilanocept, canakinumab.
  - IL-6 blockade: tocilizumab.
  - Anti-B-cell therapy: rituximab.
- Autologous or allogeneic haemopoietic stem cell rescue—see p 405.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- The choice of NSAIDs is based on taste, formulation, convenience of dosing regimen, and side effect profile (Table 9.1). No Cox-2 inhibitors are licensed for use in children.
- Slow-release preparations given in the evening may be helpful for early morning stiffness.
- High-dose ibuprofen is helpful for symptomatic relief of pericarditis.
- Check for drug interactions before use (e.g. ACE inhibitors: ↑ risk of hyperkalaemia and renal damage; warfarin: effect enhanced by NSAIDs; MTX: elimination can be reduced by NSAIDs albeit unlikely to be relevant in clinical practice).
- Check for contraindications:
  - ***Absolute (rare)***—active or previous peptic ulceration or GI bleeding. Severe heart failure, moderate to severe renal impairment.
  - ***Relative***—asthma, coagulation defects. Renal, cardiac, or hepatic impairment.
- Side effects are rare but include:
  - GI—nausea, abdominal pain, rarely bleeding, ulceration.
  - Ibuprofen has the lowest risk. Apparent intolerance of NSAIDs should raise concern of GI pathology (e.g. *Helicobacter pylori* disease, inflammatory bowel disease).
  - Central nervous system—headache, hyperactivity, dizziness, vertigo, anxiety depression, tinnitus may occur.
  - Haematological—blood disorders are rare albeit bleeding times may be prolonged.
  - Renal—may provoke renal failure, hypertension in pre-existing renal impairment. Rarely papillary necrosis or tubulointerstitial nephritis (later interstitial fibrosis) leading to renal impairment.
  - Skin—NSAIDs may cause pseudoporphyria (photosensitive blistering rash leaving scars—most common with naproxen and in fair-skinned individuals.
  - Other rare side effects—hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, eye changes, Stevens–Johnson syndrome, toxic epidermal necrolysis.

Table 9.1 Dosage/administration/formulations

Drug	Age	Dose	Formulations	Comments
Ibuprofen	>3 months	5–10mg/kg/dose 3–4 doses/day Max. total 2.4g/day	Tablet Suspension Syrup	Weakest NSAID, but least side effects May be used up to 6 doses/day in sJIA only Associated with aseptic meningitis in SLE Use sugar-free syrups where possible
Naproxen	>2yr	5–7.5mg/kg/dose 2 doses/day Max. total 1g daily	Tablets Suspension may be available as special order	Good efficacy. Generally low incidence of side effects but associated with pseudoporphyria in JIA
Diclofenac	>6 months	1.5–2.5mg/kg/dose 2–3 doses/day Max. total 150mg/day	Tablets Dispersible tablets Suppositories	Similar actions and side effects to naproxen May trigger hepatic porphyria
Piroxicam	See 'Dose'	Dose depends on patient's weight: <15kg: 5mg 16–25kg: 10mg 26–45kg: 15mg >46kg: 20mg One dose/day Max. total 20mg/day	Tablets Dispersible tabs Also available as 'melts'	More GI side effects, more serious skin reactions Should not be used 1st line and should only be initiated by physicians experienced in treating rheumatic disease Treatment should be reviewed after 2 weeks and periodically thereafter
Indomethacin	>1 month	0.5– 1mg/kg/dose (2mg/kg under specialist supervision) 2 doses/day Max. total 200mg/day	Capsules Suppositories Suspension	Mostly used to treat enthesitis-related arthritis and sJIA High incidence of side effects

Disease-modifying anti-rheumatic drugs (DMARDs)

Methotrexate (MTX)

MTX is the 1st-line DMARD for JIA and used in many other chronic conditions (see 🕮 JIA, p 129). MTX is a folate antagonist but the mechanism of action as a DMARD is unclear.

Pre-treatment considerations

- FBC, liver transaminase levels, serum creatinine.
- Varicella immunity status (consider also checking measles status)—see 🕮 Varicella, p 371):
  - Consider immunization *before treatment* starts if child is non-immune.
- Consider testing for TB in high-risk individuals p 356.
- Important aspects of patient education:
  - Patients taking MTX are immunosuppressed—effect for ≥3 months after cessation.
  - Live vaccines contraindicated; inactivated vaccines are safe, but may have reduced efficacy. Annual flu vaccine and 5-yearly pneumovax advised. See 🕮 Vaccines, p 374.
  - Alcohol and MTX; no safe proven drinking limit in children. In older patients, 5 units/week regarded as safe.
  - MTX is a teratogen; pregnancy must be avoided; male patients should not father a child. Reliable contraception advised.
- Folic acid supplementation may reduce side effects (weekly 5mg dose 3 days after MTX or 1mg/day [except MTX day]).

Contraindications

- *Absolute:*
  - Active bacterial infection, especially active TB, active herpes-zoster infection, acute hepatitis B or C, active life-threatening fungal infections.
  - Planning (or in) pregnancy, breastfeeding.
- *Relative:* chronic hepatitis B or C, hepatic disease, renal disease.

Drug interactions

- Trimethoprim-containing antibiotics are avoided in practice (↑ risk of toxicity).
- NSAIDs may potentiate MTX toxicity. In practice, however, rarely a clinical problem.

Side effects

- Bone marrow suppression: rare, but potentially fatal. More likely after the 1st year MTX.
- Hepatotoxicity: irreversible liver damage extremely rare in children. Transient elevation of liver enzymes is common (often intercurrent infection).
- Pulmonary fibrosis and renal toxicity: extremely rare in children.
- Nausea, vomiting, and anorexia are very common: may be helped by ondansetron (given 1h before MTX) *or* dividing the weekly dose

and giving 12h apart *or* administering at night *or* switch to SC route *or* daily folic acid (except MTX dosing day). Clinical psychology may help anticipatory nausea.
- Headaches, hair loss, mood changes. Less common.

Dosage/administration
- Usual starting dose **10–15mg/m^2/once weekly** SC, orally, or IV. Doses up to 25mg/m^2/dose are used but efficacy unclear and side effects common at higher doses.
- SC route gives optimal bioavailability. IM administration not recommended.

Monitoring
- FBC, and either aspartate (AST), or alanine (ALT) aminotransferase levels at **2–4 monthly** intervals. Serum creatinine at **6-monthly** intervals.
- The recommendations from BSPAR in Table 9.2 are consensus based.

Table 9.2 BSPAR monitoring recommendations

Monitoring parameter	Action
AST or ALT >3x upper limit of normal reference range	Consider omitting MTX for 1–2 weeks and repeating blood test
WCC <3.0 x 10^9/L (or steadily falling)	May necessitate dose reduction, or rarely discontinuation. Avoid abrupt cessation as may result in disease flare
Neutrophils <1.5 x 10^9/L (or steadily falling)	
Lymphocytes <0.5 x 10^9/L (or steadily falling)	Consider other more common causes for abnormal blood test results
Platelets <150 x 10^9/L (or steadily falling)	
New or worsening unexplained dyspnoea or cough	Consider omitting MTX whilst investigating cause
Rising creatinine (falling creatinine clearance)	Seek renal opinion
Rash or unexplained bruising, temperature above 38.5°C or chicken pox contact in non-immune patients	Patient must be reviewed by medical team prior to continuing with MTX

Sulphasalazine (SSZ)

The mechanism of action of SSZ is unclear. Despite a licence for use in JIA, it is not widely used.

Pre-treatment investigations
FBC, U&Es, creatinine, LFTs.

Contraindications
Absolute
- Hypersensitivity to sulphonamides, co-trimoxazole or aspirin.
- Children <2 years, severe renal failure.

Relative
- Systemic JIA—use has been associated with macrophage activation syndrome.
- G6PD deficiency: risk of haemolysis.
- Moderate renal impairment: crystalluria may develop—ensure high fluid intake.
- Slow acetylators: potential risk of drug-induced lupus—withdraw SSZ if clinically suspected (symptoms usually resolve on drug withdrawal).
- Pregnancy: assess risk:benefit ratio, folic acid supplementation should be offered to all pregnant women taking SSZ and total dose should not exceed 2g/day.

Side effects

Up to 20% of children experience dose-related side effects:
- GI disturbance (most common)—nausea, anorexia, dyspepsia, diarrhoea.
- Dermatological—photosensitive rash, hypersensitivity reactions, oral ulcers.
- Haematological—neutropenia, thrombocytopenia, macrocytic anaemia, pancytopenia.
- Drug-induced SLE, Raynaud's, interstitial pneumonitis, fibrosing alveolitis, hepatitis.
- Staining of soft contact lenses and orange discoloration of urine.
- Reversible oligospermia.
- Others: fever, headache, dizziness.

Dosage/administration
- 1st week: 5mg/kg twice daily
- 2nd week: 10mg/kg twice daily
- 3rd week: 20mg/kg twice daily
- Maintenance dose: 20–25mg/kg twice daily. Max. dose 2g/day (2–12yr) or 3g/day (12–18 yr). Time to response: minimum of 3 months.

Monitoring
- Check for G6PD before starting.
- After checking FBC and LFTs monthly for 3 months the same monitoring regime as for MTX is recommended.

Hydroxychloroquine
- Hydroxychloroquine is an anti-malarial quinolone with some immunomodulatory effects.
- Evidence of benefit in SLE including modifying cardiovascular risk (see 🕮 JSLE, p 226). It is also particularly useful for skin and joint disease, and may help reduce fatigue.

Pre-treatment considerations
- Baseline bloods including FBC, U&Es, LFTs.
- Baseline ophthalmology review (see 🕮 Monitoring, p 148).

Contraindications

Absolute
- Severe renal impairment—creatinine clearance <10mL/min/1.73m^2.
- Pre existing maculopathy.

Relative
- Mild/moderate renal impairment—reduce dose on prolonged use.
- Neurological disorders (especially a history of epilepsy).
- Liver disease—avoid concurrent use of hepatotoxic drugs.
- Severe GI disorders.
- Porphyria.
- G6PD deficiency.
- Quinine sensitivity.
- May exacerbate psoriasis and aggravate myasthenia gravis.

Drug interactions
Major
- ↑ risk of ventricular arrhythmias with: amiodarone, moxifloxacin.
- ↑ risk of seizures with: antiepileptics, mefloquine.
- May ↑ plasma concentrations of: digoxin, ciclosporin.
- Avoid other antimalarials: artemether/lumefantrine.

Minor
- Inhibits the effects of: agalsidase beta (used in Fabry's disease), laronidase (used in mucopolysaccaridosis), neostigmine, pyridostigmine.
- Effect reduced by: kaolin, antacids.
- Plasma concentrations ↑ by cimetidine.

Side effects
- GI disturbance- nausea, diarrhoea, anorexia, abdominal cramps.
- Headache, skin reactions—rash, pruritis. Rarely pigmentary changes, bleaching of hair and hair loss. Visual changes.
- Other: ECG changes, convulsions, ototoxicity.
- Rarely: blood disorders, psychological disturbance, myopathy, Steven–Johnson syndrome, acute generalized exanthematous pustulosis, exfoliative dermatitis, photosensitivity, hepatic damage.

Dosage/administration
Child 1 month–18yr: 5–6.5mg/kg once daily. Max. dose: 400mg once daily.

Monitoring
- Blood monitoring—not routinely required.
- Assessment and monitoring of vision: the incidence of hydroxychloroquine-induced retinopathy is very low and dependent on the maximum dose and duration of treatment. Visual side effects are dose related. 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.

Fertility/pregnancy/breastfeeding
- Pregnancy: not necessary to withdraw antimalarial drug during pregnancy if rheumatological disease is well controlled. However, manufacturer advises to avoid—possibly ↑ risk of cochlear damage.
- Breastfeeding: ***avoid***—risk of toxicity to infant.

Mycophenolate mofetil (MMF)

MMF is a newer DMARD. It is mainly used in SLE, esp. renal. Sometimes also used for other connective tissue diseases including scleroderma and uveitis.

Pre-treatment consideration/testing

FBC, differential WBC, U&Es, creatinine, LFTs, ESR.

Contraindications

Absolute

- Pregnancy (avoid for 6 weeks after discontinuing).

Relative

- Breastfeeding (manufacturer advises avoid).

Drug interactions

- Absorption MMF ↓ by antacids and cholestyramine.
- Absorption of phenytoin ↓ by MMF.
- ↑ risk agranulocytosis in combination with clozapine.
- ↑ plasma concentration of acyclovir, and possibly ganciclovir.

Side effects

- GI: usually diarrhoea/vomiting, but risk of ulceration/haemorrhage/perforation.
- Infections: viral, bacterial, and fungal all more.
- Hypertension: consider lower dose.
- Thrombocytopenia <150 ***Stop***. Beware falling trend.
- Neutropenia <2.0 ***Stop***. Beware falling trend.
- Oedema.
- 2° malignancies: both benign and malignant skin and lympho-proliferative are reported.

Dosage

Take on empty stomach:

- Children 600mg/m^2 twice daily (max 1g twice daily).
- Adults 1g twice a day.

Monitoring

FBC and U&Es weekly for 4 weeks, twice-monthly for 2 months, then monthly.

Azathioprine

Azathioprine is mainly used primarily to treat patients with vasculitis or inflammatory bowel disease. It takes approximately 2–4 months to achieve its effect.

Pre-treatment consideration/testing

- FBC, U&Es, creatinine, LFTs, urinalysis, zoster immune status, thiopurine methyltransferase (TPMT) activity.
- In renal or hepatic impairment dose should be reduced and frequency of blood monitoring for toxicity ↑.
- Severe myelosuppression may occur due to TPMT deficiency, an enzyme necessary in the catabolic pathway for azathioprine. Pre treatment testing of TPMT activity identifies those with TPMT deficiency (azathioprine contraindicated), low activity (azathioprine recommended to be started at a lower dose and ↑ with careful monitoring) and normal activity (full azathioprine dose can be commenced). Myelosuppression can also occur in individuals with normal TPMT activity and therefore ongoing monitoring in all patients is recommended.
- Theoretical ↑ risk of malignancy.

Contraindications

Absolute

- Hypersensitivity to azathioprine or mercaptopurine (as per BNF contraindications).
- TPMT deficiency.

Relative

- TPMT low activity (prescribe at lower dose, see 'Pre-treatment considerations/testing').
- Pregnancy.

Drug interactions

Major

- Allopurinol—enhanced effects and ↑ toxicity of azathioprine when given with allopurinol (reduce dose of azathioprine to 1/4 of the usual dose).
- ↑ haematological toxicity seen with trimethoprim and co-trimoxazole.
- Avoid concurrent use of other drugs that suppress the bone marrow.

Minor

- For a full list of drug interactions please refer to the BNFC.

Side effects

- Nausea/vomiting/diarrhoea—usually dose-related, responds to reducing the dose. Occasional patients show an idiosyncratic reaction with abdominal pain and severe vomiting; in these patients azathioprine must be discontinued permanently.
- Haematological—bone marrow suppression usually dose related. Sore throat, bruising, severe mouth ulcers or fever necessitates an urgent FBC.

Stop treatment and discuss with rheumatologist caring for the patient if:
- White cell count $<3.5 \times 10^9$/L.
- Neutrophil count $<1.5 \times 10^9$/L.
- Platelet count $<150 \times 10^9$/L.

- Rashes/mouth ulcers—usually mild but severe rash or mucosal ulceration is an indication to stop treatment.
- Hair loss—this is usually insignificant and reversible on stopping.
- Liver toxicity—this is an occasional problem. If liver transaminases are >2x levels then azathioprine should be stopped.
- Flu-like Illness—this may be 2° to azathioprine immune-mediated reaction and the drug should be stopped.

Dosage/administration

- ***Starting dose:*** 1mg/kg/day (max. 50mg) taken with/after food. Total daily dose may be given in 2 divided doses.
- ***Increments:*** 0.5–1mg/kg/day every 2–4 weeks if no side effects, depending on clinical condition and response.
- ***Maximum:*** 3mg/kg/day (doses of >200mg/day in adults are seldom necessary).

Monitoring

All patients on azathioprine should carry monitoring cards in which the results of each blood test are recorded.

- FBC and LFTs should be checked fortnightly for the first 8 weeks and for 4 weeks after an ↑ in the dose. FBC should be checked monthly once the dose is stable.
- LFTs should be checked 3-monthly once the dose is stable except in hepatic impairment when LFTs should be checked monthly.

Fertility/pregnancy/breastfeeding

- There have been reports of premature birth and low birth-weight following exposure to azathioprine, particularly in combination with corticosteroids. Spontaneous abortion has been reported following maternal or paternal exposure.
- Azathioprine is teratogenic in *animal* studies.
- Breastfeeding—teratogenic metabolite present in milk in low concentration but no evidence of harm in small studies—consider if potential benefit outweighs risk.

Ciclosporin

Ciclosporin (cyclosporin) is a DMARD used occasionally in the treatment of JIA and JDM. Its use is most limited by renal toxicity and cosmetic problems with hirsutism.

Pre-treatment consideration/testing

- FBC and differential WCC, U&Es, creatinine, LFTs, fasting lipids
- Calculated GFR
- Urinalysis
- BP.

Contraindications

Absolute

- Renal failure
- Liver failure
- Uncontrolled hypertension
- Uncontrolled infection
- Malignancy
- Severe electrolyte imbalance
- Concomitant use of tacrolimus or rosuvastatin.

Drug interactions

There are multiple drug interactions. See 🕮 Further reading, p. 430, for full listing.

- Always halve the dose of *diclofenac* if ciclosporin is co-prescribed.
- Care is also needed with other potentially *nephrotoxic drug*s, e.g. aminoglycosides, amphotericin, ciprofloxacin, trimethoprim, vancomycin.
- Ciclosporin levels can be ↑ by erythromycin, clarithromycin, ketoconazole, fluconazole, oral contraceptives, methylprednisolone (high dose), hydroxychloroquine.
- Ciclosporin levels can be ↓ by carbamazepine, phenytoin, rifampicin, St John's wort.

Side effects

Common

- Hypertension
- Renal dysfunction—dose-dependent rise in serum creatinine and urea in first few weeks of therapy
- Hyperlipidaemia, hypercholesterolaemia
- Tremor, headache
- Nausea, vomiting, abdominal pain, diarrhoea, anorexia, gingival hyperplasia
- Hepatic dysfunction
- Hyperuricaemia, hyperkalaemia, hypomagnesaemia
- Paraesthesia
- Hypertrichosis
- Muscle cramps, myalgia, fatigue
- Immunosuppression and infections—viral, bacterial, fungal and parasitic.

Other less common side effects listed in BNFC but may include a possible ↑ risk of 2° neoplasia.

Dosage/administration

Switching between formulations without close monitoring may lead to clinically important changes in blood-ciclosporin concentration. Therefore prescribing and dispensing of ciclosporin should be ***by brand name*** to avoid inadvertent switching. If it is necessary to switch a patient to a different brand or formulation of ciclosporin, the patient should be monitored closely for changes in blood-ciclosporin concentration, serum creatinine, and BP.

Dose

2–4mg/kg/day in 2 divided doses gradually ↑ over 6 weeks according to response, tolerance, and blood level to a maximum dose 6mg/kg daily.

If **no** clinical response at maximum tolerated dose for 3 months, then withdraw treatment.

- The total daily dose is given in 2 doses 12h apart, taken with food or drink.
- Grapefruit juice should be avoided for 1h prior to administration. Do not mix with grapefruit juice.
- Mix the oral solution with orange/apple juice (to improve taste) or with water immediately before administration.
- Do not administer via a nasogastric tube (interaction with plastic).
- Do not keep oral liquid in the fridge. Keep at room temperature (15–25°C).

Monitoring

- Routine monitoring of ciclosporin levels not usually necessary once desired level and steady state achieved unless concerns regarding adherence to therapy.
- U&Es, creatinine—every 2 weeks until dose and trend stable, then monthly.
  - Creatinine rise >30% from baseline, or fall in calculated GFR of >10%—withhold and discuss with specialist team.
  - Potassium rises above reference range—withhold and discuss with specialist team.
- LFTs—once a month until dose and trend stable for 3 months, then 3 monthly.
- FBC—once a month until dose and trend stable for 3 months, then 3 monthly. If platelets $<150 \times 10^9$/L or abnormal bruising withhold and discuss with specialist team.
- Fasting lipids—no clear guideline in children but suggested every 6 months.
- BP should be checked at every clinic visit. Treat BP if >95th centile for age on 2 consecutive readings 2 weeks apart. If BP cannot be controlled, stop ciclosporin.

Fertility/pregnancy/breastfeeding

Ciclosporin does cross the placenta but limited data available from organ transplant recipients indicate that, compared with other immunosuppressive agents, ciclosporin treatment imposes no ↑ risk of adverse effects on the course and outcome of pregnancy.

Ciclosporin is excreted in breast milk and breastfeeding should be avoided.

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).

The NIH protocol is often used but alternative regimens exist including the Birmingham Vasculitis protocol of which there are several modified versions. One example is as follows:

- Dose: 15mg/kg (maximum 1g) of cyclophosphamide given by IV bolus over 15mins every 2 weeks for 3 doses, then every 3 weeks for 3 doses, then every 4 weeks for 3 doses.
- After each dose of cyclophosphamide the patient may also receive 30mg/kg of methylprednisolone (maximum 1g) over 6hrs in their post-hydration fluid.
- The use of Ondansetron and MESNA is the same as for the NIH protocol.

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. 9.1.

- 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.

Personal protective equipment

Personal protective equipment (PPE) is necessary when preparing, handling, and administering cytotoxic drugs, to minimize the risk of accidental contamination.

INTRAVENOUS PRESCRIPTION CHART

WARD

CHEMOTHERAPY

SURNAME	FIRST NAME	HOSP NUMBER	D.O.B.	WEIGHT:	DATE:	HEIGHT	SURF AREA	ALLERGIES?
			AGE	WEIGHT:	DATE:			

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. 9.1 Cyclophosphamide infusion chart.

Infection and the patient on cyclophosphamide

Patients receiving cyclophosphamide are highly vulnerable to all infections, and the manifestations of infection may be less clinically obvious. This is particularly important in those pa-tients with indwelling venous catheters.

Prophylaxis

Should be commenced at the start of therapy and should only be discontinued after discussion with the consultant paediatric rheumatologist/nephrologist, and not within 2 months of finishing treatment:

- **Bacterial:** Once-daily co-trimoxazole (Septrin®). Children under 5yrs should receive 240mg od, and those over 5yrs 480mg od. Patients unable to take co-trimoxazole may be offered once-daily azithromycin 10mg/kg (max 250mg) as an alternative.
- **Fungal:** Patients with JSLE and those with complex immu-nosuppression, especially if neutropaenic (total neutrophil count <1.0) should receive once-daily itraconazole prophy-laxis 5mg/kg/day. To protect against Aspergillus a trough level of >0.5mg/L is needed so the level should be checked after 1–2 weeks of treatment and the dose altered accordingly.
- **Viral:** Prophylaxis against herpes viruses with acyclovir is not routinely needed but non-immune children with complex immunosuppression, especially if lymphopaenic (<1) may benefit. Children in contact (same room for >15mins, or face to face contact) with varicella or measles should be dealt with as follows:

Known immunity

No treatment but child must be fully undressed and examined by parent/carer twice a day and if spots develop admitted to hospital. For children who are very heavily immunosuppressed with a Varicella contact consider giving prophylactic oral acy-clovir 10mg/kg/dose qds for 7 days (discuss with consultant first).

Unknown/non-immune

Within 72 hrs of exposure these children may be given either of the following:

Exposure to varicella:

- Zoster immunoglobulin (ZIG): consider IVIG if child is thrombocytopaenic as IM ZIG may cause excessive bruising
  - <5yrs of age: 250mg
  - 5–10yrs: 500mg
  - >10yrs: 750mg
- Oral acyclovir 10mg/kg/dose QDS for 7 days.

Exposure to measles:

Children are infectious from 3 days before onset of rash until desquamation (usually ~4days). Children within 6 days (most effective if within 3 days) of contact should receive Normal Human Immunoglobulin (HI):

- Normal HI
  - <1yr: 250mg IM
  - 1-2yr: 500mg IM
  - >2yr: 750mg IM
- Standard immunoglobulin may be used only if Normal HI not available. Dose is 0.2mg/kg given IV.

Patients taking cyclophosphamide should have access to urgent paediatric assessment with

- Single episode of fever >38.5C
- Two episodes of fever > 38C within 24hrs
- Close contact with infectious disease (e.g. varicella). This normally refers to 'kissing contacts' such as close family members rather than school friends, but patients are also at risk if they have been in the same room as an infectious person for longer than 15mins. If in doubt parents should seek advice (see b Varicella zoster infections, p 371).
- Parental/patient concern. Especially in the presence of symptoms that may indicate infection (even without docu-mented pyrexia) such as nausea, vomiting, diarrhoea, cough, coryza.
- Any evidence (even 1 spot) of chickenpox, zoster (shingles), or herpes simplex (cold sore).

In all circumstances where an acute infection is suspected the patient MUST be reviewed on the paediatric ward as soon as possible (ideally within the hour) and the following checked

- FBC (note however that, although profoundly immunosup-pressed, the WCC may be: normal; low due to previous cyclophosphamide; or raised due to steroid therapy)
- ESR and CRP
- U+E, Creatinine and LFT's
- Blood cultures
- Urine cultures.

Other investigations such as throat swabs, cough swabs, viral PCR, lumbar puncture etc. should be done if clinically indi-cated but are not routine, however if respiratory signs are present (e.g. hypoxia, tachypnoea) then pneumocystis infec-tion must be considered. These patients will almost always need admission and IV antibiotics. They must be discussed with the consultant paediatric rheumatologist/nephrologist if admitted during normal working hours. Antibiotic regimes may vary according to individual circumstances but in general the following regimes are applicable in patients with normal renal function (for patients with impaired renal function this **must** be discussed with the nephrologist on-call before starting treatment):

- Central line in situ: teicoplanin 6mg/kg 12hrly for 3 doses then once-daily and meropenem 20mg/kg tds (max 2g)
- No Central line: ceftazidime 50mg/kg tds (max. 2g) and gentamycin 5mg/kg od, or meropenem 20mg/kg tds (max 1g) and gentamycin 5mg/kg od
- Varicella (chickenpox or shingles): IV acyclovir 500mg/m2/dose 8-hrly for at least 5 days, and then prophy-laxis with oral acyclovir 10mg/kg/dose twice a day until at least 2 months after finishing cyclophosphamide.

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.

Pamidronate

Pamidronate is one of bisphosphonate family of drugs. It works by inhibiting the action of osteoclasts and thus promoting ↑ in bone density. In children it has a long-standing role in the treatment of children with osteogenesis imperfecta (but has also been used to treat congenital or steroid-induced osteoporosis, bone pain due to osteoporotic vertebral or sacral insufficiency fractures (see 📖 Metabolic bone disease, p 330), chronic recurrent multi-focal osteomyelitis (CRMO), and synovitis acne pustulosis hyperostosis osteitis syndrome (SAPHO) (see 📖 CRMO, p 297).

Contraindications

Absolute

Patient must not be hypo-calcaemic and should be taking regular calcium and vitamin D3 supplements.

Relative

Caution must be used in renal impairment. Patients should be well hydrated and pamidronate should not be given if creatinine clearance is <30mL/min/1.73m^2.

Drug interactions

↑ risk of hypocalcaemia when given with aminoglycoside antibiotics.

Side effects

(See BNFC for full listing.)

- Hypocalcaemia—maximum effect occurs a few days post administration.
- Hypophosphataemia.
- Fever and flu-like reactions.
- Transient bone pain- this can be quite severe.
- Nausea, vomiting, headaches, arthralgias, myalgias, diarrhoea, and rash.
- Acute renal failure has been reported, especially in pre-existing renal impairment.

Dosage and administration

- Usual dose is 1mg/kg given once a day for 3 days every 3 months. However, because of the risk of fever and flu-like reactions the dose on the 1st day of the first ever infusion given is often reduced to 0.5mg/kg. All subsequent doses are 1mg/kg.
- Pamidronate is dissolved in a 250mL bag of 0.9% saline and given by IV infusion over 2h. In patients requiring lower fluid volumes the maximum stated concentration is 60mg/250mL for Aredia® and 90mg/250mL for Medac® and longer infusion times may be needed accordingly.

Monitoring

- Patients with osteoporosis or osteogenesis imperfecta should all have a DEXA scan done before starting pamidronate and yearly whilst receiving ongoing treatment. Children with CRMO or SAPHO syndromes do not need this checking.
- Before commencing infusion—check FBC, ESR, U&Es, LFTs, Ca, Mg, CRP.

- During infusion—monitor temperature, pulse and BP:
  - At baseline.
  - After 15 min, 30min, 1h, 90min, and at completion.
  - Children should remain for 1h after completion of pamidronate infusion.

Epoprostenol/iloprost

Epoprostenol (prostacyclin), and its synthetic analogue iloprost may be used to treat severe Raynaud's syndrome where digital infarction is likely. Both are given by IV infusion via a syringe driver to ensure accurate and consistent dosing (see 📖 Overlap syndromes, p 275).

Contraindications

- *Absolute:* severe coronary heart disease, pulmonary veno-occlusive disease where there is risk of haemorrhage.
- *Relative:* half the dose of iloprost in liver disease.

Side effects

- Hypotension
- Facial flushing
- Bradycardia
- Nausea
- Sweating
- Abdominal discomfort
- Headaches.

Dosage

Epoprostenol

Between 1–5 nanogrammes (ng) per kilogramme (kg) bodyweight per minute (1–5ng/kg/min).

- The rate is started at 1ng/kg/min.
- ↑ rate every 20min as tolerated up to 5ng/kg/min.
- Once the maximum rate is achieved this is continued for a further 5–7h (depending on tolerance and patient convenience). This is given daily, for 1–5 days. Dose of 1–20ng/kg/min (or higher) continuously for many days have been used to treat peripheral ischaemia due to vasculitis, under expert supervision only.

Iloprost

Between 0.5–2ng/kg/min. Start at 0.5ng/kg/min and increase as for epoprostenol to maximum of 2ng/kg/min. Run for 6h/day for 3–5 days.

Monitoring

Postural hypotension may be marked and patients should be nursed lying down.

BP and pulse should be measured:

- Every 20min for the first hour.
- Every 30min thereafter until finished.

Fertility/pregnancy/breastfeeding

Toxic in animal studies during pregnancy so manufacturers advise to avoid, no information available for breastfeeding.

Etanercept (Enbrel®)

(See 🕮 Biologics, NICE, p 399.)

Clinical/drug information summary

- Blocks the action of the pro-inflammatory cytokine TNF-α.
- Licensed for use in JIA and approved by NICE (🖱 http://www.nice.org.uk) for children whose disease is not well controlled by, or who are intolerant of SC MTX. Etanercept may take between 2–12 weeks to become effective.

Pre-treatment investigations

- Before starting etanercept the following should be checked:
  - FBC, U&Es, creatinine, LFTs.
  - Auto-antibody screen including baseline ANA and anti-dsDNA.
  - TB screening: this may take several forms but most include a combination from CXR, Mantoux test, and/or Quantiferon-GOLD or similar immunological test.
  - Varicella zoster immune status—as for MTX.
- Before starting etanercept the patient/carer must be informed of the following:
  - Pregnancy and breastfeeding—there is insufficient data to suggest either are safe.
  - Diet—patients are particularly susceptible to *Salmonella* and *Listeria* food-poisoning.
  - Immunizations—as for MTX.
  - Tattoos and body piercing—these are strongly discouraged. There is an ↑ risk of soft tissue infections described in children taking anti-TNF treatment.
  - Chronic active infection or recent severe infection.
  - Known/suspected TB.
  - Previous history of demyelinating disease.
  - Previous history of, or susceptibility to, malignancy.

Drug interactions

There are no specific drug interactions reported for this drug but combining its use alongside other 'biologic' treatments is not recommended.

Side effects

- Immunosuppression—particularly soft tissue infections, and re-activation of latent TB.
  - Good skin/nail care important (ingrowing toenails can become infected).
- Injection site inflammation is common, but usually improves with continued use.
- Generally well tolerated. Reports of exacerbation of eczema, headache, dizziness, rash, abdominal pain, or indigestion.
- Neutropenia.
- Demyelinating diseases—case reports but causal relationship with etanercept is unclear.

- Malignancy—theoretical concern but no evidence to date in paediatric use.
- Anecdotal reports of worsening of pre-existing uveitis, or de novo uveitis.

Dosage and administration

- *Dose:* usual starting dose 0.4mg/kg given SC twice a week—may be ↑ up to 0.8mg/kg if necessary in refractory disease.
- *Maximum dose:* usually 25mg twice a week, but doses up to 50mg twice-weekly have been used.

Formulation

There are several different formulations of etanercept available from the manufacturer. All are injected SC.

- 25mg vial of dry powder with accompanying water for home reconstitution.
- 25mg/50mg pre-filled syringes and 50mg auto-injector pen—not yet licensed for children.

Monitoring

FBC, ESR, U&Es, LFTs, CRP, ANA, and anti-dsDNA should be checked every 3 months for the first year on etanercept. Thereafter the frequency of monitoring may be reduced to 6–12-monthly. Those who do develop anti-dsDNA antibodies without clinical features of SLE should continue to receive treatment but should be monitored more closely. Those developing any features of SLE should stop taking the drug. The same response to abnormal results/side effects as with MTX should be used.

Other anti-TNF-α: adalimumab (Humira®) and infliximab (Remicade®)

Adalimumab is a fully humanized monoclonal antibody; infliximab is a chimeric monoclonal antibody. Both work by binding to the receptor for the TNF-α and thus preventing its action. Adalimumab is licensed for use in children aged 4–17 years with JIA whose disease is not well controlled by, or who are intolerant of SC MTX.

Infliximab is not licensed but in practice both are widely used for children with JIA whose arthritis justifies treatment with an anti-TNF drug but for whom the risk of a flare of their uveitis would exclude the use of etanercept.

Both may take between 2–12 weeks to become effective after commencing treatment or a dose increase

Pre-treatment investigations/contraindication/drug interactions

As for etanercept.

Side effects

- As for etanercept except that neither are associated with an ↑ risk of flares of uveitis. Indeed both are most often used to treat uveitis that complicates JIA.
- The formation of human anti-chimeric antibodies (HACA) may prevent long-term use of infliximab but the risk of this may be lessened if MTX is co-administered.
- The risk of hypersensitivity reactions is greater with Infliximab.

Dosage and administration

Adalimumab

- Usual starting dose is 24mg/m2 (usually rounded to the nearest 10mg) given SC every 14 days. Weekly treatment is sometimes used in adults.
- Maximum dose 40mg alternate weeks.

Infliximab

- Usual starting dose is **6mg/kg** given IV.
- 2nd dose is usually given 2 weeks after the first. Thereafter doses may be given at 3–8-week intervals depending on severity of symptoms and therapeutic response. Most children require 4–6-weekly dose intervals.
- Dose range 3–10mg/kg.
- Co-treatment with MTX recommended.

Formulation

- Adalimumab—40mg pre-filled syringe.
- Infliximab—100mg dry powder for reconstitution.

Monitoring As for etanercept.

Note Pergolimumab and certolizumab are other anti-TNF treatments, but are not yet available in the UK and are therefore not dealt with in this chapter.

Anti-IL-1 treatments: anakinra (Kineret®), rilonacept (Regeneron®), and canakinumab (Ilaris®)

Anakinra, rilonacept, and canakinumab bind to IL-1β to inhibit its activity. None are licensed in the UK for use in children but nonetheless anakinra is the 1st-line therapy for children with cryopyrin-associated periodic syndrome (CAPS) and evidence to support its use in sJIA is now very strong and it is increasingly being used as a 1st-line therapy.

Rilonacept and cankinumab are authorized in the EU for treatment of CAPS in adults and children ≥12yr but are not currently licensed in sJIA.

Pre-treatment investigations

As for etanercept.

Contraindications/drug interactions

As for etanercept except:

- No documented dietary restrictions.
- For anakinra:
  - Patients with known hypersensitivity to *E coli*-derived proteins.
  - Latex allergy—needle cover (natural rubber) may induce allergic reactions.

Side effects

Most common is injection site reaction (redness, swelling, and pain). The incidence of this appears to be much lower with canakinumab. Other mild side effects reported include coryza, headache, nausea, diarrhoea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain.

All can cause serious side effects including:

- Infections—cellulitis, pneumonia (especially in asthmatics), and bone and joint infections.
- Neutropenia.
- Hypersensitivity reactions—hypersensitivity reactions including anaphylactic reactions, angio-oedema, urticaria, rash, and pruritis have been reported rarely.
- Malignancies—the role of IL-1 blockers in the possible development of malignancy is unknown.

Dosage and administration

Anakinra

- Dose: usual starting dose is 1–2mg/kg or 60mg/m^2 given daily SC, max. dose 100mg daily.
- Moderate—severe renal failure may need a lower dose or alternate-day dosing.
- Can be used alongside MTX, but not recommended for use with other 'biologics'.

Canakinumab
Dose is 2–4mg/kg (max.150mg) injected SC every 4 weeks. Higher doses can be used in children with CAPS under expert supervision only.

Rilonacept
1st dose 4.4mg/kg injected SC; subsequent doses 2.2mg/kg, max. 320mg, which is followed a week later by once-weekly injections of 2.2mg/kg (max. 160mg).

Formulation

- *Anakinra:* 100mg in 0.67mL pre-filled syringes
- *Canakinumab:* 150mg dry powder for reconstitution with 1mL water for injections
- *Rilonacept:* 80mg dry powder for reconstitution in 1mL water for injections

Monitoring

As for etanercept.

Abatacept (Orencia®)

Abatacept (Orencia®) blocks the co-stimulatory pathway between T cells and antigen-presenting cells. It is licensed for use in children with JIA over the age of 6yr whose disease is not well controlled by, or who are intolerant of SC MTX. It can be used as monotherapy, or in combination with MTX. Time to respond ~3 months.

Pre-treatment investigations/contraindications

As for etanercept, except demyelinating disorders not reported with abatacept.

Drug interactions

Patients receiving both abatacept, and another biologic therapy such as anti-TNF had a much higher risk of serious infection. Thus combination of abatacept with other biologic agents is ***not*** recommended.

Side effects

- Most common are headache, upper respiratory tract infection, sore throat, and nausea.
- Other side effects may include diarrhoea, cough, fever, and abdominal pain.
- Abatacept can cause ***serious*** side effects including:
  - Serious infections: pneumonia, infections caused by viruses, bacteria, or fungi.
  - Allergic reactions: can occur at the time of infusion or can be delayed (even next day)—pre-dosing with hydrocortisone may reduce this risk.
  - Malignancies: exact relationship is unclear.
  - Respiratory problems have been reported in adults with chronic obstructive lung disease.

Dosage and administration

- Dose: usual starting dose is ***10mg/kg given IV.*** Max. dose 1g
- 2nd dose is usually given 2 weeks after the 1st, thereafter at 4- weekly intervals.

Monitoring

As for etanercept.

Anti-IL-6 treatment: tocilizumab (Ro-Actemra®)

Tocilizumab is recombinant humanized anti-human IL-6 receptor monoclonal antibody, binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and inhibits sIL-6R and mIL-6R-mediated signalling. Used to treat severe JIA, including sJIA. In May 2011 the committee for Medicinal Products for Human Use recommended that tocilizumab (Ro Actemra, Roche) is indicated for the treatment of active systemic juvenile idiopathic arthritis (JIA) in patients aged 2 years and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.

Pre-treatment investigations/contraindications/drug interactions/monitoring

As for etanercept.

Side effects

Most common are infusion reactions and pre-dosing with hydrocortisone is advised. Tocilizumab has also been reported to cause severe infections (pneumonia, varicella), deranged LFTs (ALT/AST and bilirubin) and neutropenia.

Dosage and administration

Doses usually 4-weekly but 2-weekly in sJIA has been used:

- <30kg body weight—dose: 10–12mg/kg given by IV infusion over 1h.
- >30kg body weight—dose: 8mg/kg/dose given by IV infusion over 1h.

Anti-B-cell therapies: rituximab (Mabthera®)

(See 🕮 on anti-B cell therapy in SLE, p 241.)

Chimeric monoclonal antibody directed against B cells, binds to CD20 antigen located on pre-B and mature B lymphocytes, thus causing B-cell lysis. Counter-intuitively, the main efficacy in autoimmune disease is thought not to be due to reduced autoantibody production. Rituximab spares B cell progenitors (and antibody secreting plasma cells), and B cells reappear 4–12 months after therapy. However memory B cells can remain suppressed for 2 years. Rituximab is licensed for use in adults with RA but not in children. Reports of good effect in adolescents with poly-articular JIA (RF+ve), treatment-resistant (JSLE), JDM, and some forms of vasculitis (particularly ANCA associated). Takes approximately 3 months to be effective.

Pre-treatment investigations/contraindications/cautions—as for etanercept plus:

- Check BP before, during, and after treatment.
- Pregnancy is contraindicated and recommended that breastfeeding is avoided.
- Patients with a history of cardiovascular or renal impairment may require dose reduction.
- Live vaccines are currently contraindicated post rituximab whilst B cells are depleted.
  - Anti-CD 19 and immunoglobulins should also be measured, see 'Monitoring', and in the 🕮 Anti B cell therapy in SLE, p 241.

Drug interactions

Renal toxicity has been reported in combination with cisplatin in clinical trials.

Side effects

- Infusion reactions (fever, rigor, dyspnoea and bronchospasm, pruritis and rashes, angio-oedema, and transient hypotension) usually present ≤12h.
  - Pre-medication with chlorphenamine, paracetamol and hydrocortisone may reduce the incidence of infusion reactions.
- A decline in immunoglobulin levels may make children more susceptible to infections, especially varicella.

Dosage and administration

- Dose: 2 doses of 750mg/m^2 (maximum dose 1g) given by IV infusion 2 weeks apart. Other regimens, e.g. 375mg/m^2 weekly for 4 weeks have been described.
  - 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 ↑ by increments of 25mg/h every 30min up to a maximum of 200mg/h as tolerated.
- In SLE each rituximab may be followed the next day by 375mg/m^2 of IV cyclophosphamide: see 🕮 Anti B cell therapy in SLE, p 241.

- In JIA concomitant use of MTX is recommended.
- Maximum dose per infusion is 1g.
- *Re-treatment*: conventionally re-treatment with rituximab is considered once peripheral B-cell count is >2%. However conventional flow cytometry may be insensitive and 'lesional' B cells can be present even if peripheral B-cell count is still <2%, thus re-treatment before formal recovery of B-cell numbers may be warranted if clinical features of active disease return before B-cell numbers have recovered to >2%.

Monitoring

As a minimum, the following immune monitoring is recommended:

- Lymphocyte subsets requesting CD19 (or CD20 if available) On day 7–10 after infusion, then monthly from 4 months after first dose until peripheral B cells return (repopulation may occur earlier than 4 months, particularly in SLE).
- Immunoglobulins (GAM): day 7–10; 2 months after 1st dose; then monthly from 4 months after 1st dose until B cells return.

Systemic corticosteroids (oral, intramuscular, and intravenous)

Systemic corticosteroid therapy is often needed at 'induction' or to treat flares of disease (e.g. polyarticular JIA, sJIA, JSLE, scleroderma, JDM or vasculitis—see 🕮 relevant chapters.

Pre-treatment consideration/testing

- Consider need for prevention and treatment of steroid-induced osteoporosis with daily vitamin D and calcium supplementation. Use of activated vitamin D (such as 1-alpha calcidol, or calcitriol) or bisphosphonates to prevent corticosteroid-induced osteoporosis cannot yet be routinely recommended, and is the subject of an ongoing clinical trial in the UK.
- Give steroid card and advice re: chicken pox and measles.
- FBC, ESR, CRP, U&Es, creatinine, glucose, and LFTs (if not done already as part of disease monitoring). Varicella zoster serology prior to the 1st dose.
- Avoid live virus vaccines during, and for 3 months after, administration of oral or IV steroids (live vaccines may be given if patients have received IA steroids only and >6 weeks before systemic immunosuppression (e.g. MTX) started.

Contraindications/cautions

Major

- Active peptic ulceration, acute infections.

Minor

- Diabetes, benign intracranial hypertension, previous peptic ulcer disease, hepatic impairment.
- Reduce the dose or the rate of IV infusion in patients more at risk of hypertension/renal crisis such as those with SLE nephritis or systemic sclerosis patients.
  - Some advise avoiding high-dose IV methylprednisolone in those with systemic sclerosis because of the risk of renal hypertensive crisis. This recommendation is made for adults with this disease in particular, with little or no data to support this recommendation in paediatric patients. If in doubt ***seek expert advice***.

Drug interactions

Major

- NSAIDS (including aspirin)— ↑ risk of GI bleeding. Gastroprotection should be given, usually with a proton pump inhibitor.
- Anticoagulants—corticosteroids may enhance effect of warfarin.
- Ciclosporin—corticosteroids may ↑ plasma levels of ciclosporin.

Minor

- The effect of antihypertensive treatments may be mitigated/negated by corticosteroids.

Side effects

- ***Mild:*** facial flushing, metallic taste, hyperactivity, mood changes, blurred vision, tiredness.
- ***Rare:*** hypertension (even with IV infusions) and often responds to slowing infusion rate and only occasionally requires treatment (e.g. nifedipine).
- ***Extremely rare:*** altered conscious state or psychosis, seizures.

Dosage/administration

Intravenous

- Usual dose is 30mg/kg/day IV methylprednisolone (max. 1000mg/day).
- Each dose is normally given over 30–60min in 30–250mL of 0.9% sodium chloride—and usually given once per day for 3 days.
- This may need to be repeated in subsequent weeks depending on the nature and severity of the condition being treated.
- Oral steroids are stopped on days that methylprednisolone is given, and restarted with a weaning regimen appropriate for the individual and disease being treated.

Intra-muscular

- Usual dose is 1mg/kg, max. 80mg, of triamcinolone acetonide (Kenolog®).
- Must be given by deep IM injection to the gluteal muscles to try and avoid causing SC atrophy.
- In larger doses, consider splitting the dose and giving half the dose to each buttock.
- Pain of administration limits use in children but often tolerated well by older adolescents.

Oral

- The starting dose is entirely dependent on the disease (and its severity) being treated, but usually is in the range of 1–2mg/kg/day.
- Aim to wean as quickly as possible thereafter (dependent on clinical response and toxicity in individual patients).

Monitoring

- Urinalysis for glycosuria prior to 1st dose. If patient is known to have diabetes, hyperglycaemia should be expected, insulin requirements will rise and can be unpredictable; blood glucose (BM stix) must be monitored regularly.
- ***For IV route only:*** temperature, pulse, respiratory rate (RR), BP—before, during and after infusion. If the patient feels unwell, check TPR, BP, and blood glucose; consider slowing rate of infusion.

Intra-articular corticosteroid use in JIA

(See 🕮 JIA, p 129 and 🕮 Corticosteroid intra-articular injections, p 390.)

- IA corticosteroid injections:
  - Result in minimal systemic steroid absorption.
  - Are the treatment of choice for oligo-articular JIA.
  - Act as useful bridging agents whilst starting MTX.
  - Minimize exposure to systemic corticosteroids.
- Efficacy is good: often ≥6 months of complete remission in the injected joint.
- Re-injection ≤6months is advised if synovitis recurs.
- If recurrent swelling despite 2 injections within 6 months then the diagnosis and treatment should be reviewed.

Dosage

Triamcinolone hexacetonide

- 1mg/kg/joint for large joints (knees, ankles, elbows, shoulders). Usual max. 40mg/joint—larger doses may be used in older patients with resistant disease albeit expert opinion is advised.
- 0.5mg/kg/joint for medium joints (hips, sub-talars, wrists, and TMJs).
- 0.2–2mg/joint for digits.

Triamcinolone acetonide

The dose is double that of triamcinolone hexacetonide, but systemic absorption is greater.

General notes:

- In young children, or if multiple joints are to be injected, general anaesthesia is needed.
- Children older than 6–8yr may be able to use Entonox® as adequate analgesia. Older teenagers may be able to use local anaesthesia such as EMLA® cream.
- Aseptic technique must be observed at all times. Correct needle placement should reduce risk of SC atrophy and injection of corticosteroid into the cartilage that can cause growth disturbance. X-ray or US imaging may aid accuracy, and is strongly recommended in deep joints such as hips, and in small joints such as fingers.
- Joint injection followed by casting may help to reduce contractures if combined with intensive physiotherapy.

Side effects

- Septic arthritis is a potential risk but with good technique, rarely observed.
- Facial flushing and Cushingoid appearance are transient. Cushing syndrome and adreno-suppression are very rare.
- Peri-articular calcification may occur (≤5% of injections).
- Diabetic patients may notice ↑ insulin requirements transiently after injections.

- SC atrophy can occur, mainly smaller joints; skin changes may fade but unlikely to resolve completely.
- Chemical synovitis may cause ↑ pain and swelling 12–24h post injection (albeit rarely observed in practice).
- Post-injection pain is uncommon; simple analgesia (with paracetamol) usually suffices. Post-injection rest is impossible to achieve and should not be enforced.

Chapter 10

Rashes in paediatric rheumatology

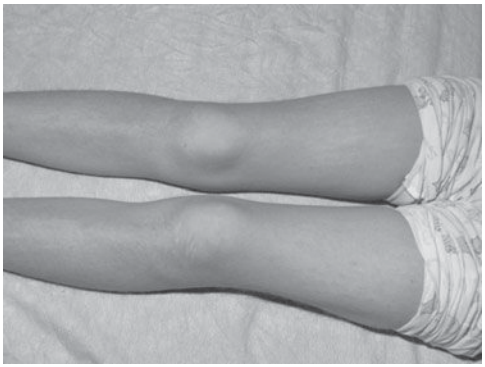

Fig. 10.1 (Also see Plate 4.) Systemic JIA. Note the rash occurring in linear streaks and exhibiting Koebner phenomenon.

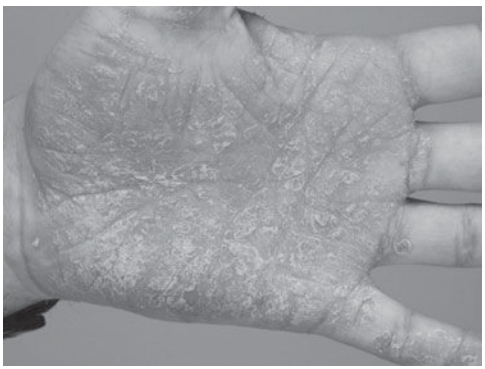

Fig. 10.2 (Also see Plate 5.) Palmar psoriasis in a patient with psoriatic JIA.

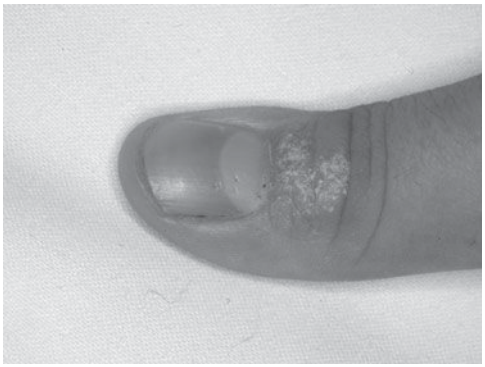

Fig. 10.3 (Also see Plate 6.) Nail pits and psoriasis in a patient with psoriatic JIA.

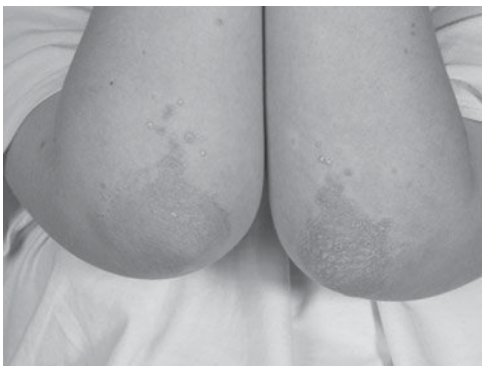

Fig. 10.4 (Also see Plate 7.) Psoriatic JIA (elbows).

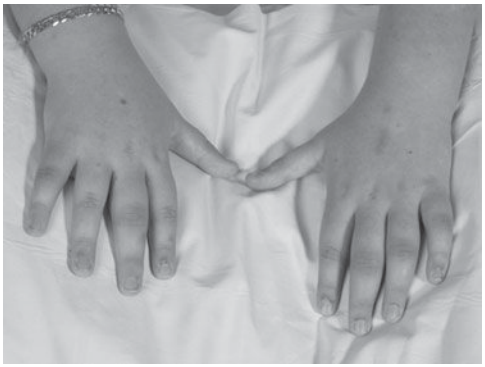

Fig. 10.5 (Also see Plate 8.) Psoriatic JIA (hands).

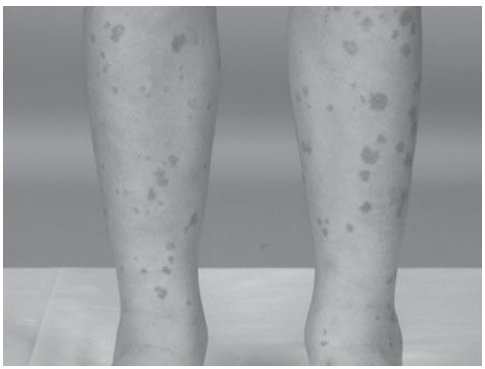

Fig. 10.6 (Also see Plate 9.) HSP with bilateral ankle swelling.

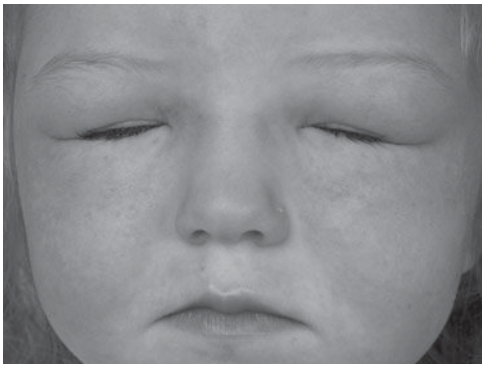

Fig. 10.7 (Also see Plate 10.) Juvenile dermatomyositis with periorbital oedema.

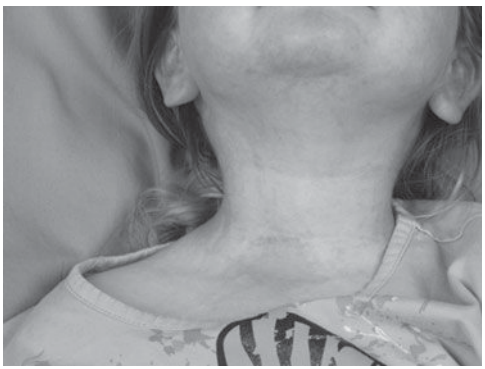

Fig. 10.8 (Also see Plate 11.) Severe juvenile dermatomyositis with anterior chest wall vasculitis—'shawl sign'.

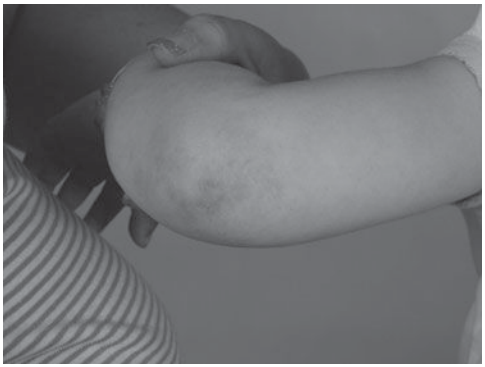

Fig. 10.9 (Also see Plate 12.) Extensor surface vasculitis in juvenile dermatomyositis.

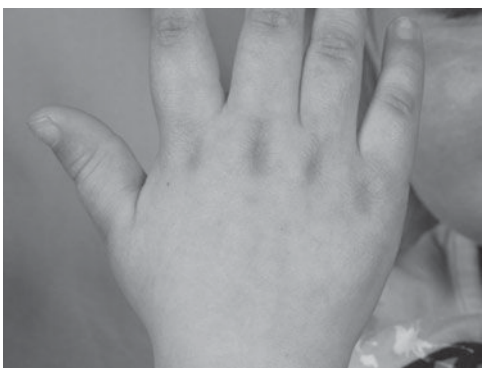

Fig. 10.10 (Also see Plate 13.) Subtle Gottron's papules in a patient with severe juvenile dermatomyositis.

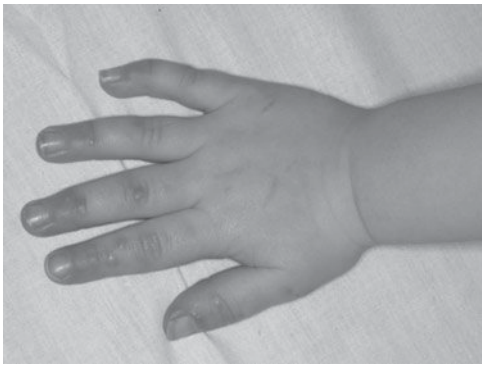

Fig. 10.11 (Also see Plate 14.) Periungual erythema in undifferentiated connective tissue disease.

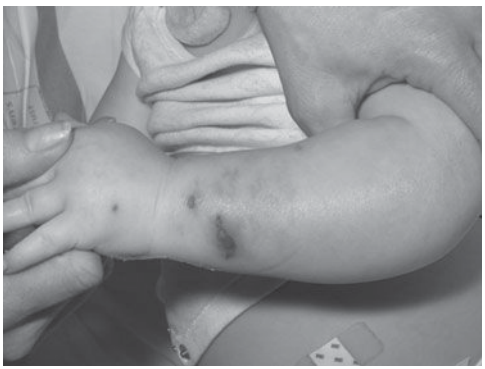

Fig. 10.12 (Also see Plate 15.) Systemic vasculitis with pyrexia, livido reticularis, vasculitic rash with skin necrosis.

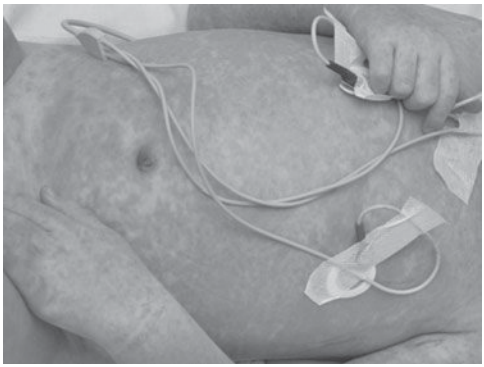

Fig. 10.13 (Also see Plate 16.) Maculo-papular rash of Epstein–Barr virus associated with haemophagocytic lymphohistiocytosis (HLH).

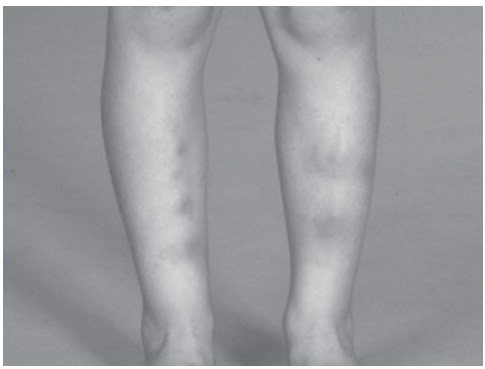

Fig. 10.14 (Also see Plate 17.) Erythema nodosum.

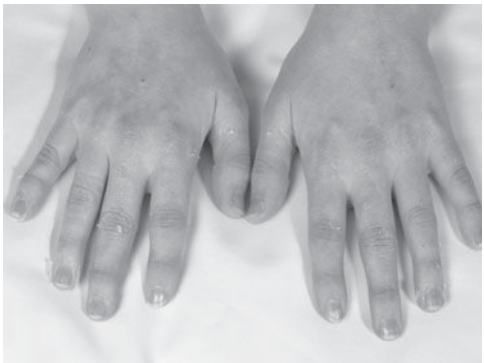

Fig. 10.15 (Also see Plate 18.) Generalized peeling in Kawasaki disease.

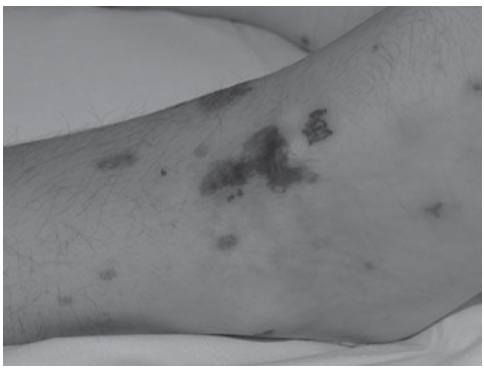

Fig. 10.16 (Also see Plate 19.) Purpura in Wegener's granulomatosis.

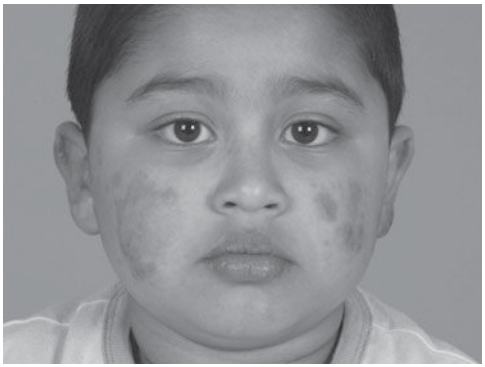

Fig. 10.17 (Also see Plate 20.) SLE associated with congenital C1q deficiency.

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