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The fourth edition of the ABC of Rheumatology marks a change in Editor. I would like to thank my predecessor Mike Snaith for his sterling work in producing such excellent previous editions of this book which has led to its worldwide recognition and appeal. The fact that the book is now in its fourth edition is testimony to the great foundation that he laid.

I have kept the tradition as well as enriched the strengths of previous editions to ensure that this book continues to provide a good and up to date foundational knowledge of Rheumatology and Musculoskeletal Medicine for a wide spectrum of those interested in this field. This ranges from family doctors, medical students, nurse specialists, allied health professionals to doctors in training and others besides.

I would like to thank all those who have contributed to this current edition including my colleagues, not only in Sheffield but also across the United Kingdom and indeed other parts of the world. I am particularly pleased to have so many authors from North America where this book is increasingly being used.

Finally, I wish to thank the publishers for their dedication and professionalism.

Ade Adebajo
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<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AHPS</td>
<td>allied health professionals</td>
</tr>
<tr>
<td>ANA</td>
<td>antinuclear antibody</td>
</tr>
<tr>
<td>ANCA</td>
<td>anti-neutrophil cytoplasmic antibodies</td>
</tr>
<tr>
<td>APLA</td>
<td>antiphospholipid antibody</td>
</tr>
<tr>
<td>APLS</td>
<td>antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>arc</td>
<td>The Arthritis Research Campaign</td>
</tr>
<tr>
<td>ARMA</td>
<td>Arthritis and Musculoskeletal Alliance</td>
</tr>
<tr>
<td>AS</td>
<td>ankylosing spondylitis</td>
</tr>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BSR</td>
<td>British Society for Rheumatology</td>
</tr>
<tr>
<td>CATS</td>
<td>clinical assessment and treatment services</td>
</tr>
<tr>
<td>CHB</td>
<td>congenital heart block</td>
</tr>
<tr>
<td>CMCJ</td>
<td>carpometacarpal joint</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CTGF</td>
<td>connective tissue growth factor</td>
</tr>
<tr>
<td>CWP</td>
<td>chronic widespread pain</td>
</tr>
<tr>
<td>DIPJ</td>
<td>distal interphalangeal joint</td>
</tr>
<tr>
<td>DMARDs</td>
<td>disease-modifying antirheumatic drugs</td>
</tr>
<tr>
<td>DMS</td>
<td>dermatomyositis</td>
</tr>
<tr>
<td>DRUJ</td>
<td>distal radio-ulnar joint</td>
</tr>
<tr>
<td>DXA</td>
<td>dual X-ray absorptiometry</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ERA</td>
<td>enthesitis-related arthritis</td>
</tr>
<tr>
<td>ESP</td>
<td>extended-scope physiotherapist</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>ESWT</td>
<td>extracorporeal shock wave therapy</td>
</tr>
<tr>
<td>GCA</td>
<td>giant cell arteritis</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GP</td>
<td>general practitioner</td>
</tr>
<tr>
<td>GPsSI</td>
<td>GP with special interest</td>
</tr>
<tr>
<td>GU</td>
<td>genito-urinary</td>
</tr>
<tr>
<td>HRCT</td>
<td>high-resolution computed tomography</td>
</tr>
<tr>
<td>HSP</td>
<td>Henoch–Schönlein purpura</td>
</tr>
<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>ICP</td>
<td>integrated-care pathway</td>
</tr>
<tr>
<td>IL-1</td>
<td>interleukin-1 etc.</td>
</tr>
<tr>
<td>IPJ</td>
<td>interphalangeal joint</td>
</tr>
<tr>
<td>JDM</td>
<td>juvenile dermatomyositis</td>
</tr>
<tr>
<td>JIA</td>
<td>juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>JCA</td>
<td>juvenile chronic arthritis</td>
</tr>
<tr>
<td>JRA</td>
<td>juvenile rheumatoid arthritis</td>
</tr>
<tr>
<td>KD</td>
<td>Kawasaki disease</td>
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<td>LBP</td>
<td>low back pain</td>
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<tr>
<td>MCPJ</td>
<td>metacarpophalangeal joint</td>
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<tr>
<td>MCTD</td>
<td>mixed connective tissue disease</td>
</tr>
<tr>
<td>MDT</td>
<td>multidisciplinary team</td>
</tr>
<tr>
<td>MMP-3</td>
<td>matrix metalloproteinase-3</td>
</tr>
<tr>
<td>MPO</td>
<td>myeloperoxidase</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NOGG</td>
<td>National Osteoporosis Guideline Group</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>OA</td>
<td>osteoarthritis</td>
</tr>
<tr>
<td>PAH</td>
<td>pulmonary arterial hypertension</td>
</tr>
<tr>
<td>PIPJ</td>
<td>proximal interphalangeal joint</td>
</tr>
<tr>
<td>PMR</td>
<td>polymyalgia rheumatica</td>
</tr>
<tr>
<td>PsA</td>
<td>psoriatic arthritis</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>ReA</td>
<td>reactive arthritis</td>
</tr>
<tr>
<td>RVSP</td>
<td>right ventricular systolic pressure</td>
</tr>
<tr>
<td>SAA</td>
<td>serum amyloid A</td>
</tr>
<tr>
<td>SCLC</td>
<td>subacute cutaneous lupus erythematosus</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SpA</td>
<td>spondyloarthritides</td>
</tr>
<tr>
<td>SRC</td>
<td>scleroderma renal crisis</td>
</tr>
<tr>
<td>SSC</td>
<td>systemic sclerosis</td>
</tr>
<tr>
<td>ST</td>
<td>spinal stenosis</td>
</tr>
<tr>
<td>TGF</td>
<td>transforming growth factor</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
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CHAPTER 1

Community Rheumatology: Delivering Care Across Boundaries

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OVERVIEW

- The importance of a multidisciplinary care pathway in the management of musculoskeletal patients is now well recognized globally.
- The need to provide a whole-community approach to the management of these patients is also being increasingly recognized globally.
- The shared-care monitoring of rheumatology patients on disease-modifying drugs between primary and secondary care is an example of a successful model using this approach.
- A community-wide approach encompassing the involvement and education of both patient and primary care physician will lead to earlier diagnosis, speedier and more appropriate secondary care referrals, quicker treatment and ultimately improved clinical outcomes.
- A community-wide approach will ensure that psychosocial factors are not overlooked and that “red flags” for regional pain syndromes are not missed.
- This approach will also ensure that evidence-based primary care treatments for musculoskeletal problems are developed and implemented.

The ever-increasing demand upon the acute hospitals to deliver emergency medicine, together with technological (but time-consuming and expensive) advances means that in the UK and elsewhere follow-up of many chronic conditions has been squeezed out of the acute setting and, by default, delegated to primary care. Unfortunately this shift in activity has not always been mirrored by an appropriate shift in resources and skills. This chapter discusses new ways of working to try to ensure that patients with musculoskeletal conditions receive timely, appropriate treatments within the limitations imposed by restricted resources.

Shared care—how to make it work

With hospital services running at full (or over) capacity, one way forwards is to develop models of shared care appropriate to local need, responsive to local demands and in the patients’ best interests. Simply transferring the workload from rheumatologists to general practitioners (GPs) will not work—primary care is also bursting at the seams. One way of transferring rheumatological expertise to the community, without increasing the burden on the primary care team, is to develop the roles of health professionals such as nurses, physiotherapists and occupational therapists. Such practitioners, working in an extended role, operate at a high level of clinical practice and cross traditional professional boundaries. Their expertise includes assessment (of the disease and psychosocial factors), follow-up and management of patients with musculoskeletal conditions and inflammatory arthritis. Their roles and responsibilities have recently been defined (Carr, 2001).

What is the role of the specialist nurse?

Specialist nurses are highly skilled and provide holistic care for patients and their significant others by addressing their physical, psychological and social needs. They can play a pivotal role in the management of people with musculoskeletal conditions, acting as effective communicators between the patient, their GP and hospital consultant. Like GPs, they tend to stay in post for many years and become a “constant presence” in the patient’s illness journey, thus ensuring the continuity of care that those with a chronic disease value so highly. The role of the specialist nurse is essentially to provide care management, education and support for patients and their families, and to act as an educator and resource for other health professionals. The role includes those activities shown in Box 1.1. Some nurse specialists also undertake advanced practices such as intra-articular injections (Meadows and Sheehan, 2005). This can be particularly useful to GPs, who may be inexperienced in this procedure. After specialist training these nurses can also prescribe drug therapy (Carr, 2001). Of all these activities, patient education remains one of the priorities of the specialist nurse (Department of Health, 2006).

Why educate patients?

Patient education enables people with complex chronic diseases to care for themselves, bringing benefits for everyone. Supporting
patients to self care has been shown to reduce their GP visits by 40–69% (Schillinger et al., 2003). Patient education is not a treatment in itself but a treatment enhancer, magnifying the effects of standard treatments by persuading patients to adhere to them more closely, or to adopt actions that are believed to be beneficial. To do this, patients must be active collaborators in their care and believe in their ability to perform a specific task or achieve a certain objective. This is known as “self-efficacy”. For changes to occur patients must acquire knowledge and skills, and so patient education involves the multidisciplinary team and the patient and their partner/carers in both primary and secondary care. Every consultation is an opportunity to educate and provide information. In order to care for themselves, patients will need to know about the topics shown in Box 1.2.

Patients should be given both verbal and written explanations. The Arthritis Research Campaign (arc), Arthritis Care, and the National Rheumatoid Arthritis Society are good reliable sources of the latter.

Skill enhancement can be gained from attendance at an Expert Patients Programme, and giving the patient the address of local and national community support networks offers great benefits.

It is important to remember that simply because information has been provided does not mean that it has been understood or acted upon. One quick and easy method to ensure assimilation is the “teach me back” method (Schillinger et al., 2003), which involves the patient being asked to “teach me” or “show me” as if the professional does not understand the problem. This quickly identifies any misunderstandings and allows purposeful correction.

Who should be referred to secondary care?

Waiting times for new rheumatology appointments vary widely and depend on local resources but also, to some extent, on how clinicians triage referrals from GPs. To make the system work effectively, care pathways need to be developed in which the patient is a partner, and which take psychosocial as well as biomechanical factors into consideration. The outcome, in terms of whether the patient is given an appropriate priority with an appropriate healthcare professional, depends largely upon the information contained within the referral letter. Standardized referral forms may help but have the disadvantages that they are time-consuming to complete and rather impersonal. Helpful information to include in a referral letter is shown in Box 1.3.

It has been estimated that 15–30% of all GP consultations are for musculoskeletal conditions. Most of these are for osteoarthritis in the over 50s age group and back pain in the under 50s. One challenge for the GP is how to spot the small number of patients with early inflammatory arthritis among this caseload who will benefit from early referral to hospital and prompt treatment with DMARDs. There are no specific clinical, radiological or immunological markers for rheumatoid arthritis (RA). Normal blood test results and X-rays do not exclude RA, but equally a positive rheumatoid factor does not clinch the diagnosis. Most rheumatology departments encourage an “inclusive approach” to referral and encourage GPs to maintain a high index of suspicion and not delay patients with possible inflammatory arthritis. Ideally, patients suspected of having inflammatory problems will be fast-tracked to secondary care. Box 1.4 highlights certain features thought to be indicative of early RA.

---

**Box 1.1 Role of the specialist nurse**

- Supervise treatment safety—e.g. monitoring disease-modifying antirheumatic drugs (DMARDS)
- Review treatment effectiveness
- Coordinate the multidisciplinary team
- Provide a communication channel between the patient and the team
- Act as the patient’s advocate
- Promote continuity of care
- Identify and address psychosocial patients’ issues
- Man telephone advice lines
- Facilitate education for patients, carers and health professionals

**Box 1.2 Knowledge necessary for self care**

- Disease aetiology and progress
- Drugs and how to take them; what the side effects are and what to do if they occur
- How to exercise
- How to protect joints and acquire appropriate devices and home changes
- How to control pain
- Coping strategies

**Box 1.3 Important information to include in a rheumatology referral letter**

- Length of history
- Pattern of joint involvement
- Presence of joint swelling
- Presence of early morning stiffness
- Previous treatments and response
- Level of distress/disability
- Results of investigations
- Other relevant medical or psychosocial factors

**Box 1.4 Symptoms and signs suggestive of early inflammatory arthritis**

- Symmetrical soft-tissue swelling (synovitis) of wrists and/or metacarpophalangeal joints and/or proximal interphalangeal joints
- Joint stiffness a significant problem—especially in the early mornings for >30 minutes
- Soft-tissue swelling of any joints
- Good response to a trial of non-steroidal anti-inflammatory drugs
Primary care management of musculoskeletal problems

Clearly, the majority of patients presenting to GPs will not have inflammatory arthritis. Indeed, often a precise pathological diagnosis based on symptoms and signs and results of investigations will not be possible, and may not be the most appropriate approach to management. This “medical model” of care often fails to address other important influences on pain perception, such as emotional and behavioural factors, and may encourage chronicity by using terms such as “arthritis”, “wear and tear” or “degeneration”, which emphasise the unchanging nature of the condition. Doctors are trained to diagnose “disease”, whereas the patient’s concern is what to do about their musculoskeletal pain, not just what to call it.

An alternative approach, which may be more useful in primary care, limits the diagnostic process to identifying potentially serious pathology—the so-called “red flag” disorders—and other specific diseases or disorders. This system was initially developed for back pain, and has been effective in changing the primary care management of this condition. It is equally applicable to other widespread or regional pain disorders, however (Box 1.5) (reviewed in Carr, 2001). Patients with “red flags” and certain other patients with specific diagnoses, including inflammatory arthropathies and connective-tissue disorders, should be considered for referral to secondary care for further investigation and management.

Having excluded and dealt with the small proportion of patients with potential serious pathology and specific diagnoses, the next step is to decide how best to manage the remainder. Two areas need to be addressed: how to deal with the presenting pain and distress (discussed below), and how to prevent future disability. Guidelines for the management of low back pain highlight the importance of identifying factors that predict chronicity. It is important to give positive messages about likely recovery and lack of long-term harm, taking particular account of psychosocial barriers to recovery (“yellow flags”). These principles have been described elsewhere (Department of Health, 2007) and are summarized in Box 1.6.

Evidence-based primary care treatments for musculoskeletal problems

The shift in emphasis towards self-management of musculoskeletal problems means that the primary health-care team is of central importance. There is a growing evidence base supporting the effectiveness of a number of simple primary care interventions for musculoskeletal problems (reviewed in Schillinger et al., 2003). Direct access physiotherapy reduces wait times and costs for treatment and is one way to facilitate the use of exercise and self-management regimes. These have been demonstrated to be beneficial for patients with a variety of regional and widespread musculoskeletal conditions, including osteoarthritis, back pain, fibromyalgia and shoulder problems. Prescribed exercise need not be the province of the physiotherapist alone. Often, wait times to see a physiotherapist are excessively long, and many self-limiting musculoskeletal conditions can be managed with sensible exercise regimes undertaken outside the hospital setting. This has the advantage of promoting self-help and “demedicalizing” common musculoskeletal problems. arc publishes a wide range of patient information leaflets and booklets, which are useful adjuncts to advice and education provided by health-care professionals (Box 1.7).

Local steroid injections are effective for reducing pain from soft-tissue problems such as tennis elbow and shoulder problems in the short term but do not improve long-term outcome. They should be reserved for patients in whom pain is restricting rehabilitation

---

**Box 1.5 “Red flags” for regional pain syndromes**

**History of significant trauma**  
- Fracture  
- Major soft-tissue injury

**Localized joint swelling and/or redness**  
- Septic arthritis  
- Inflammatory arthritis  
- Haemarthrosis

**Unremitting night pain**  
- Malignancy  
- Inflammation/infection

**Bone tenderness**  
- Fracture  
- Malignancy  
- Infection

**Systemic disturbance**

**Significant co-morbidity**

---

**Box 1.6 Psychosocial factors that predict chronicity**

- Belief that pain is due to progressive pathology  
- Belief that pain represents harm or injury  
- Belief that avoiding activity will speed up recovery  
- Tendency to social isolation  
- Tendency to anxiety/depression  
- Expectation that passive treatments rather than self-help programmes will be of benefit

---

**Box 1.7 arc publications**

Arthritis Research Campaign (arc) leaflets, booklets and other publications are available from:  
Dept RD  
ard Trading Ltd  
Brunel Drive  
Northern Road Industrial Estate  
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with the measures discussed above. Although the risks from local steroid injections are minimal, certain precautions need to be adhered to (Box 1.8).

Non-steroidal anti-inflammatory drugs may be beneficial for the short-term treatment of osteoarthritis but have a worrying side-effect profile in the patient group most likely to be prescribed them (elderly females). Simple analgesics are the preferred option where possible.

**Global issues**

The issues discussed in this chapter have global application, as the burden of illness from musculoskeletal conditions is high in both the developed and developing world and developing countries alike, particularly with an ever-increasing elderly population worldwide. In developing countries, it is essential to involve local community leaders and community health workers in the management of patients with these conditions. Awareness of the importance of musculoskeletal conditions, in terms of morbidity but also mortality, needs to be raised among all health-care workers, governments and members of the public. With increasing travel and migration, knowledge of the global spectrum of musculoskeletal conditions is important. There also needs to be an increasing emphasis on prevention through encouraging healthy lifestyles and joint protection and by tackling modifiable risk factors such as falls prevention. Whether in primary or secondary care, or whether in a developing or developed country, what is key is not where musculoskeletal care takes place, but that it is appropriately given.

**Conclusion**

Over the last 10 years there has been a shift in thinking about how best to care for patients with rheumatological disorders (Box 1.9). For those with inflammatory arthritis the emphasis is on prompt referral to secondary care so that treatment with potentially disease-modifying agents can be instituted early, before irreversible joint damage has occurred. For patients with non-inflammatory conditions, such as osteoarthritis and regional or widespread musculoskeletal pain, optimal management depends on developing an efficient triage system that can identify those with "red flags" who will benefit from referral to secondary care for further investigation and management. The first-line management for the remainder should be by health-care professionals in primary care, using the strategies outlined above.

**References**


Schillinger D, Piette J, Grumbach K et al. Closing the loop: physician communication with diabetic patients who have low health literacy. *Archives of Internal Medicine* 2003; 163: 83–90.


**Further reading**


White C, Cooper RG. In Practice: Prescribing and Monitoring of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) for Inflammatory Arthritis. Arthritis Research Campaign, Chesterfield, 2005.
Hand or wrist pain and resultant impaired function are often the cause of great anxiety for patients. Hands, as prehensile organs, give us a great deal of information about the world in which we live. They are capable of performing incredibly fine and delicate movements and are essential for work, sport, hobbies and social interaction.

**Functional anatomy**

The wrist is a complex structure comprising three groups of joints: the radiocarpal joints, which allow flexion, extension, abduction, adduction and circumduction; the inferior radio-ulnar joint, which allows pronation and supination; and the intercarpal joints (Figure 2.1).

The eight carpal bones, in two rows of four, form a bony gutter and are the base of the carpal tunnel. The flexor retinaculum, a strong fascial band, forms the palmar side of the tunnel. Running through the carpal tunnel are the eight carpal bones, the metacarpals, proximal phalanges, middle phalanges, distal phalanges and sesamoid bones. A sesamoid bone lies at the base of the thumb in the tendons of flexor pollicis brevis. The first metacarpal bone of the thumb is the shortest and most mobile of the metacarpals and lies in a different plane to the others. This is important to allow opposition, i.e. pincer action to grasp objects. The carpometacarpal and trapezoscaphoid joints are prone to osteoarthritis.

Individual tendon sheaths for the deep and superficial flexor tendons start at the level of the distal transverse crease of the palm and end at the bases of the distal phalanges. The sheath for flexor pollicis longus continues from the carpal tunnel to the distal phalanx. During flexion, five fibrous bands, or pulleys, hold the flexor tendons in position.

The second to fifth metacarpophalangeal joints flex to about 90°. Active extension is rarely more than 30°. Passive extension varies from 60° to more than 100° in people with hypermobility. The proximal and distal interphalangeal joints are hinge joints. The lumbrical and interossei muscles produce complex movements that involve extension of the interphalangeal joints and flexion at the metacarpophalangeal joints and are essential to fine hand functions, such as writing.

There are many possible causes of pain in the wrist and hand (Table 2.1).

**Tendon problems**

**Flexor tenosynovitis**

Unaccustomed or repetitive use of the finger and inflammatory arthritis cause flexor tenosynovitis (Figure 2.2), inflammation of the synovial sheath of the finger flexor tendons, which leads to volar swelling and tenderness just proximal and distal to the wrist. The flexor tendon sheaths in the palm or finger may also be affected. The hand feels stiff, painful and swollen, particularly in the morning. Rest helps. Injection is sometimes needed. Local anaesthetic helps introduce the needle alongside the tendon in the palm just proximal to the metacarpophalangeal joint.
Carpal tunnel syndrome is a peripheral nerve entrapment syndrome of the median nerve, often caused by flexor tenosynovitis. It can occur in the third trimester of pregnancy. Repetitive use of the hand increases the risk of developing carpal tunnel syndrome but its status as a work injury is controversial (Yagev et al., 2001).

A ganglion, or very rarely amyloidosis or myxoedema, causes carpal tunnel syndrome. Pain, tingling and numbness in a median nerve distribution (thumb, index finger, middle and radial side of ring finger) are typically present on waking or can wake the patient. The fingers feel swollen and intense aching is felt in the forearm. The symptoms may appear when the patient holds a newspaper or the steering wheel of a car. Permanent numbness and wasting of the thenar eminence (flexor pollicis and opponens pollicis) cause clumsiness. The patient’s history often indicates the diagnosis (Pal et al., 2001), or using a scored questionnaire may help (Kamath and Stothard, 2004).

Tests and investigations—Tinel’s sign (tapping the median nerve in the carpal tunnel) or Phalen’s test (holding the wrist in forced dorsiflexion) may provoke symptoms. Weakness of abduction of the thumb distal phalanx with the thumb adducted towards the fifth digit is typical. The carpal tunnel and median nerve are seen on ultrasonic images, although US and MRI are not usually needed.

Management and injection technique—A splint worn on the wrist at night relieves or reduces the symptoms of carpal tunnel syndrome. This is diagnostic and may be curative. A corticosteroid injection into the carpal tunnel (Figure 2.3) may also be considered, as this often helps rapidly, although recurrence is common. The needle is inserted at the distal wrist skin crease, just to the ulnar side of the palmaris longus tendon, or about 0.5 cm to the ulnar side of flexor carpi radialis at an angle of 45° towards the middle finger. The local anaesthetic is injected superficially. If a small test injection of corticosteroid causes finger pain, the needle is in the nerve and needs to be repositioned. An injection of a locally acting...
steroid preparation, e.g. hydrocortisone acetate, often precipitates the symptoms, but it is effective and non-toxic (O’Gradaigh and Merry, 2000; Wong et al., 2001).

Recurrent daytime symptoms, unrelieved by splints, warrant nerve-conduction studies. Slowing of median nerve conduction at the wrist suggests demyelination due to local compression. The action potential is reduced or absent due to nerve-fibre loss if the lesion is severe or prolonged. Needle electromyography is unpleasant but detects denervation.

Decompression surgery should be considered for: recurrent symptoms not eased by splints or injection; significant nerve damage; muscle wasting; and/or permanent numbness (Trumble et al., 2001). Pins and needles often worsen briefly post-operatively while the nerve recovers. Recovery of sensation or strength, or both, may be limited or non-existent if the lesion is severe and longstanding.

**Finger flexor tenosynovitis and trigger finger**

Gripping and hard manual work cause palpable thickening and nodularity of the finger flexor tendon; tendon sheath synovitis may also be present. The affected fingers are stiff in the morning, when the patient also has pain in the palm and along the dorsum of the finger(s). The pain is reproduced by passive extension of the finger. This is common in rheumatoid arthritis and in dactylitis caused by seronegative arthritis. Nodular flexor tenosynovitis is more common and less responsive to treatment in patients with diabetes than in other patients (Stahl et al., 1997).

Trigger finger is caused by a nodule catching at the pulley that overlies the metacarpophalangeal joint in the palm. The patient wakens with the finger flexed and has to force it straight with a painful or painless click. Triggering also occurs after gripping. The nodule and the “catch” in movement are felt in the palm.

*Management and injection technique*—A low-pressure injection of local anaesthetic followed by a locally acting steroid preparation alongside the tendon nodule in the palm helps (Rankin and Rankin, 1998) (Figure 2.4). If symptoms are persistent or recurrent, surgical release is needed.

Overuse and local injury (after opening a tight jar) are the most common causes of thumb flexor tenosynovitis and trigger thumb. Either the interphalangeal joint cannot be flexed or it sticks in flexion and snaps straight. The sesamoid bone in the flexor pollicis brevis tendon is tender on the volar surface of the thumb's metacarpophalangeal joint. Corticosteroid injection next to the sesamoid bone at the site of maximal tenderness helps.

**De Quervain’s tenosynovitis**

De Quervain’s stenosing tenosynovitis affects the tendon sheath of abductor pollicis longus and extensor pollicis brevis at the radial styloid. It causes pain at or just proximal or distal to the styloid, in contrast with first carpometacarpal osteoarthritis, which causes pain at the base of the thumb. Tenderness, swelling and Finkelstein’s test—pushing the thumb into the palm while holding the wrist in ulnar deviation—increases the pain. Crepitus or a tendon nodule may cause triggering.

*Management and injection technique*—Rest is essential, with avoidance of thumb extension and pinching, but immobilization splints are inconvenient. Therapeutic ultrasound or local anti-inflammatory gels help; injection of local anaesthetic, then a locally acting steroid preparation alongside the tendon under low pressure at the point of maximum tenderness rapidly relieves the pain (Figure 2.5). A second injection may be needed. Surgery is rarely necessary, unless stenosis or nodule formation develops.
**Extensor tenosynovitis**
Inflammation of the common extensor (fourth) compartment causes well-defined swelling that extends from the back of the hand to just proximal to the wrist. The extensor retinaculum causes a typical “hourglass” shape proximal and distal to the wrist. This contrasts with wrist synovitis, which causes diffuse swelling distal to the radius and ulna. Repetitive wrist and finger movements, especially with the wrist in dorsiflexion, are the cause, and this is one of the several causes of forearm and wrist pain seen in keyboard workers. It is also common in rheumatoid arthritis. Rest helps extensor tenosynovitis, but often a corticosteroid injection into the tendon sheath is needed. Workplace reviews and wrist supports for those who use a keyboard and mouse help prevent recurrences.

**Mallet finger**
This is a flexion deformity affecting the distal interphalangeal joint of the finger and is due to either distal extensor tendon rupture or avulsion with a bony fragment after traumatic forced flexion of the extended fingertip. The resultant weakness is often painless and presents with an inability to actively extend the fingertip. Treatment is usually by splinting the distal interphalangeal joint in extension or, rarely, surgery.

**Osteoarthritis**

**Nodal osteoarthritis**
Nodal osteoarthritis most commonly involves the distal interphalangeal joints and is familial. The joint swells and becomes inflamed and painful, but the pain subsides over a few weeks or months and leaves bony swellings (Heberden’s nodes). Most patients manage with local anti-inflammatory gels or no treatment once they know the prognosis is good. The appearance sometimes causes distress. Occasionally, the joint becomes unstable and limits pinch gripping. Surgical fusion of the index distal interphalangeal joints or thumb interphalangeal joint in slight flexion improves grip, although this is rarely necessary. Involvement of the proximal interphalangeal joints (Bouchard’s nodes) is less common and may be mistaken for early rheumatoid arthritis (Figure 2.6). Stiffness of the proximal joints impairs hand function significantly.

**First carpometacarpal osteoarthritis**
Pain at the base of the thumb in the early phase of first carpometacarpal osteoarthritis (Figure 2.7) is disabling, but with time the joint stiffens and adducts, and pain and disability decrease. The hand becomes “squared”. Management is usually conservative, but
Surgical anterior transposition of the nerve is occasionally needed. In some cases the ulnar nerve is compressed in Guyon’s canal at the wrist.

### Systemic disorders causing hand pain

#### Inflammatory arthritis

The hands are often affected early in rheumatoid arthritis, with symmetrical swelling of the metacarpophalangeal joints, proximal interphalangeal joints and wrists. The feet and other joints are usually also affected. Psoriatic and other forms of seronegative arthritis are less common, are more likely to be asymmetrical, and may be associated with marked skin and tendon changes that produce a “sausage” finger. The distal interphalangeal joints and adjacent nails may also be affected in psoriasis. Morning pain and stiffness are typical. Intra-articular steroids are often useful adjuncts to systemic medication.

#### Acute pseudogout and chondrocalcinosis of the wrist

Sudden wrist inflammation in an older patient may be due to calcium pyrophosphate arthritis (pseudogout). Marked swelling and inflammation are observed—the joint feels hot, and infection may need to be excluded. Chondrocalcinosis (Figure 2.9), although often asymptomatic, is usually seen in the triangular ligament of the wrist on X-ray radiography. The joint aspirate is turbid and contains weakly positively birefringent crystals under polarized light. Steroid injection or a short course of a non-steroidal anti-inflammatory drug or colchicine usually helps; regular use of non-steroidal anti-inflammatory drugs or colchicine can be used to manage frequent attacks.

#### Acute gout and chronic tophaceous gout

Acute urate gout rarely affects the hands. Tophaceous deposits in individuals in renal failure or who have been on long-term diuretic treatment are initially painless, chalky subcutaneous deposits. The tophi can ulcerate and a few such patients also develop acute gout in the hand and elsewhere.
Other disorders

Ganglion
A ganglion is a cystic swelling in continuity with a joint or tendon sheath through a fault in the capsule. It is filled with clear, viscous fluid rich in hyaluronan. Ganglia are common on the dorsal wrist, are often painless and resolve spontaneously (50% at 6 years; see http://www.medicine.ox.ac.uk/bandolier/booth/miscellaneous/wristgang.html). Often, only reassurance of the patient is required. Wrist splints relieve the pain. Aspiration and injection are rarely effective, and surgical excision is best if the ganglion is persistent and painful.

Chronic (work-related) upper limb pain
The main symptom of chronic upper limb pain is pain (Box 2.1). A local cause (carpal tunnel syndrome, flexor tenosynovitis, or tennis elbow) may be the initial trigger. The patient develops widespread pain that is often disproportionate to the findings but causes great distress. A prior change in work pattern may exist, and often disharmony is found at the workplace. The cause is unclear, but neurophysiological and psychosocial factors are probably involved. The phenomenon of central “wind up” of pain seen in many chronic pain syndromes probably plays a role. It is easy for the doctor to find the problem exasperating and difficult to understand, but it is best managed non-judgmentally. Early reductions in work activities and pain-control measures are important, but it is best not to ask the person to take too much time off. Advice to the employer to review work practices reduces the risk of litigation. Referral to a specialist pain clinic should be considered.

Osteonecrosis (rare)
Kienböck’s disease is the late result of a dorsiflexion injury often seen in manual labourers. Fragmentation and collapse of the lunate causes shortening of the carpus and secondary osteoarthritis. Osteonecrosis takes up to 18 months to appear on X-ray radiography.

Scaphoid bone fracture
Pain in the anatomical snuffbox after a fall onto an outstretched hand requires an immediate X-ray examination, although a...
fracture is not always visible. Any severe wrist injury should be managed as a potential scaphoid fracture with a plaster, and a further X-ray radiograph should be taken 3 weeks later. Unrecognized scaphoid fracture leads to pain associated with failed union, osteonecrosis and secondary osteoarthritis.

**Writer’s cramp**

Writer’s cramp is the most common type of focal dystonia and occurs during complex hand activities—writing or playing a musical instrument. Clumsiness and painful tightness in the hand and forearm occur during writing or playing, and abnormal tension and strange posturing develop. Focal dystonias are often inappropriately described as “psychological.” Local botulinum toxin injection produces temporary relief. Retraining and learning new techniques help some patients, but the outlook is poor and may lead to the end of musical careers.

**Septic arthritis**

Septic arthritis of the hand or wrist is rare. It is an important differential diagnosis of acute pseudogout. If septic arthritis is suspected, it should be treated as a medical emergency and referred to Accident and Emergency or a specialist unit for investigation and appropriate intravenous antibiotic treatment. The patient is usually febrile and unwell. It is essential not to start antibiotics before all the necessary samples have been taken for culture. Non-steroidal anti-inflammatory drugs and analgesics can be given for pain, which is often severe.

**Local corticosteroid injection technique**

During local corticosteroid injections (Box 2.2), an injection of local anaesthetic (or topical anaesthetic) is followed by 0.2–1 ml of a suitable steroid preparation, such as hydrocortisone acetate 25 mg/ml or depot methylprednisolone 40 mg/ml. Methylprednisolone is about five times as powerful as hydrocortisone on a mg per mg basis. It is best first to introduce the needle with local anaesthetic and then to inject the steroid under low pressure. Patients should be warned that the pain might increase for a day or two after injection. Superficial injections or, very rarely, leakage of the corticosteroid along the needle track, cause local skin depigmentation and atrophy of subcutaneous fat; this is more likely with depot injections of steroid. Consent from the patient should always be obtained.

**References**


**Further reading**


Pain in the Neck, Shoulder and Arm

Rachelle Buchbinder\(^1\) and Caroline Mitchell\(^2\)

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\(^2\)University of Sheffield, Sheffield, UK

OVERVIEW

- Neck, shoulder and lateral elbow pain are common musculoskeletal problems for which patients seek care in general practice.
- Non-specific neck pain is often acute and self-limiting, attributed to a mechanical basis, but persistence or recurrence is common. For most patients with acute neck pain and no “red flags”, further investigation is not necessary.
- Neck pain usually responds to analgesia and advice about simple mobilization and exercises. High-quality evidence for the effectiveness of many treatment modalities is limited and often contradictory.
- Most shoulder complaints are due to rotator cuff disease, which is more prevalent with increasing age. Adhesive capsulitis, or “frozen shoulder”, is a self-limiting condition, occurring most commonly in middle age. It can be distinguished from rotator cuff disease by the presence of global restriction of shoulder movements. It is also more common in people with diabetes.
- For most patients with shoulder pain the diagnosis can also usually be made clinically. Treatment aims to control pain and restore movement and function of the shoulder.
- Lateral epicondylitis is thought to be an overload injury at the origin of the common extensors at the lateral epicondyle. Patients present with pain and tenderness over the lateral epicondyle and pain with resisted movements. Prognosis is generally favourable, with 80% recovery within a year. Management is directed towards controlling pain, avoiding aggravating activities and maintaining movement.

The neck and shoulder are two of the most common sources of musculoskeletal pain. Neck pain has a self-reported point prevalence of between 10 and 20%. The majority of neck pain is acute and self-limiting and can be attributed to a mechanical or postural basis. However moderate or severe symptoms may persist in up to 30% of patients.

Shoulder pain has a self-reported point prevalence of between 14 and 26% in the general population. The incidence of shoulder pain increases with age, as does its functional impact. About one-quarter of all new episodes presenting for care resolve fully within 1 month, and nearly half have resolved within 3 months of onset. However, persistence or recurrence of shoulder symptoms within a year of initial presentation is common (in up to 50% of people).

Anatomy and function of the neck and shoulder joint

The neck moves almost constantly during waking hours through flexion, extension and rotation at the intervertebral and facet joints of the seven cervical vertebrae, through the actions of the surrounding muscles.

The shoulder is a series of articulations, including the scapulothoracic articulation, where the scapula slides on the ribcage (Figure 3.1). Soft tissue structures—capsules, ligaments, muscles, tendons, bursae and neurovascular elements—complete the framework and allow remarkable mobility to be achieved. The glenohumeral joint is extremely mobile and relies on the rotator cuff for stability. Instability, caused by laxity (congenital or acquired) or lack of muscular control because of pain, is a common feature of shoulder complaints.

The elbow is a compound synovial joint composed of a complex of two closely related articulations between the humerus and both the ulna and radius. It is supported by the ligaments and muscles.

Clinical evaluation

Neck and arm pain have a wide differential diagnosis. It is sometimes hard to distinguish between pain arising from the neck or the shoulder (Figure 3.2). Pain proximal to the shoulder, in the shoulder girdle or over the scapula indicates referred pain from the neck.

It is important to assess the patient’s concerns, expectations, functional disability and any psychosocial and occupational issues. Details of hand dominance, any injury, hobbies, sporting activities and treatments for this or any other similar previous musculoskeletal problems should be noted. Significant past and current medical history—prescribed drugs and adverse reactions—should also be explored. The history should elicit the presence of any clinical features that indicate potentially serious pathology.

Determine the mode of onset and duration of the pain, nature, site, radiation, temporal characteristics, exacerbating and relieving
It includes careful inspection, palpation, movement, special tests, neurological assessment and further investigations, as appropriate.

Neck pain

Pain in the neck usually arises because of poorly defined mechanical influences, although it can occur because of pathology within the spine or be referred from elsewhere. A list of differential diagnoses of neck pain is shown in Box 3.1. When considering the diagnosis it is important to look for “red flags” or clinical features that indicate that there might be a serious underlying cause of the complaint (Table 3.1). Restricted cervical movements and local tenderness help to confirm the local origin of neck pain. Risk
motor signs of myelopathy below the level of spinal cord involvement may include weakness with increased reflexes and tone (upper motor neurone signs), decreased pinprick sensation and loss of position and/or vibration sense. These symptoms warrant urgent referral for specialist assessment.

Whiplash injury, an abrupt flexion/extension movement of the cervical spine as a result of sudden acceleration–deceleration, may occur in road traffic or sporting injuries, and is characterized by quite localized or diffuse neck and arm pain with muscle spasm, and limited neck movements. Symptoms may be persistent, although 50% of patients recover within 3 months and 80% within 12 months. Risk factors for chronicity after whiplash include the severity of the initial symptoms and psychological disturbance.

Neck pain is common in inflammatory arthritis, and atlantoaxial and sub-axial subluxation may develop, particularly in rheumatoid arthritis. Immobility due to osteophytic linking of vertebrae may be seen in ankylosing spondylitis.

### Investigation of neck pain

For most patients with acute neck pain and no “red flags”, further investigation (radiographs, blood tests) is not necessary. Due to the high prevalence of asymptomatic degenerative changes in the cervical spine, plain radiographs are rarely diagnostic, and pain severity correlates poorly with radiographic abnormalities. Magnetic resonance imaging (MRI) is highly sensitive in detecting disc and cord abnormalities if these are suspected, whereas computed tomography is better for evaluation of bone.

### Treatment of neck pain

Patients should be informed of the generally favourable prognosis of neck pain and the fact that serious underlying conditions are very unlikely. Pertinent psychosocial and occupational issues may need to be explored.

Neck pain usually responds to simple analgesia and advice about simple mobilization and exercises. High-quality evidence for the effectiveness of many treatment modalities is limited and often contradictory.

**Advice to stay active**—Encourage patients to persist with their normal activities. There is no evidence that collars reduce pain or improve function, nor is there evidence about special pillows. In general patients are advised to sleep on their side with a single pillow under the knees, not on their back. This promotes normal neck alignment with rotation and normal shape.

Factors to consider in the management of neck pain include:

- **Personal factors**: Age, gender, social interaction, work demands, and psychosocial factors. Features of an overly structured lifestyle may act as predisposing factors. Patients who have a high level of work and social demands and high levels of anxiety and depression are more likely to be symptomatic.
- **History of neck pain**—Patients should be informed of the generally favourable prognosis of neck pain and the fact that serious underlying conditions are very unlikely. Pertinent psychosocial and occupational issues may need to be explored.
- **General management**—Encourage patients to persist with their normal activities.
- **Advice to stay active**—Encourage patients to persist with their normal activities. There is no evidence that collars reduce pain or improve function, nor is there evidence about special pillows. In general patients are advised to sleep on their side with a single pillow under the knees, not on their back. This promotes normal neck alignment with rotation and normal shape.

<table>
<thead>
<tr>
<th>“Red flags”</th>
<th>Potential pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of cancer, symptoms and signs of cancer, unexplained deformity, mass or swelling</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Fever, systemically unwell, redness and swelling</td>
<td>Infection</td>
</tr>
<tr>
<td>Trauma, epileptic fit, electric shock, loss of rotation and normal shape</td>
<td>Unreduced shoulder dislocation</td>
</tr>
<tr>
<td>Recent trauma, acute disabling pain and significant weakness, positive “drop arm” sign</td>
<td>Acute rotator cuff tear</td>
</tr>
<tr>
<td>Diffuse poorly localized pain and/or abnormal sensation, unexplained wasting, loss of power or altered reflexes</td>
<td>Neurological lesion, cervical radiculopathy, myelopathy</td>
</tr>
<tr>
<td>Referred pain: neck pain, myocardial ischaemia, referred diaphragmatic pain, apical lung cancer, metastases</td>
<td>Pain arising from elsewhere</td>
</tr>
<tr>
<td>Bilateral shoulder pain with or without neck pain, early morning stiffness</td>
<td>Polymyalgia rheumatica, rheumatoid arthritis, giant cell arteritis</td>
</tr>
<tr>
<td>Rapid swelling after trauma</td>
<td>Haemarthrosis of the shoulder</td>
</tr>
</tbody>
</table>

**Table 3.2 Arm dermatomes**

<table>
<thead>
<tr>
<th>Nerve root</th>
<th>Weakness</th>
<th>Reflex change</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Shoulder abduction</td>
<td>Biceps</td>
</tr>
<tr>
<td>C6</td>
<td>Wrist extension, supination, elbow flexion</td>
<td>Radial</td>
</tr>
<tr>
<td>C7</td>
<td>Elbow extension, wrist flexion</td>
<td>Triceps</td>
</tr>
<tr>
<td>C8</td>
<td>Finger flexors</td>
<td>NA</td>
</tr>
<tr>
<td>T1</td>
<td>Finger abductors</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Table 3.1 “Red flags” or clinical features indicative of potentially serious pathology in the neck and/or shoulder**

<table>
<thead>
<tr>
<th>“Red flags”</th>
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<td>Rapid swelling after trauma</td>
<td>Haemarthrosis of the shoulder</td>
</tr>
</tbody>
</table>
pillow supporting the neck. Early mobilization and return to normal activity may reduce pain in people with acute whiplash injury more than immobilization or rest with a collar.

Drug therapy—There is limited evidence about the relative benefits of paracetamol, opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressants. Potential benefits versus risks of NSAIDs should be considered, particularly in high-risk patients (consider potential drug interactions, the elderly, coexisting asthma, past history of peptic ulcer, renal impairment). All patients on regular analgesia should be reviewed regularly for both efficacy and adverse effects. If there is significant nocturnal pain, a tricyclic antidepressant (e.g. amitriptyline 10 to 50 mg orally, at night) may be helpful.

Exercises—Gentle neck exercises may be a useful and effective treatment for acute neck pain. The best type and mix of exercise has not been defined, but includes stretching, strengthening and proprioceptive retraining exercises (usually prescribed by a physiotherapist). Exercises for cervical radiculopathy are unproven. Exercise therapy is contraindicated in the presence of myelopathy.

Mobilization or manipulative techniques—Mobilization or manipulative techniques for both acute and chronic pain (typically performed by physiotherapists, chiropractors or osteopaths), either alone or in combination with other physical interventions, may have a modest effect, although this is unproven.

Multidisciplinary biopsychosocial rehabilitation—The principle underlying multidisciplinary rehabilitation is to simultaneously address all components (physical, psychological and social) of the patient’s pain experience. Cognitive behavioural therapy has been shown to decrease time off work and other behavioural manifestations of pain but not to change the degree of pain.

Other non-operative treatments—The efficacy of most passive non-manipulative therapies (e.g. heat, massage, transcutaneous electrical nerve stimulation, pulsed electromagnetic field treatment) is not supported by evidence. Acupuncture might provide short-term pain relief in people with chronic neck pain, but evidence is limited. There is also limited evidence about the effectiveness of massage for neck pain. There is limited evidence that myofascial trigger-point injections using local anaesthetic into tender points are beneficial in reducing chronic neck pain. There is inconclusive evidence about the effectiveness of traction for neck pain with or without cervical radiculopathy, and it should not be used before imaging to exclude spinal cord compression or a large disc protrusion. A short course of oral glucocorticoids prescribed by a specialist, and after appropriate investigation, may be of benefit for cervical radiculopathy but is unproven. Facet joint injections, medial branch blocks and percutaneous radiofrequency denervation are performed under the premise that pain arises from the facet joint; however, the evidence to support these procedures is very limited. Botulinum A intramuscular injections have been shown to be ineffective for neck pain with or without radiculopathy.

Surgery—Surgery is not indicated for patients with neck pain in the absence of neurological symptoms of radiculopathy or myelopathy. Surgery for cervical radiculopathy is indicated for progressive motor weakness, and it may be also be a reasonable option for those who have failed 6–12 weeks of conservative treatment. In both instances, there should be evidence of nerve root compression at the appropriate level to fit the presentation. Anterior cervical discectomy with or without and fusion is the most commonly used procedure. Surgery may also be indicated in people with myelopathy to prevent neurological progression.

Shoulder pain

The differential diagnosis of shoulder pain is summarized in Box 3.2. Pain may also arise in the scapulothoracic region, and a list of differential diagnoses is shown in Box 3.3. “Red flags” or clinical
features suggestive of serious underlying pathology in people who present with shoulder pain are shown in Table 3.1.

**Rotator cuff disease**

Most shoulder complaints (60–70%) are due to rotator cuff disease, a broad term that includes a wide array of diagnostic labels. Some labels derive from clinical features (e.g. painful arc syndrome); some from assumed pathophysiology (e.g. impingement syndrome—impingement upon the cuff tendons between the acromion and head of the humerus (Figure 3.4) and some from the imaging appearance (e.g. calcific tendinitis, rotator cuff tendinitis or tendinopathy, subacromial bursitis and partial- or full-thickness tears).

Based upon MRI scans, asymptomatic cuff tears are common. The incidence increases with age (over half those over 60 years of age have tears), suggesting that it may be part of the normal ageing process combined with repetitive microtrauma. A significant number of asymptomatic tears will become symptomatic over time, and longstanding tears can result in glenohumeral arthritis. Rotator cuff disorders commonly occur in young people engaged in sport involving overhead activities, but are most common in middle and older age. Occupational associations include repetitive movements, working with vibrating tools, working in awkward postures and performing similar work for a prolonged period.

The patient typically complains of pain felt in the shoulder and/or lateral aspect of the upper arm that is worse with overhead activities and at night, particularly when lying on the affected side.

Characteristic features of the examination include pain in the mid-range of active abduction (Figure 3.5) and on resisted shoulder abduction with or without external rotation, and evidence of impingement (production of pain at the anterior shoulder if the arm is flexed forwards to 90°, adducted and internally rotated, elicited by asking the patient to place their hand on the contralateral shoulder and push up against resistance). In contrast to adhesive capsulitis, which causes global restriction of both active and passive movements, passive range of motion is often normal in rotator cuff disease, although certain movements may be restricted by pain. It is therefore important to assess both active (patient moves the shoulder) and passive (the examiner moves the shoulder) movements to distinguish apparent from true restriction of shoulder motion.

Painful weakness and atrophy suggest significant tears. Winging or asymmetry of the scapula may indicate a degree of shoulder instability. The “drop arm” test suggests a complete or large rotator cuff tear.

Calcific tendinitis usually affects women aged 30–50 years and is associated with the formation and resorption of calcific deposits within the cuff. The patient typically presents with acute onset of severe pain, occasionally with a fever and severe limitation of shoulder movements due to pain. In the more chronic stages, pain and catching are reported, and signs of impingement may be noted.

Diagnosis—The diagnosis of rotator cuff disease can usually be made clinically. Blood tests and plain radiographs are not necessary in the absence of “red flags” unless there is a failure to respond to treatment. Plain radiographs may exclude other causes of shoulder pain, such as significant glenohumeral osteoarthritis. If calcific tendinitis is suspected, there may be fluffy calcific deposits, situated just proximal to the rotator cuff insertion (Figure 3.6), and the erythrocyte sedimentation rate and white cell count may also be raised. The diagnostic utility of shoulder ultrasound and MRI in primary care is unknown. Due to the high prevalence of asymptomatic abnormalities in the rotator cuff, these investigations have little to add to the largely conservative management of rotator cuff disease in primary care. Ultrasound and MRI can detect full-thickness rotator cuff tears but have less accuracy for detecting partial-thickness tears.
Treatmen—The aims of treatment of rotator cuff disease are to control pain and restore movement and function of the shoulder. Paracetamol is suitable as first-line therapy and may be supplemented by mild opioids such as codeine phosphate if needed. NSAIDs may provide short-term pain relief if there are no contraindications to their use. Initially patients may need to modify their activities and address occupational factors.

Subacromial injection of depot corticosteroid and local anaesthetic may provide rapid relief of pain, but its effect may be small and not maintained beyond a few weeks. If initial response is good, injections may be repeated up to two or three times at six-weekly intervals. Although injections performed under fluoroscopy or ultrasound might increase the accuracy of needle placement, it is not clear whether or not this results in significantly better outcomes.

Physiotherapy comprising a combination of mobilization techniques and directed exercises designed to strengthen and stabilize the cuff and scapular muscles can be used alone or combined with other measures. Global strengthening and proprioception training may reduce instability and minimize impingement in those with glenohumeral joint hypermobility.

Benefits of heat or ice packs, low-power laser, ultrasound and pulsed electromagnetic field therapy are unproven, as trials have yielded conflicting results. There is limited evidence for transitory pain relief following acupuncture, and suprascapular nerve block may also provide short-term pain relief. Trials have failed to establish the efficacy of extracorporeal shock wave therapy (ESWT) for rotator cuff disease.

Surgery may be required when symptoms fail to respond to conservative treatment. Operative treatment involves decompression of the subacromial space, with or without rotator cuff repair. MRI may be useful to plan surgery (Figure 3.7). Observational studies have reported good outcomes of surgery, although three randomized controlled trials found that surgery was not superior to treatment with supervised exercises.

Subacromial steroid injections, needling of the calcific deposits under fluoroscopic guidance and percutaneous needle aspiration and lavage by ultrasound guidance have each been advocated to relieve pain in calcific tendinitis, although no data are available from controlled trials. Ultrasound may provide short-term pain relief and, like ESWT, may improve the radiological appearance of calcific deposits. Surgical removal of calcific deposits may be of benefit if conservative treatments fail.

Adhesive capsulitis
Adhesive capsulitis (“frozen shoulder”, or painful stiff shoulder) affects 2–5% of the population, women slightly more often than men, and 10–36% of people with diabetes, in whom it is more severe. It occurs most commonly in the fifth and sixth decades of life and is rare before the age of 40 years. The cause is poorly understood. It is usually idiopathic, although it may occur in the context of prolonged shoulder immobility (e.g. following a stroke or cardiac, breast or shoulder surgery).

Three phases have been described: initial gradual development of diffuse and severe shoulder pain, typically worse at night with inability to lie on the affected side, lasting between 2 and 9 months; a stiff phase with less severe pain present at the end range of movement, characterized by global stiffness and severe loss of shoulder movement, lasting about 4 and 12 months; and finally a recovery phase characterized by a gradual return of movement over 5 and 24 months. Severe disability may result in absence from work and inability to perform leisure activities. Although generally thought to run a self-limiting course over 2 to 3 years, some studies have found that up to 40% of patients have persistent symptoms and restricted movement beyond 3 years.

Diagnosis—The diagnosis can be made clinically, as the restriction of both active and passive movement in all planes of movement, especially external rotation, distinguishes it from other causes of shoulder pain. Plain radiographs are not necessary in primary care.
unless glenohumeral arthritis is suspected. Likewise, MRI is seldom necessary to establish the diagnosis, even in specialist care.

**Treatment**—Treatment is needed to control severe pain, improve range of movement and promote function. Patients should be informed of the generally favourable prognosis.

Treatment with analgesia and NSAIDS is the same as for rotator cuff disease.

Intra-articular injection of corticosteroid combined with local anesthetic using either an anterior or posterior approach may provide rapid pain relief, but the effect may not be sustained beyond 6–7 weeks. There are limited data to provide guidance about frequency, dose and type of corticosteroid for adhesive capsulitis.

Arthographic distension of the glenohumeral joint (or hydrodilatation) is performed under radiological guidance, usually using a combination of local anaesthetic, corticosteroid and saline to a mean volume of 20–45 ml. It has recently been demonstrated to have a sustained beneficial effect on pain, function and range of movement and is the standard of care in some settings. It may be more effective in the intermediate (stiff) and recovery stages and may also be repeated if the effect wanes over time.

Physiotherapy in the early, painful phase of the condition may aggravate the pain. However, gentle mobilization and strengthening exercises can improve mobility and reduce the duration of disability in the later phases. There is also evidence that mobilization and strengthening exercises following either steroid injection or arthrographic distension provide additional benefits over these treatments alone.

A short course of oral glucocorticoids, prescribed by a specialist, may provide rapid pain relief, although the effect may diminish beyond 6 weeks. Although treatment may be more effective in the very early phase of the condition, benefit has been demonstrated in patients with an average duration of symptoms of 5 to 6 months.

Suprascapular nerve blocks may provide short-term pain relief.

Manipulation under anaesthesia, possibly combined with intra-articular steroid injection and/or arthroscopic debridement of adhesions, may be helpful if conservative options have failed. Manipulation under anaesthesia can however, cause iatrogenic damage such as fractures, haemarthroses and tears of the labrum, tendons or ligaments.

**Other shoulder disorders**

**Acromioclavicular and sternoclavicular joint disorders**—Osteoarthritis of the acromioclavicular joint is common and presents with well-localized pain and tenderness over the joint. It can be managed symptomatically with analgesics, and local corticosteroid injections may provide relief. Surgery can be effective in resistant cases. The acromioclavicular joint can be strained or dislocated as a result of traumatic or sports injuries. Examination may find a superior painful arc of abduction (Figure 3.5) and restriction of passive horizontal adduction (flexion) of the shoulder, with the elbow extended across the body. This can be managed with taping and analgesia, and in severe cases, surgery may be required.

The sternoclavicular joint can be the presenting site of an inflammatory arthritis, but it is frequently overlooked. Rarely the sternoclavicular and/or acromioclavicular joints can be involved in the rare SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteomyelitis).

**Glenohumeral joint arthritides**—Isolated osteoarthritis of the shoulder is rare but may occur following fractures of the humeral head or neck or large rotator cuff tears, or as the end result of rheumatoid arthritis. It may be suspected, particularly in the older age group, if there is a limited range of painful movement sometimes accompanied by crepitus. Plain radiographs are useful in this instance. New onset of bilateral shoulder pain and stiffness should prompt consideration of polymyalgia rheumatica in those over 50 years of age and in rheumatoid arthritis. Milwaukee shoulder, which mainly affects elderly women, is a severe destructive apatite-associated arthropathy that presents with shoulder pain, limited movements and large joint effusion. Aspiration reveals a large amount of blood-tinged synovial fluid, which contains calcium phosphate crystals.

**Biceps tendinitis/rupture**—The long head of the biceps tendon passes through the bicipital groove of the anterior proximal humerus and is often involved in rotator cuff disease but can present as an isolated problem. It presents with anterior shoulder pain, aggravated by lifting, carrying objects and overhead reaching. Sudden onset of worsening symptoms, which may occur after heavy lifting or be spontaneously accompanied by a swelling just above the antecubital fossa and sometimes bruising, suggests an acute rupture. In most instances proximal tendon rupture is cosmetic and does not require repair. However, distal biceps tendon rupture should be referred urgently for consideration of surgical repair.

**Shoulder instability**—General glenohumeral instability or looseness may be seen in young women with weak shoulder muscles, in young athletes (especially swimmers and throwers) and following large rotator cuff tendon tears. There may be diffuse shoulder pain, and instability may be multi- or unidirectional.

**Glenoid labrum (cartilage) injuries**—These can cause persistent shoulder pain and instability, and they usually occur after an episode of trauma or dislocation or with overuse. Diagnosis can be difficult, requiring magnetic resonance arthrography or arthroscopy. Management involves pain control and rehabilitation, which is followed by surgery if necessary.

**Neurological causes**—Shoulder pain may result from neurological causes, including nerve root entrapment at the neck, brachial plexus lesions or peripheral nerve lesions, including the axillary, long thoracic, suprascapular, radial or musculocutaneous nerves. Brachial neuritis can affect one or more components of the brachial plexus. Often idiopathic, some cases occur after a viral infection, immunizations or mechanical trauma. A sudden onset of diffuse pain in the shoulder, upper arm and occasionally forearm is accompanied by weakness, wasting, scapular winging and variable sensory loss of the affected neuromuscular structures. Electromyographic studies may be confirmatory. Tricyclic agents, carbamazepine, gabapentin or pregabalin may be helpful. Rehabilitation is started early to prevent stiffness and improve function.
Thoracic outlet syndrome—Compression of the neurovascular structures of the thoracic outlet, brachial plexus and subclavian artery may occur due to local masses, a high first or cervical rib or fibrous bands. Symptoms depend on the structures compressed, but they are usually exacerbated by heavy manual work. Neurogenic symptoms usually predominate, including aching in the arm, paraesthesia and weakness. Vascular symptoms are usually intermittent; trophic skin changes can occur. A causative structure is rarely identified, and management is symptomatic.

Elbow and forearm pain

Lateral and medial epicondylitis

The 12-month period prevalence of elbow pain has been estimated to be 11.2%. Box 3.4 displays a list of differential diagnoses of elbow pain. Most complaints of elbow pain are due to lateral epicondylitis (“tennis elbow” or lateral elbow pain), which has an estimated annual incidence in general practice of 4–7 per 1000 patients. People aged between 40 and 50 years are most commonly affected. Lateral epicondylitis is thought to be an overload injury at the origin of the common extensors at the lateral epicondyile, and typically follows minor and often unrecognized trauma of the extensor muscles of the forearm. In spite of the title “tennis elbow”, tennis is a direct cause in only 5% of cases. Risk factors include repetitive wrist turning or hand gripping. Medial epicondylitis, or “golfer’s elbow”, is a similar but less common condition involving the common flexors at their origin at the medial epicondyile.

Both conditions are characterized by pain and tenderness over the respective epicondyle, and pain on resisted movements: resisted dorsiflexion of the wrist, middle finger, or both, in lateral epicondylitis (Figure 3.8), and resisted flexion of the wrist in medial epicondylitis. Both may be aggravated by repetitive movements and lifting. There may be night pain, early morning stiffness and stiffness after periods of inactivity. Pain referred from the neck or shoulder is distinguishable by less localized symptoms, associated neurological symptoms and the lack of local signs. Pain arising from the elbow joint is usually more posterior and less well localized and may be associated with an elbow effusion and difficulty straightening the elbow because of restriction.

Lateral and medial epicondylitis are generally self-limiting and patients should be informed of the generally favourable prognosis. In a general practice trial, 80% of patients with elbow pain of already greater than 4 weeks’ duration were recovered after 1 year, simply following an expectant policy without any specific treatment. Prognostic factors found to be at least moderately associated with a poorer outcome at 1 year include previous occurrence, high physical strain at work, manual jobs, high baseline levels of pain and/or distress, passive coping and less social support.

Treatment—Interventions have mainly been tested for lateral epicondylitis, but the results are probably generalizable to medial epicondylitis. Treatment in the acute stage involves relative rest and avoidance of specific activities that aggravate the discomfort. Ice may be applied, but there are no data about its effects. Use of a tennis elbow brace or strap is common and may provide short-term pain relief while worn, allowing some return to activity. Topical and oral NSAIDs may provide short-term relief of pain, although evidence is limited. Local skin reactions may occur with topical treatment.

Stretching and strengthening exercises may be helpful. Most studies have assessed their effect as part of multimodal interventions involving mobilization techniques at the elbow other physical therapies, with mixed results.

Corticosteroid injection with local anaesthetic may provide short-term pain relief (less than 3 months), although over the long term may be less effective than no treatment or physiotherapy (consisting of ultrasound, deep friction massage and an exercise programme). After an initial favourable response lasting 6 or more weeks, there may be a recurrence of symptoms. It is important to consider the close proximity of the ulnar nerve when performing...
steroid injection for medial epicondylitis. Adverse effects of injection are generally mild and transient and include post-injection pain, depigmentation and local skin and subcutaneous atrophy.

Trials of ultrasound have been conflicting but have generally reported marginal or no benefit, while laser therapy trials and trials of various other physical therapies have consistently been negative. There is no strong and consistent evidence that ESWT provides benefits in terms of pain and function in lateral epicondylitis. Acupuncture (needle, laser or electro-acupuncture) may provide short-term pain relief. Botulinum toxin injection and topical glyceryl trinitrate have recently been proposed as treatments for lateral epicondylitis, but further research is required before these therapies can be recommended.

Surgery is reserved for patients with recalcitrant, limiting symptoms, although evidence of benefit from controlled trials is limited. The most common operations are open excision, debridement and release and/or repair of the extensor or flexor tendon origins at the lateral or medical epicondyle. Percutaneous and arthroscopic procedures have also been described.

**Other elbow disorders**

Arthritis of the elbow joint may be due to systemic inflammatory arthritides, including rheumatoid and seronegative arthritis, crystal-induced synovitis (gout or pseudogout) and, rarely, septic arthritis. Neisseria gonococcus arthritis should be suspected in at-risk individuals. Osteoarthritis of the elbow is rare and usually relates to prior fractures or trauma.

Olecranon bursitis (“student’s elbow”) presents with discrete swelling, pain and inflammation at the posterior point of the elbow and may be caused by acute or repetitive trauma, crystals or sepsis (Figure 3.9, Box 3.5). The presence of nodules suggests either rheumatoid arthritis (seen in active disease or as a side effect of methotrexate) or gout (tophi). Infection may follow an abrasion or initial cellulitis and the most common causative organism is *Staphylococcus aureus*. Systemic symptoms such as fever, leucocytosis and elevated inflammatory markers occur with sepsis and crystals. When olecranon bursitis is suspected, blood cultures and aspiration for crystals, Gram stain, and culture are essential.

Steroid injection is often helpful for olecranon bursitis due to inflammatory or crystal arthritis. Broad-spectrum antibiotics and possibly open drainage and lavage are used when there is sepsis.

Entrapment or inflammation of the ulnar, radial and median nerves can cause neurological disturbances involving the elbow and forearm. Paraesthesia and numbness involving the fourth and fifth fingers accompanied by weakness of the interossei may be caused by ulnar neuropathy, the most common compression neuropathy affecting the elbow. Tapping over the ulnar groove (Tinel’s sign) may reproduce pain or numbness in the fourth and fifth fingers. Nerve conduction studies are helpful in diagnosis. Management depends on the severity and cause.

**Reference**


**Further reading**


Low back pain (LBP) is the most common musculoskeletal symptom and poses a major socio-economic burden. An estimated 80% of the population will experience back pain during their lifetime; 90% of these patients will have resolution of their symptoms within 4 weeks.

Sciatica is the result of nerve root impingement and occurs in <1% of patients. The pain is radicular (and almost invariably radiates below the level of the knee) in the distribution of a lumbosacral nerve root, sometimes accompanied by sensory and motor deficits. Sciatica should be differentiated from non-neurogenic sclerotomal pain, which arises from pathology within the disc, facet joint or paraspinal muscles and ligaments. Sclerotomal pain is non-dermatomal in distribution and often radiates into the lower extremities but not below the knee or with associated paraesthesiae as with sciatica.

Causes of LBP

LBP usually originates from the lumbar spine (Figure 4.1); pain is rarely referred to the spine from other structures (Box 4.1). Over 95% of LBP is mechanical. Mechanical pain is generally due to an anatomical abnormality that increases with physical activity and is relieved by rest and recumbency. Systemic disease (infection, neoplasm and spondyloarthropathy) accounts for only 1–2% of LBP.

ABC of Rheumatology, 4th edn. Edited by Ade Adebajo. ©2010 Blackwell Publishing Ltd. 9781405170680.
Spondylolisthesis
Spondylolisthesis is the anterior displacement of a vertebra on the one beneath it. It is usually secondary to degenerative changes in the disc and facet joints (degenerative spondylolisthesis) but may result from a developmental defect in the pars interarticularis of the vertebral arch (spondylolysis), which produces isthmic spondylolisthesis (Figure 4.3). Patients with minor degrees of spondylolisthesis are usually asymptomatic, although some may have mechanical LBP. Greater degrees of spondylolisthesis occasionally cause sciatica or spinal stenosis.

Spinal stenosis
Spinal stenosis (ST) is defined as a narrowing of the spinal canal and its lateral recesses and neural foramina, which may result in a herniation, 95% involve the L4-5 or L5-S1 disc. Generally, the more caudal nerve root is impinged; that is, the L5 nerve root with L4-5 herniation and S1 nerve root with L5-S1 herniation. In most patients the sciatic pain resolves over a period of weeks.

Rarely, a large midline disc herniation compresses the cauda equina. This is a surgical emergency. The full cauda equina syndrome usually presents with bilateral sciatica and motor deficits. It needs to be recognized and treated before urinary retention and/or incontinence occur for a completely successful outcome. Common symptoms are presented in Box 4.2.

Box 4.2 Common symptoms of cauda equina syndrome
The patient will develop some or all of the following:
- Altered saddle or/and urinary sensation
- Rectal/perineal pain
- Change/reduced awareness of bladder filling
- Need to strain to maintain urine flow
- Difficulty in walking or the legs just “do not feel right” (very early symptoms)
- Urinary retention with overflow incontinence and faecal incontinence (late manifestations of the full syndrome)
Low Back Pain

Compression of lumbosacral nerve roots (20% of adults over age 60 have imaging evidence of ST but are asymptomatic). Degenerative changes (leading to disc herniation, facet joint osteophytes and ligamentum flavum hypertrophy) are the causes of ST in most patients (Figure 4.4).

The hallmark of ST is pseudoclaudication (neurogenic claudication). Symptoms are often bilateral with pain, weakness and sometimes paraesthesiae in the buttocks, thighs and legs. Symptoms are induced by standing or walking and relieved by sitting or flexing forward. Forward flexion increases the canal diameter and may lead to the adoption of a simian stance. Unsteadiness of gait is common. Physical examination is usually unremarkable, and severe neurologic deficits are rarely seen. The diagnosis is best confirmed by magnetic resonance imaging (MRI).

Idiopathic low back pain

A definitive pathoanatomical diagnosis with precise identification of the pain generator cannot be made in 80% of patients. Non-specific terms such as lumbago, strain and sprain (which have never been anatomically or histologically characterized) have come into use for this mostly self-limited syndrome of LBP.

Assessment

A major focus of the evaluation is to identify the few patients with an underlying systemic disease (infection, neoplasm or spondyloarthropathy) or significant neurologic involvement that may require urgent and/or specific intervention. It is essential to take a full history and perform a comprehensive physical examination.

History

The patient’s back pain should be characterized. Severe mechanical LBP with an acute onset in a slender postmenopausal woman is suspicious for a vertebral compression fracture secondary to osteoporosis. Non-mechanical LBP, especially when accompanied by nocturnal pain, suggests the possibility of underlying infection or neoplasm. Inflammatory LBP, as seen in the spondyloarthropathies, is accompanied by night-time waking with pain and stiffness.
and/or prolonged morning stiffness that improves with exercise but not with rest. The radicular pain of sciatica suggests nerve root impingement. It should be differentiated from non-neurogenic sclerotomal pain. Pseudoclaudication is seen with spinal stenosis.

**Physical examination**

This rarely leads to a specific diagnosis. Inspection may reveal a structural or functional scoliosis. Structural scoliosis is secondary to structural changes of the vertebral column. Functional scoliosis is usually the result of paravertebral muscle spasm or leg-length discrepancy. Functional scoliosis disappears with spinal flexion, whereas structural scoliosis persists.

Paravertebral muscle spasm often leads to loss of the normal lumbar lordosis. Point tenderness on percussion over the spine has sensitivity but not specificity for vertebral osteomyelitis. A palpable step-off between adjacent spinous processes indicates spondylolisthesis.

Limited spinal motion is not associated with any specific diagnosis, because LBP due to any cause may limit motion. Range-of-motion measurements can help in monitoring treatment. Examine the hip for arthritis: this normally causes groin pain, and occasionally referred back pain.

A straight leg raise test (Figure 4.5) should be performed on all patients with back pain that radiates into the lower extremities. This test places tension on the sciatic nerve and stretches the sciatic nerve roots (L4, L5, S1, S2 and S3). Patients with existing nerve root irritation, e.g. impingement from a herniated disc, will experience radicular pain that extends below the knee. This test is very sensitive (95%) but not specific (40%) for clinically significant disc herniation at the L4-5 or L5-S1 level. The straight leg raise test is usually negative in patients with spinal stenosis.

For lower extremities, neurologic evaluation should include motor testing, determination of knee and ankle deep tendon reflexes, and dermatomal sensory loss tests (Figure 4.6). This can help identify the specific nerve root involved (Table 4.1), e.g. a significant left-sided L5-S1 posterolateral disc herniation often impinges upon the left S1 nerve root. Patients will have left-sided sciatica in the distribution of the S1 dermatome and may develop left plantar flexion weakness, diminished light touch and pinprick sensation over the lateral aspect of the foot, and a diminished or absent left ankle jerk.
Low Back Pain

Imaging studies

Diagnostic testing is rarely indicated unless symptoms persist beyond 4 weeks, as 90% of patients will have recovered within this time, thus avoiding unnecessary testing. "Red flags" indicate early investigations, e.g. underlying systemic disease or patients with a significant neurologic deficit (Box 4.3).

A major problem with all imaging studies is that many of the anatomical abnormalities (often the result of age-related degenerative changes) are common in asymptomatic people. Abnormalities such as single disc degeneration, facet-joint degeneration, Schmorl's nodes, spondylolysis, mild spondylolisthesis, transitional vertebrae (lumbarization of S1 or sacralization of L5), spina bifida occulta and mild scoliosis are equally prevalent in people with and without LBP. Plain radiographs are usually unhelpful in determining the cause of LBP and should be limited to patients with findings suggestive of systemic disease (infection, neoplasm, spondyloarthropathy) or trauma, or those with continued LBP after 4–6 weeks of conservative care.

Computed tomography and MRI (Figure 4.7) should be reserved for patients in whom underlying infection or cancer is suspected, or for patients with significant or progressive neurologic deficits. MRI is the preferred modality for the detection of spinal infection, neoplasm, herniated discs and spinal stenosis. Bone scanning is used primarily to detect bony metastases, occult fractures and infection.

Table 4.1 Neurological features of lumbosacral radiculopathy

<table>
<thead>
<tr>
<th>Disc herniation</th>
<th>Nerve root</th>
<th>Motor</th>
<th>Sensory (light touch)</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3-4</td>
<td>L4</td>
<td>Dorsiflexion of foot</td>
<td>Medial foot</td>
<td>Knee</td>
</tr>
<tr>
<td>L4-5</td>
<td>L5</td>
<td>Dorsiflexion of great toe</td>
<td>Dorsal foot</td>
<td>None</td>
</tr>
<tr>
<td>L5-S1</td>
<td>S1</td>
<td>Plantar flexion of foot</td>
<td>Lateral foot</td>
<td>Ankle</td>
</tr>
</tbody>
</table>

Box 4.3 “Red flags” that indicate need for early diagnostic testing

Spinal fracture
- Significant trauma
- Prolonged glucocorticoid use
- Age >50 years

Infection or cancer
- History of cancer
- Unexplained weight loss
- Immunosuppression
- Injection drug use
- Nocturnal pain
- Age >50 years

Cauda equina syndrome
- Urinary retention
- Overflow incontinence
- Faecal incontinence
- Bilateral or progressive motor deficit
- Saddle anaesthesia

Spondyloarthopathy
- Night-time waking with pain and stiffness
- Morning stiffness in the back
- Low back pain that improves with activity
- Age <40 years

Figure 4.7 MRI showing a posterolateral disc prolapse

Treatment

Most patients, regardless of the cause, respond to a general programme that includes analgesia, education, back exercises, aerobic conditioning and weight control. Specific treatment is available only for the small number of patients with major neurologic compression or underlying systemic disease.

For treatment purposes, patients are considered to have acute LBP (duration <3 months), chronic LBP (duration >3 months) or a nerve root compression syndrome.

Acute LBP

Patients are advised to stay active, and bed rest is discouraged. Acetaminophen/paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) offer symptomatic relief; some people will need short-term narcotic analgesics, and muscle relaxants used for a few days will help others.
Once the acute episode of pain has subsided, a programme of regular back exercises (including stretching), aerobic conditioning and loss of excess weight is used to prevent recurrences. Back exercises help to stabilize the spine. Flexion exercises strengthen the abdominal muscles and extension exercises the paraspinal muscles. Educational booklets that include back exercises and safe lifting techniques are helpful.

Many patients ask about chiropractic and osteopathy treatments. There is no evidence that spinal manipulative therapy is superior to standard treatment for back pain.

### Chiropractic focuses on the diagnosis, treatment and prevention of mechanical disorders of the musculoskeletal system, and on the effects of these disorders on the nervous system and on general health. It was founded in the USA by DD Palmer in 1895 who based it on his belief that disorders are caused by misaligned vertebrae which cause nerve compression (subluxations) and dysfunction. The primary chiropractic technique being adjustment of the spine. Chiropractors may specialize in low back pain problems, or they may combine chiropractic with manipulation of the extremities, physiotherapy, nutrition or exercise to improve the strength of the spine.

The General Chiropractic Council (www.gcc-uk.org) has regulated the chiropractic profession since 1994.

### Osteopathy is a manual therapy that is primarily focused on the treatment of musculoskeletal conditions. It was founded by Andrew Still in the USA in 1886, who believed that disease was caused when the flow of nerve impulses was disrupted when a person’s bones were out of place. He concluded that manipulating bones back into place would restore the interrupted flow of nerve impulses and cure disease.

Underpinning osteopathy is the idea that the body has self-regulatory mechanisms and therefore that it has the capacity to heal itself, that the structure and function of the body are closely inter-related, and that the somatic aspects of disease aren’t just manifestations of disease but also contribute to maintenance of the disease state. Osteopaths will commonly treat back pain by manipulation, but may also use soft, tissue massage or advise exercise.

Osteopathy was established in the UK in 1917, and has been subject to statutory regulation since 1993. It is regulated by the General Osteopathic Council (www.osteopathy.org.uk).

There is limited evidence supporting the use of epidural glucocorticoid injections for short-term relief of radicular pain. Nerve-root blocks and injection of anaesthetic agents or glucocorticoid into trigger points, ligaments, sacroiliac joints and facet joints are of unproven efficacy.

Ultrasound, shortwave diathermy, transcutaneous electrical nerve stimulation and other treatments such as lumbar braces, traction, acupuncture and biofeedback are ineffective.

### Chronic LBP

Treatment of chronic LBP is focused on relief of pain and restoration of function. Complete relief of pain is an unrealistic goal for most. Acetaminophen/paracetamol and NSAIDs may provide some degree of analgesia. Long-term use of narcotic analgesics should be avoided. Low-dose tricyclic antidepressants may help some patients.

Back exercises, aerobic conditioning, loss of excess weight and patient education are effective in managing chronic LBP. A multidisciplinary approach focusing on functional restoration through an intensive rehabilitation programme based on cognitive behavioural therapy is often helpful.

The results of back surgery are disappointing when the goal is relief of back pain (such as by spinal fusion or artificial discs) rather than relief of radicular symptoms from neurologic compression.

### Nerve root compression syndromes

**Disc herniation**—Patients with radicular pain secondary to nerve-root compression should be treated conservatively, as described for acute LBP, for the first 6 weeks unless there is severe or progressive neurologic deficit: approximately 90% will improve. Elective surgery may be considered in a few patients among those who have a significant persistent neurologic deficit or severe sciatica after 6 weeks of conservative care. Laminotomy with limited discectomy is generally the procedure of choice.

**Spinal stenosis**—The symptoms remain stable for years in most patients. Analgesics, NSAIDs, loss of excess weight, exercises (including those that reduce lumbar lordosis) and epidural glucocorticoids may provide symptomatic relief. Surgical treatment, aimed at decompression of the neural elements, is offered to patients with either disabling pseudoclaudication or significant neurologic deficit.

### Further reading


Acknowledgements

Table 4.1 and Box 4.3, and Figures 4.1, 4.2, 4.3, 4.4 and 4.6 are taken from Imboden et al., 2007, with permission. Figure 4.5 is taken from Standards in Rheumatology: a Suggested Management Plan for Some Common Conditions in Rheumatology. The Medicine Group, 1987.
CHAPTER 5

Pain in the Hip

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OVERVIEW

- Osteoarthritis of the hip is common in adults, and osteoporotic hip fractures are epidemic in the elderly.
- Always examine the hip in patients presenting with knee pain, as referred pain from the hip is common.
- Childhood hip conditions require prompt treatment to reduce the risk of problems in later life.

Hip pain in children

A child with hip disease may not present with pain or a history of trauma but with an unexplained limp. Unexplained thigh or knee pain should also raise the suspicion of hip abnormality. See Box 5.1 for a summary of important causes of childhood hip pain.

Congenital dislocation of the hip

Physical examination and/or ultrasound screening should detect at-risk cases (Figure 5.1), but missed cases may present as a delay in walking, a limp or discrepancy in leg length. Children usually present before 5 years of age. Missed cases may lead to a non-congruent joint and early osteoarthritic degeneration in adulthood.

Perthes’ disease

Perthes’ disease—disintegration of the femoral head, with subsequent healing and deformity of the hip—usually occurs in boys aged 5–10 years. The precise cause is unclear, but segmental avascular necrosis of the femoral head is probably responsible. A limp, hip pain or knee pain may result. Treatment aims to contain the femoral head in the acetabulum to reduce the risks of future osteoarthritis.

Slipped upper femoral epiphysis

This condition is typically seen in overweight, hypogonadal boys, who often present with pain referred to the knee, although girls may also experience this condition. The diagnosis may be difficult, but a “frog lateral” X-ray radiograph will show the deformity (Figure 5.2).

Surgical stabilization is needed as a matter of urgency to prevent further slippage of the epiphysis. The contralateral hip is at high risk of slippage, and patients and parents should be warned to return if any knee or hip pain occurs.

Septic arthritis

This is relatively uncommon, but it should be suspected in a child who is ill, toxic and unable to walk. Movement of the affected joint is not possible because of pain. Diagnosis is confirmed by raised white cell count and erythrocyte sedimentation rate and perhaps by effusion on ultrasound images. No test is perfectly sensitive or specific, so expert clinical judgement is required. Urgent surgical drainage is vital to reduce the risk of late osteoarthritis. Diagnosis may be particularly difficult in neonates. Staphylococcus aureus is the usual infective organism.

Transient synovitis or “irritable hip”

A reactive effusion may occur in the hip in association with a systemic viral illness. Affected children are not acutely ill and can move the hip, but with some degree of stiffness. An effusion may be seen on ultrasound images and the condition is usually self-limiting and responsive to non-steroidal anti-inflammatory drugs. Distinguishing this condition from septic arthritis can be a challenge, and occasionally these children must undergo aspiration to exclude a septic hip. Perthes’ disease may present in the early stages with an effusion without changes visible on X-ray examination.
Pain in the Hip

These functional limitations may prevent activities of daily living, such as getting in and out of baths, putting on shoes, and foot care. See Box 5.2 for a summary of the causes of hip pain in adults.

**Box 5.2 Causes of hip pain in adults**

- Osteoarthritis
- Other arthritides
  - Rheumatoid arthritis
  - Psoriatic arthritis
  - Ankylosing spondylitis
- Hip fracture
- Paget’s disease
- Avascular necrosis
- Malignancy
- Infection
- Painful soft-tissue conditions around the hip
  - Trochanteric bursitis
  - Iliopsoas bursitis
  - Ischial bursitis
  - Meralgia paraesthetica
  - Snapping iliopsoas tendon
  - Torn acetabular labrum

These functional limitations may prevent activities of daily living, such as getting in and out of baths, putting on shoes, and foot care. See Box 5.2 for a summary of the causes of hip pain in adults.

**Osteoarthritis**

Osteoarthritis is one of the most common causes of hip pain in adults (Figure 5.3). Although patients with osteoarthritis of the hips usually present in their 60s or even 70s, the problem can present earlier, especially in patients with prior hip trauma or congenital abnormalities (see previous sections on hip pain in children). Rest, simple analgesia, prescribed range-of-motion and

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**Other arthritides**

Juvenile chronic arthritis may present with hip pain. General management of the arthritic process is important, with physiotherapy to prevent joint contracture. Systemic therapy with disease-modifying agents (such as methotrexate, tumour necrosis inhibitor agents) can be very effective. These therapies have important potential toxicities and must be prescribed knowledgeably.

**Hip pain in adults**

Pain from the hip is usually felt in the groin or lateral or anterior thigh. Hip pain may also be referred to the knee; this may confuse the unwary! Although buttock pain may originate from the hip, the lumbar spine is the usual source. Hip disorders often produce a limp, a reduction in the distance that can be walked, and stiffness.

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**Figure 5.1** Anteroposterior radiograph of child with dislocated right hip. Note the lateral displacement of the femur and the poorly developed ossific nucleus of the hip

**Figure 5.2** X-ray radiograph of a child’s right hip. Displacement of the epiphysis relative to the femoral neck is easily seen

**Figure 5.3** Osteoarthritis of the right hip, with joint space loss, subarticular cysts, peripheral osteophytes and subchondral sclerosis
strengthening exercises and a walking stick often relieve the pain. A limp may develop, with associated stiffness. As hip abductors weaken, the patient may develop a Trendelenburg gait. In extreme situations, leg length is lost, and the hip adopts a fixed flexion and adduction deformity. Total hip replacement is extremely effective at relieving pain and improving functional status in osteoarthritis.

**Other arthritides**
Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis can also produce hip pain. The latter is particularly associated with stiffness. Total hip replacement is often needed.

**Hip fracture**
Osteoporotic hip fracture in elderly women is epidemic. A fall followed by inability to bear weight and a short externally rotated leg are diagnostic. An undisplaced fracture may not stop the patient from bearing weight, and it may not be visible on initial X-ray examination. Repeat films are usually required, including a bone scan (Figure 5.4) or magnetic resonance imaging (MRI) if there is doubt. Treatment is typically surgical and includes stabilization with plates and/or screws, or by replacement of the femoral head (hemiarthroplasty) or total hip replacement.

**Paget’s disease**
The pelvis is often involved in Paget’s disease, and can cause hip pain. Treatment of the disease with bisphosphonates can reduce pain, but coexistent osteoarthritis of the hip can also occur.

**Avascular necrosis**
Segmental avascular necrosis of the weight-bearing portion of the femoral head can occur. This produces progressive pain, limp and late secondary osteoarthritis. An MRI gives a diagnosis in the early stages, but if radiological evidence is established, surgical treatment to arrest the disease is less successful. Hip replacement may ultimately be required. See Box 5.3 for a summary of the causes of avascular necrosis.

**Malignancy**
Metastases in the pelvis or proximal femur will produce hip pain. Treatment with local radiotherapy or bisphosphonates, or both, may slow the disease progress. Surgical stabilization of impending fractures may be required. Primary bone tumours as a cause of hip pain are extremely rare.

**Infection**
Primary septic arthritis is rare in adults. Risk factors include immuncompromise, prior hip joint disease and infection elsewhere. Plain X-ray examination may miss the diagnosis. Ultrasound scanning may show the presence of an effusion. Aspiration under fluoroscopic guidance is generally necessary to establish the diagnosis. Surgical drainage is usually necessary, along with prolonged intravenous antibiotics.

**Painful soft-tissue conditions around the hip**
*Trochanteric bursitis*—This is a usually self-limiting inflammation of the bursa between the greater trochanter and fascia lata. It is characterized by pain over the trochanter (not in the groin). This condition frequently accompanies other musculoskeletal problems, such as spinal stenosis, that alter gait and attendant muscle forces across the greater trochanter. Local physiotherapy, anti-inflammatory agents, rest, and occasionally local anaesthetic and steroid injections, can help.

*Iliopsoas bursitis*—The iliopsoas bursa is deep to the psoas muscle and anterior to the hip joint. Pain occurs in the groin and anterior thigh and can be exacerbated by resisted hip flexion and passive hip extension. This condition occasionally has an infectious aetiology. Thus, when the presentation is acute, especially painful and accompanied by systemic features, the work-up should be aggressive and include imaging-guided aspiration.

*Snapping iliopsoas tendon*—This causes a painful “clunk” in the groin when the hip goes from extension to flexion. The hip is otherwise normal. The psoas tendon impinges on the capsular of the hip anteriorly to produce discomfort. Diagnosis is made if movement of fluoroscopic X-ray contrast agent injected into the psoas tendon is abnormal. Surgical release may be needed.

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**Box 5.3 Causes of avascular necrosis**
- Most cases are idiopathic
- Associated conditions include:
  - Excess alcohol
  - Prolonged steroid therapy
  - Working in pressurized environments (for example, deep-sea divers)
Pain in the Hip

Labral tears can be associated with deformity of the femoral head or acetabulum. An MRI shows the abnormality, and the torn labrum can be removed arthroscopically (Figure 5.5).

Management of hip pain

The most important step in management of the painful hip is to establish the underlying aetiology and to treat it as specifically as possible. Thus infection of the hip should be diagnosed expeditiously and treated with surgical drainage and prolonged parenteral antibiotics. Fractures should be diagnosed and stabilized.

Inflammatory arthritis can be treated with systemic therapy. Here we present a few general principles that apply to the management of hip pain due to any number of aetiologies. First, a cane can be extremely helpful in unloading the painful hip and relieving pain. Patients must be shown the proper use of the cane in the contralateral hand.

Second, as with most other joints, the hip can become stiff with disuse and develop flexion contractures. This can be avoided with gentle range-of-motion exercises. If patients are losing motion, referral to a physiotherapist can be helpful.

Finally, it is important to recognize that one musculoskeletal problem can lead to another. Patients with spinal stenosis frequently develop trochanteric bursitis, for example. So while it is tempting to make a single, fully encompassing diagnosis in patients with musculoskeletal pain, the reality is that more than one condition could be present. While a patient's underlying problem may lie in the back, injection of a secondarily involved trochanteric bursa may provide dramatic benefit.

Further reading

The knee is the largest joint in the body. It is a complex hinge that is made up of two separate articulations: the tibio-femoral joint and the patello-femoral joint. Knee motion occurs in a complex manner involving three planes, although the vast majority of its motion occurs in the sagittal plane (from full extension through to 140° of flexion).

Pain in the knee joint is one of the most common musculoskeletal complaints that presents to primary care physicians, and may arise from a broad range of pathologies. In the younger patient, pain most commonly arises from sporting or overuse injuries, which may affect the intra-articular or extra-articular structures of the knee. The knee is also a common site for inflammatory and infective pathologies. In the older patient, the most common cause is degenerative disease. Knee pain arising from osteoarthritis is a major cause of disability in the older patient, the prevalence and health-care costs of which continue to rise as the population ages.

The evaluation of knee pain centres on a thorough history and physical examination supplemented, where necessary, with appropriate imaging and laboratory tests (Figure 6.1).

**Traumatic causes of knee pain**

Injuries are a common cause of knee pain. Most knee injuries in sport occur as a result of indirect trauma, such as a twisting moment to the knee. The structures most commonly injured by this mechanism are the menisci, the collateral ligaments and the cruciate ligaments. These structures may be damaged in isolation, or may occur in combination (for example the anterior cruciate ligament, medial collateral ligament and medial meniscus may be injured in O’Donoghue’s triad). Direct trauma to the knee (such as during contact sport, an industrial accident or a motor-vehicle collision) most commonly causes bone contusions, fracture or dislocation that may affect the patello-femoral or tibio-femoral joint. Dislocation of the tibio-femoral joint indicates high-energy trauma, and is commonly associated with neurovascular damage.

**Meniscus injury**

Meniscus injury in young people can present as an acute injury or as a chronic condition with an insidious onset. The majority of meniscus tears in young people occur after mild- to moderate-energy twisting injuries and are typically isolated injuries or associated with a collateral ligament strain. The medial meniscus is damaged three times more commonly than the lateral meniscus (Figure 6.2). Higher-energy twisting injuries are commonly associated with an anterior cruciate ligament injury, an acute haemarthrosis and inability to bear weight. Patients with meniscus tears have focal tenderness over the joint line and may experience mechanical catching and locking symptoms in the knee in addition to joint effusion and pain. Magnetic resonance imaging (MRI) can aid in establishing the diagnosis in cases where the history and physical examination are equivocal. Acute tears that occur in the well-vascularized peripheral portion of the meniscus are amenable to arthroscopic repair, which preserves meniscus function. Where an anterior cruciate ligament injury is also present this is reconstructed concurrently. Chronic meniscal tears are typically avascular with degenerative characteristics and will not heal if repaired. Arthroscopic resection is confined to the torn and degenerate portions of meniscus, as early-onset osteoarthritis of the knee commonly follows complete meniscal resection.

**Articular cartilage injury**

Articular cartilage injury is often the result of a traumatic episode...
Pain in the Knee

removal for displaced osteochondral fragments. Occult episodes of trauma to the knee may result in separation of cartilage from the subchondral bone, termed osteochondritis dissecans. Patients complain of poorly localized pain. The diagnosis is made from plain radiographs or MRI scans, and treatment commonly involves arthroscopic resection of loose cartilage.

A detailed history of the mechanism of injury and physical examination provide valuable information to differentiate between the various traumatic causes of knee pain. Knee pain from injury has a sudden onset at the time of the injury episode and is often accompanied by local soft-tissue swelling and an effusion. Certain fractures and dislocations may exhibit gross deformity; however, the majority of knee and patellar dislocations spontaneously reduce before presentation. A haemarthrosis develops quickly (over a period of minutes to a few hours) and indicates significant intra-articular injury, such as an anterior cruciate ligament tear, intra-articular fracture or osteochondral injury, or patellar dislocation. Effusions, which develop over several hours, tend to be associated with meniscal injuries (Table 6.1).

Radiographs should be obtained when evaluating any knee injury to exclude a fracture, dislocation or other significant abnormality. After obtaining radiographs, additional diagnostic tests may be indicated, including a computed tomography scan in the case of intra-articular fractures, or MRI when a soft-tissue or osteochondral injury is suspected. In the absence of neurovascular compromise or gross deformity, initial treatment of traumatic knee pain should consist of restricted weight bearing, ice and elevation. Severe injuries require immediate referral for orthopaedic surgical evaluation.

Knee pain in younger people and athletes

Knee pain in younger people and athletes can be caused by overuse syndromes, meniscus injury or articular cartilage abnormality. Common overuse syndromes include patellar tendonopathy, anterior knee pain syndrome, pes anserine bursitis and iliotibial band friction syndrome (Table 6.2).

Patellar tendonopathy

Patellar tendonopathy is caused by repetitive activity, particularly “explosive” athletics such as jumping. Patients complain of pain and soft-tissue swelling about the patellar tendon, usually at its...
proximal attachment to the patella. Treatment consists of ice, pain-relieving medication, activity modification and strengthening exercises focusing on eccentric loading of the tendon.

**Anterior knee pain syndrome**

Anterior knee pain syndrome occurs in patients who engage in repetitive athletic activity, in those with abnormalities in extensor mechanism alignment and in those who are overweight. Patients with anterior knee pain syndrome complain of pain in the front of the knee, which is accentuated by ascending and descending stairs, squatting, kneeling and by sitting for long periods of time. The pain may be located directly behind the patella or in the medial or lateral retinaculum. Treatment should include activity modification, weight control if necessary, physiotherapy to strengthen the quadriceps muscles (particularly vastus medialis) and core musculature, and appropriate pain-relieving medication.

**Pes anserine bursitis**

Pes anserine bursitis is an inflammation of the bursa overlying the insertion site of the semitendinosus, gracilis and sartorius tendons in the anteromedial aspect of the proximal tibia. Patients complain of medial knee pain distal to the medial joint line. Treatment can include activity modification, strengthening exercises and anti-inflammatory medication. Chronic symptoms may respond to local corticosteroid injection.

**Iliotibial band friction syndrome**

Iliotibial band friction syndrome is an inflammation of the iliotibial band, the distal portion of the tensor fascia lata muscle that inserts into the anterolateral aspect of the proximal tibia. Patients are usually runners or cyclists who complain of activity-related lateral knee pain. This condition responds well to activity modification, stretching and strengthening exercises, ice and anti-inflammatory medications.

**Knee pain in older people**

Twenty-five percent of people over the age of 50 report chronic knee pain, and degenerative arthritis of the knee is common in this age group (Box 6.1). However, clinical symptoms and radiological severity of arthritis are poorly correlated. Many older people with knee pain have minor radiological evidence of arthritic change. Conversely, many people with advanced radiological changes are pain-free. Arthritis of the knee is often associated with periarticular soft-tissue problems, and indeed these can often be a major source of knee pain. Pes anserine bursitis is a common example. Plain radiographic imaging is not always helpful in the assessment of patients with knee pain, and the diagnosis of osteoarthritis is often a clinical one. An MRI scan may assist in the diagnosis of an occult degenerate meniscal tear.

The management of osteoarthritis is, for most people, the management of their knee pain and lifestyle modification (Box 6.2). The high prevalence of knee pain in the community means that such treatments should be simple, safe, cost-effective and, ideally, self-administered. Initial treatments consist of simple measures such as weight loss, exercise regimes and use of simple analgesics.

Local treatments, such as topical non-steroidal anti-inflammatory gels are effective in the short term, particularly in the setting of acute symptomatic flares. Injected treatments include corticosteroids and hyaluronans. Intra-articular steroids can be very effec-

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Table 6.2 Symptoms associated with overuse injuries

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Likely diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain adjacent to patella</td>
<td>Anterior knee pain syndrome</td>
</tr>
<tr>
<td>Pain ascending/descending stairs</td>
<td></td>
</tr>
<tr>
<td>Pain when sitting for prolonged periods</td>
<td></td>
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<tr>
<td>(“movie theatre sign”)</td>
<td></td>
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<tr>
<td>Pain in patellar tendon</td>
<td>Patellar tendonopathy</td>
</tr>
<tr>
<td>Pain with jumping</td>
<td></td>
</tr>
<tr>
<td>Lateral knee pain with repetitive activity</td>
<td>Iliotibial band friction syndrome</td>
</tr>
<tr>
<td>Medial knee pain distal to joint line</td>
<td>Pes anserine bursitis</td>
</tr>
</tbody>
</table>

Box 6.1 Diagnosis of osteoarthritis

- Osteoarthritis is diagnosed clinically by the presence of:
  - Chronic knee pain
  - Morning stiffness lasting less than 30 minutes
  - Joint crepitus
  - Range of movement restricted by pain
  - Presence of osteophytes

Box 6.2 Non-pharmacological treatments

- Non-pharmacological treatments with an evidence base include:
  - Weight loss
  - Aerobic exercise
  - Specific knee-strengthening exercise
  - Patellar taping
  - Acupuncture
  - Knee bracing
Pain in the Knee

Hyaluronans have a longer-lasting effect, but are very much more expensive and require a series of injections over time. Both have good safety profiles, although certain hyaluronans can cause pseudo-septic joint inflammation and effusion.

Arthroscopic surgical treatment for arthritis of the knee is reserved for the treatment of mechanical symptoms such as joint catching, locking or instability due to a loose body or meniscal tear. In the absence of mechanical symptoms, arthroscopic interventions are no more effective than placebo.

In up to 40% of patients, disease does not progress significantly after initial presentation, or does so very slowly. In these patients use of simple, safe, cost-effective treatments is essential for effective and economic management. Joint replacement surgery is indicated in those patients whose disease progresses such that their symptoms become poorly controlled despite the treatment measures outlined above. In most patients this entails total knee replacement (Figure 6.3). In a small proportion of patients the arthritis is limited to one compartment of knee, in which case a unicompartmental joint replacement is an effective alternative to total knee replacement, and is associated with good functional outcomes in suitable patients (Figure 6.4). The results of joint-replacement surgery are excellent in over 90% of patients in terms of improvement in health-related quality of life.

Knee pain in systemic disease

Pain and swelling in the knee may be a feature of systemic illness. Patients should be asked about pain in other joints, previously painful, swollen joints and a family history of joint disease. Systemic symptoms such as malaise, pyrexia, anorexia and weight loss may provide clues to the origin of the knee pain. Symptoms affecting other organs, such as the skin, bowel, eyes or genito-urinary tract, may also be of diagnostic relevance.
The knee is the most commonly affected large joint in rheumatoid arthritis. The knees are usually affected bilaterally, and symptom onset usually occurs early in the course of the disease. The knee is also commonly affected in the other chronic inflammatory arthritides, including psoriatic arthritis and ankylosing spondylitis. The treatment of the knee pain in these conditions is considered along with the management of the systemic disease and includes lifestyle modification, physiotherapy, disease-modifying agents, NSAIDs, novel biological agents and total joint-replacement surgery.

The knee is the most commonly infected joint. Joint infection presents with a red, swollen, hot knee, difficulty in weight bearing and a limitation in the range of passive motion. Occasionally, the infection may originate in the metaphyseal region of the tibia or femur, rather than the knee joint itself (Figure 6.5). A suspected infection of the knee requires immediate referral to secondary care for assessment and treatment. The most common infecting organism is *Staphylococcus aureus*. Less common infections include *Streptococcus, Gonococcus, Brucella* and, rarely, tuberculosis. Infective arthritis should always be considered in the immunocompromised and other patients with increased infective risk, e.g. intravenous drug users.

Aspiration of the joint for microbiological culture is the most important investigation for the accurate diagnosis of infection. This must be carried out at initial assessment, and before the administration of antibiotics. Aspiration of the knee made after antibiotic administration often results in a false-negative microbiological culture result and a missed diagnosis. Other useful diagnostic tests include concurrent aspirate microscopy for crystals, and serological measurement of white cell count, erythrocyte sedimentation rate and C-reactive protein. The treatment of the infected knee includes initiation of systemic antibiotics immediately after knee aspiration, typically using an agent with broad Gram-positive antimicrobial activity, and serial joint aspiration or arthroscopic-assisted washout. The choice of antibiotic is adjusted as indicated by the aspirate microbiological culture sensitivities, and may be continued for up to 6 weeks orally, although specialist microbiological advice should be taken where infection is confirmed from aspirate culture.

The differential diagnosis of the hot, swollen, painful knee includes systemic inflammatory conditions such as calcium phosphate arthropathy, gout, Reiter’s disease and pre-patellar bursitis. Aspiration of joint fluid for crystal microscopy and culture is important, as are appropriate serological investigations, both in confirming the correct diagnosis and in excluding joint infection. Rarely, infections of the genito-urinary tract and viral infections may present with bilateral swollen, tender knees with a large effusion of sympathetic origin. Radiographs are frequently of limited diagnostic utility in such cases.

### Other causes of knee pain

Hip pain may occasionally refer to the anterior distal thigh or the knee. A complete examination of the patient with knee pain includes an examination of the hip to exclude this cause of knee pain. Knee pain may also present as part of a chronic widespread pain syndrome. An adequate general musculoskeletal assessment is essential if appropriate treatment of the knee pain is to be effected. In the presence of polyarthralgia, or symptoms suggestive of a fibromyalgia syndrome, the knee pain is unlikely to be adequately managed by focusing on the knee alone. Attention should be paid to management of the global pain problem.

### “Red flags”

Although primary bone tumours are rare, the knee is one of the most commonly affected sites for benign tumours, including osteoid osteoma, enchondroma and chondroblastoma, and malignant tumours, including osteosarcoma and chondrosarcoma. Ewing’s sarcomas also commonly affect the knee. In children and young adults who are very active, knee pain may be related to recent activity. Unexplained pain, pain that is worse at night, unexplained swelling and systemic symptoms are all “red flag” features that may indicate a bone tumour. Patients in whom a bone tumour is suspected should be referred early to a centre specializing in their management.

### Further reading


Pain in the Knee


Foot pain is common. It may be caused by local disease, be associated with systemic disease or be a reflection of chronic widespread pain. In general, a multidisciplinary approach to treatment is preferable. This is reflected in increasingly close liaison between podiatry, rheumatology and orthopaedic departments. State-registered podiatrists offer a range of treatments, from skin lesion care to orthoses and, more recently, ambulatory forefoot surgery. To understand dysfunction, clinicians should be familiar with the normal development and anatomical variants of the foot (Figures 7.1 and 7.2; Boxes 7.1 and 7.2).

Foot pain in children

Foot pain may be associated with congenital abnormalities, such as equinovarus deformity. Such structural abnormalities may reflect underlying neurological diseases, such as cerebral palsy. A rigid pronated foot in the early teens may be the first symptom of a tarsal coalition (Figure 7.3). Gait abnormalities, such as in-toeing, may be of concern to parents, but they are seldom treated actively.

Juvenile chronic arthritis

The knee and ankle joints are most often affected in all subtypes of juvenile chronic arthritis. Children may present with a limp or reluctance to walk. In the hind foot, pain and reflex muscle spasm can lead to valgus deformity (in two-thirds of cases) or varus deformity (in one-third of cases). In some patients, this may progress to bony ankylosis. The child may be reluctant to push off with the forefoot during walking, and pressure studies show poor contact of the foot to the floor. Lack of use can lead to delayed maturation of bone or soft tissue, and, in such cases, discrepancy in leg length should be sought carefully.

OVERVIEW

- Foot pain is common and can be associated with a number of local or generalized conditions.
- Clinical examination and simple investigations can usually identify the cause of the pain.
- Foot pain is a common feature in most rheumatic diseases, including rheumatoid arthritis and osteoarthritis.
- Podiatrists, general practitioners, rheumatologists and orthopaedic surgeons are involved in the management of foot pain.

Box 7.1 Characteristics of the adult foot

Three main types of foot
- Normal
- Pronated (flat)
- Supinated (high arch)

Examination
- Examine the foot when bearing weight and when unloaded and be sure to look at the plantar surface of the foot for callus formation (often associated with high pressure)
- Inspect the patient’s shoes for abnormal or uneven wear
- Consult a podiatrist if a structural or mechanical abnormality is suspected—many can be treated with orthoses

Box 7.2 Characteristics of children’s feet

Normal foot
- Flexible foot structure (may look flat with a valgus heel)
- Medial longitudinal arch forms when child stands on tiptoe
- Heel-to-toe walking
- Forefoot in line with rear foot
- Mobile joints with painless motion and no swelling
- Adopts adult morphology by about 8 years of age

Abnormal foot
- Inflexible
- Lesser toe deformities
- Rigid valgus (pronated) foot with everted heel position
- High-arch foot with toe retraction and tight extensor tendons
- Toe walking
- Delay or difficulty in walking or running
- Abducted or adducted forefoot relative to heel
- Pain, swelling or stiffness of joints
- Hallux deformity
Pain in the Foot

Clinical features — Clinical features include a gradual onset, with sudden attacks of neuralgic pain or paraesthesia during walking—often in the third and fourth toe. Examination may show lesser toe deformities, slight splaying of the forefoot, abnormal pronation and hallux valgus. These often occur in women who wear court shoes. Compression of the cleft or laterally across the metatarsal heads may produce acute pain and the characteristic “Mulder’s click.”

Treatment — Patients should be given advice about suitable footwear and possibly should be given orthoses to control abnormal pronation. Injections of local anaesthetic and hydrocortisone around the nerve, or surgical excision, can be helpful.

Stress fracture (march fracture)
Stress fractures are associated with increased activity, and lesions can affect any of the metatarsal shafts, often along the line of the surgical neck. They can occasionally be seen in patients with osteoporosis as a pathological fracture.

Clinical features — Clinical features include a gradual onset, with sudden attacks of neuralgic pain or paraesthesia during walking—often in the third and fourth toe. Examination may show lesser toe deformities, slight splaying of the forefoot, abnormal pronation and hallux valgus. These often occur in women who wear court shoes. Compression of the cleft or laterally across the metatarsal heads may produce acute pain and the characteristic “Mulder’s click.”

Treatment — Patients should be given advice about suitable footwear and possibly should be given orthoses to control abnormal pronation. Injections of local anaesthetic and hydrocortisone around the nerve, or surgical excision, can be helpful.

Pain in the forefoot (metatarsalgia)

Morton’s metatarsalgia (interdigital neuroma)
This normally affects the proximal part of the plantar digital nerve and accompanying plantar digital artery. Trauma to these structures leads to histological changes, including inflammatory oedema, microscopic changes in the neurolemma, fibrosis and, later, degeneration of the nerve. Morton’s neuroma is the result of an entrapment lesion of the interdigital nerve.

Clinical features — Patients have a history of a change in the amount of activity, change in occupation or footwear, or sudden weight gain. The symptom is a dull ache along the affected metatarsal shaft, which changes to a sharp ache just behind the metatarsal head. The pain is exacerbated by exercise and is more acute at “toe off.” Tenderness and swelling is felt over the dorsal surface of the shaft. Pain is produced by compression of the metatarsal head or traction of the toe. X-ray examination may not show the fracture for 2–4 weeks, but if it is important to confirm the diagnosis—e.g. for an athlete who needs advice on whether to continue playing sport—a bone scan can reveal it earlier.
Acute inflammation of anterior metatarsal soft tissue

This common condition is generally found in middle-aged women. It affects the soft tissues of the plantar aspect of the forefoot and is associated with increased shear forces, such as occur when wearing “slip-on” and high-heeled court shoes.

Clinical features—Patients present with a burning or throbbing pain localized to the soft tissues anterior to the metatarsal heads. The pain usually develops over a few weeks, is often associated with walking in a particular pair of shoes, and is usually relieved by rest. The tissues are inflamed, warm and congested. Direct palpation, rotation and simulation of shear forces on the foot exacerbate the pain. Examination of patients’ shoes may reveal a worn insole, with a depression under the metatarsal heads.

Management—Advice on footwear, with adequate support or cushioning, should be given. Associated abnormal pronation or lesser toe deformities should be corrected with orthoses.

Osteochondritis (Freiberg’s infraction)

This quite common condition generally affects the second or third metatarsal heads. It is an aseptic necrosis or epiphyseal infraction associated with trauma and localized minute thrombosis of the epiphysis.

Clinical features—Osteochondritis affects teenagers and is associated with increased sporting activity. The presenting complaint is often a limp, with dull pain associated with movement of the metatarsal phalangeal joint, exacerbated at “toe off”. The long-term result is a flattened metatarsal head, which can progress to arthritis. The affected joint may be slightly swollen, with a disparity in toe length and width. Traction causes pain. Restricted movement may be due to muscle spasm in the early stages and later to arthritis. Radiographs show distortion of the metatarsal head.

Treatment—In the early stages, rest and immobilization are enough, but sometimes patients eventually need corrective surgery.

Plantar metatarsal bursitis

This condition may affect the deep anatomical or superficial adventitious bursae. In the acute form—such as in dancers, squash players or skiers—the first metatarsal is usually affected, while the second to fourth metatarsals are affected in chronic inflammatory arthritis (Figure 7.6).

Clinical features—Patients present with a throbbing pain under a metatarsal head that usually persists at rest and is exacerbated when the area is first loaded. The acute condition affects men and women equally, usually in younger adults. If a superficial bursa is affected, there will be signs of acute inflammation, with fluctuant swelling and warmth. With deep bursitis, the tissues are tight and congested. Direct pressure or compression produces pain, as does dorsiflexion of the associated digit.

Treatment—Anti-inflammatory drugs are useful; in practice, local gels and systemic oral drugs help. Injections of corticosteroid may help if trauma is the cause. Anti-inflammatory drugs sometimes help. Previously unsuspected systemic arthritis should be investigated.

*Figure 7.4* Pressure profile of the right foot of a 54-year-old patient with rheumatoid arthritis. Note absent lesser toe contact and high pressure (hot colours) over central metatarsal heads.

*Figure 7.5* Advanced destruction in the forefoot of a patient with rheumatoid arthritis.
be indicated in severe cases. Patients must rest the affected part; this may be achieved by protective padding. Any underlying deformity or foot type with abnormal function should be assessed and treated.

A summary of causes of pain in the forefoot is presented in Box 7.3.

### Plantar fascia affections

Pain along the medial longitudinal arch is quite common. Most affected patients have abnormal foot mechanics, such as abnormal pronation, valgus heel (Figure 7.7) or flat foot. Mechanical dysfunction and change in medial arch posture can place strain on soft tissues, which results in localized or more diffuse pain—the foot's equivalent to low back pain syndrome. Other conditions include true plantar fasciitis, which is characterized by a few fast-growing nodules in the fascia, and plantar fibromatosis, which is characterized by fibrous nodules and contracture of the fascia.

Treatment of true plantar fascial strain requires rest, control of abnormal function with orthoses, and stretching exercises. Ultrasound treatment seems helpful, but controlled trials are lacking.

### Painful heel

#### Sever's disease (calcaneal apophysitis)

This was thought to be an avascular necrosis of growing bone but is now interpreted as a chronic strain at the attachment of the posterior apophysis of the calcaneus to the main body of the bone, possibly from pull of the Achilles tendon. It is analogous, therefore, to Osgood-Schlatter disease of the tibial tuberosity.

**Clinical features**—The condition usually affects boys aged 8–13 years, who complain of a dull ache behind the heel of gradual onset that is exacerbated by jumping or occurs just before “heel lift”. A limp is usually seen with early heel lift. Rest normally relieves the pain. Tenderness is seen over the lower posterior part of the tuberosity of the calcaneus. Radiographs are usually normal.

**Treatment**—In most cases, reassurance and advice about reducing activities will suffice: the condition usually subsides spontaneously. In some cases, heel lifts help; occasionally, if the pain is severe, a below knee walking cast is needed.

#### Plantar calcaneal bursitis (“policeman’s heel”)

This is inflammation of the adventitious bursa beneath the plantar aspect of the calcaneal tuberosities (Figure 7.8). It is associated with shearing stress caused by an altered angle of heel strike.
Clinical features—The condition is characterized by an increasingly severe burning, aching and throbbing pain on the plantar surface of the heel. A history of increased activity or weight gain is usual. The heel seems normal but may feel warm. Direct pressure or sideways compression causes pain. The tissues may feel tight and congested.

Treatment—Rest and anti-inflammatory drugs may be useful. Heel cushions and medial arch supports are also used. Stretching exercises (such as rolling a bottle under the foot) can help. Little evidence supports ultrasound treatment, local steroid injections or shortwave diathermy.

Chronic inflammation of the heel pad
This is a distinct clinical condition that usually results from trauma or heavy heel strike. It is sometimes seen in elderly people as their fat pads atrophy or in those who suddenly become more active.

Clinical features—A generalized warm, dull throbbing pain is felt over the weight-bearing area of the heel; this develops over a few months. The pain is most intense typically on first rising. Tenderness is experienced over the heel, which feels tight and distended.

Treatment—Normally, this condition improves with time and rest. Soft heel cushions and medial arch fillers sometimes help. Ultrasound treatment and shortwave diathermy are often used, but controlled trials are few. Steroid injections have an early effect but do not influence the condition’s favourable natural history. Steroid injections can be more painful than the condition unless they are done carefully, with adequate slow infiltration of local anaesthetic (or an ankle tibial nerve block) before injection.

Achilles tendon affections
Inflammation of the Achilles tendon and surrounding soft tissue may be associated with overuse or systemic inflammatory disorders (Box 7.4). Inflammation of the tendon, peritendon tissues and bursae give slightly different clinical pictures. Conditions such as xanthoma can also affect the Achilles tendon and produce fusiform swelling in the tendon. In such cases, cholesterol concentrations should be checked and treated if raised. Rheumatoid nodules, and occasionally gouty tophi, can also be found within the substance of the Achilles tendon.

Clinical features—Clinical features vary according to the tissues affected. Increased activity leading to an overuse syndrome may be a feature in younger, active patients.

Treatment—Treatment depends on the primary cause. Partial or complete ruptures of the tendon need immobilization and surgical repair. For inflammatory conditions, non-steroidal anti-inflammatory drugs may help, as may ultrasound treatment, friction, rest and shock-absorbing heel lifts. Inflammation may be triggered by overuse through poor foot mechanics; in such cases, orthoses may control the pronation. Hydrocortisone injections may be useful if the bursa or peritendons are affected, but they are contraindicated for the tendon itself. Ultrasound imaging may be useful.

A summary of common causes of painful heel is presented in Box 7.5.

---

**Box 7.4 Achilles tendon affections**

Tendinitis
- Presents as painful local swelling of the tendon, which moves with the tendon as the foot is dorsiflexed and plantar flexed
- Important to check the tendon for evidence of partial or complete rupture, which is often missed because of inflammation
- Note recent use of quinolone antibiotics (e.g. ciprofloxacin)

Peritendinitis
- Presents as large diffuse swelling of tissues surrounding the tendon that remains static as the tendon is stretched
- Patients experience pain and crepitus on palpation

Achilles tendon bursitis
- Presents as diffuse fusiform swelling inferior to the Achilles tendon that fills the normal indentation seen below the malleoli and deep to the Achilles tendon

**Box 7.5 Common causes of painful heel**

**Pain within heel**
- Disease of calcaneus-osteomyelitis, tumours, Paget’s disease
- Arthritis of subtalar joint complex

**Pain behind heel**
- Haglund’s deformity (“pump bumps”, “heel bumps”)
- Rupture of Achilles tendon
- Achilles paratendinitis
- Posterior tibial paratendinitis or tenosynovitis
- Peroneal paratendinitis or tenosynovitis
- Posterior calcaneal bursitis
- Calcaneal apophysitis

**Pain beneath heel**
- Tender heel pad
- Plantar fasciitis

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**Figure 7.8 Chronic painful plantar heel bursitis**

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Arthropathies that affect the foot

Osteoarthritis
Osteoarthritis in the foot may be asymptomatic, but it can lead to pain, joint stiffness, functional loss and disability. The most common sites are the first metatarsophalangeal joint (hallux rigidus) and the tarsus joints. Biomechanical factors are often involved in the development of degenerative joint changes (for example, compensatory foot pronation in subtalar osteoarthritis). Trauma, recurrent urate gout, and the demands of fashion—such as inappropriate footwear—are other factors; however, the broad style of modern shoes may be beneficial.

Rheumatoid arthritis
Rheumatoid arthritis often starts in the foot, particularly at the metatarsophalangeal joints. The forefoot is painful and stiff, and direct transverse pressure to the forefoot or squeezing a single metatarsophalangeal joint is painful. Non-specific metatarsalgia is often diagnosed. In the early stages of the disease, the hind foot, particularly the subtalar joint, may also be painful. Synovitis of tendon sheaths around the ankle may also occur. In chronic rheumatoid feet, severe pain in the forefoot may continue, with a sensation of walking on pebbles. Gross deformity causes dysfunction and disability (Figures 7.9–7.12).

Seronegative spondyloarthritis
This group includes ankylosing spondylitis (Figure 7.13), psoriatic arthritis (Figure 7.14), undifferentiated seronegative arthropathy and reactive arthritis. Achilles peritendinitis and retrocalcaneal bursitis can be seen. In radiographs, inflammatory spurs may be seen on the calcaneum at the insertion points of the Achilles tendon and plantar fascia. Asymmetrical heel pain may result from a plantar calcaneal enthesopathy.

The pattern of articular involvement in the foot may vary from a single “sausage toe” (dactylitis) (Figure 7.15) to a very destructive arthritis. Painful stiff interphalangeal and metatarsophalangeal joints, often in an asymmetrical pattern, are common. Claw toe
and hallux valgus deformity are more obvious. Nail dystrophy may be seen, with typical psoriatic pitting, onycholysis, subungual hyperkeratosis, discoloration and transverse ridging.

Pustular psoriasis and keratoderma blennorrhagica on the plantar aspect of the foot may contribute to pain when walking.

The diabetic foot—In the presence of neuropathy, the diabetic foot is vulnerable to developing an acute progressive Charcot-like arthropathy. Patients complain of (paradoxically) pain and swelling in the foot, often after minor trauma. The rear and midfoot areas are most often involved. Untreated this will rapidly deteriorate, leaving a disorganized and dysfunctional foot. Treatment must be early and intensive with immobilization of the foot and intravenous bisphosphonates. Early referral is recommended.

Sudeck’s atrophy—A similar condition can develop in the non-diabetic foot following trauma. Sudeck’s atrophy (“reflex sympathetic dystrophy”, or “complex regional pain syndrome type I”) is a painful condition of the foot and ankle associated with regional bone loss, tissue inflammation and vascular abnormalities. This may be mediated by abnormalities of the autonomic nervous system. The foot may look blue and swollen and is painful at rest and exercise. Plain X-ray may show widespread osteoporosis in the affected area. Treatment is effective pain control and physiotherapy. Sympathetic blockade and intravenous bisphosphonates are sometimes used.

Gout
Chapter 10 discusses the manifestations of acute gout in the foot. In the chronic state, tophi in the foot (Figure 7.16) may ulcerate if they act as pressure points. Permanent destructive joint damage and deformity may result and lead to painful dysfunction in the foot.
Pain in the Foot

Management of rheumatic foot conditions

Patients with rheumatic foot problems (Box 7.6) are best managed by a team that includes a physician, a surgeon and therapists. Podiatrists have a particular role in several aspects of care (Figure 7.17).

Use of orthoses for rheumatic foot problem needs suitable footwear. Podiatrists and orthotists should liaise when extra-depth shoes or surgical shoes are needed

Tissue viability

Joint deformity causes pressure lesions such as callosities (Figure 7.18), corns or ulceration and may be compounded by other factors, such as ingrowing toenails, peripheral neuropathy or the effects of systemic corticosteroids. Podiatrists undertake procedures such as scalpel reduction, design and manufacture of insoles and orthoses, and surgery under local anaesthesia to relieve pain and restore or maintain tissue viability.

Foot function and joint protection

Foot dysfunction due to arthritis can be improved with orthoses, which can be ready-made or individually designed from casts. Orthoses may be used to control deformities—such as the valgus heel seen in rheumatoid arthritis—but they also have a major role in maintaining tissue viability and relieving pain (be it joint, soft tissue or skin lesion in origin) (Figure 7.19). Training towards gait modification may be necessary, and pressure-relieving orthoses of a total contact design may serve to reduce pressures at painful joint sites.

Foot health promotion

Patients will often need advice on daily care of feet. Family members may be involved when patients cannot reach their feet or are unable

Box 7.6 Common abnormalities in the rheumatoid foot

- Hallux valgus
- Lesser toe deformities—e.g. hammer toes and claw toes
- Prominent metatarsal heads with overlying painful callosities or ulceration
- Pronation of foot with valgus heel deformity and collapse of midtarsal joint, giving a flat-footed appearance
- Tenosynovitis, especially of tibialis posterior and peroneal tendons, plantar heel bursitis, calcaneal spur and tendo-Achilles bursitis
- Tarsal tunnel nerve compression syndrome
to perform tasks on the feet because of other disability. Advice may be needed on splints, walking aids, footwear (Figure 7.20), insoles, foot hygiene and exercise.

**Foot surgery**

Many rheumatic patients have conditions of the toenails that need surgery under local anaesthetic; they are best dealt with by an experienced clinician such as a podiatrist. Foot surgery may be effective for relieving pain and improving deformity when conservative measures have failed (Figure 7.21).

**Further reading**


Fibromyalgia syndrome describes widespread musculoskeletal pain and hyperalgesic tender spots with no single identifiable organic cause. Some papers refer to chronic widespread pain, but we will concentrate on fibromyalgia, which represents one end of a spectrum (Figure 8.1). Fibromyalgia is not simply related to pain, and patients often have stiffness, fatigue and sleep disturbance among other physical and psychological symptoms.

The concept of fibromyalgia is useful for patients and doctors as a starting point for management; and this management, described later, has an evidence base.

Doctors will meet patients with fibromyalgia in a variety of settings, and commonly so, as the prevalence is about 2% of the population. Chronic widespread pain can affect up to 12% of the population. There are similarities between patients with fibromyalgia, chronic fatigue syndrome/myalgic encephalopathy (ME), multiple chemical sensitivities and depression. A common approach to treatment will be found with each of these conditions. It is important for all doctors to understand these conditions so that patients may receive appropriate evidence-based treatment in order to avoid the significant functional impairment and high use of health services seen in the past. Although patients may present in a variety of settings, the most appropriate setting for diagnosis and ongoing management is primary care. Recent evidence has shown that general practitioners may not be labelling patients with either fibromyalgia or chronic widespread pain. Nevertheless they may be using a holistic approach to these patients, which is similar to the management we describe in this chapter.

**Diagnosis**

In 1990 the American College of Rheumatology developed criteria in order to define the condition of fibromyalgia for research purposes (Box 8.1). Clinicians tend to look at these criteria in addition to their own assessment of the history and examination findings. It is important not to use these criteria too literally. However, the history will be of at least 3 months and the pain will be widespread. The story given and the objective findings are often in discordance. The main finding on examination will be multiple hyperalgesic tender sites (Figure 8.2). Patients without fibromyalgia may find pressure on these sites uncomfortable, but in general will not wince or withdraw in the manner that a patient with fibromyalgia will.

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**Box 8.1 American College of Rheumatology diagnosis of fibromyalgia (1990)**

- Widespread musculoskeletal pain in all four quadrants of the body and some axial pain (cervical spine, anterior chest, thoracic spine or low back)
- Present for at least 3 months
- Hyperalgesic points positive on digital pressure of 4 kg in 11 out of 18 points on the figure (hyperalgesia is absent in other control areas of the body, e.g. forehead)
- The points are all bilateral and situated in:
  - suboccipital muscle insertions at the base of the skull
  - low cervical spine C5-7-interspinous ligaments
  - trapezius muscles at the midpoint of the upper border
  - supraspinatus origins above the scapulae spines
  - second costochondral junctions on upper surface lateral to junction
  - 2 cm distal to lateral epicondyles
  - upper outer quadrants of buttocks in anterior fold of gluteus medius
  - greater trochanters posterior to trochanteric prominence
  - medial fat pads of knee proximal to the joint line
Fibromyalgia occurs as a stand-alone condition or can occur as a consequence of other rheumatological conditions, e.g. rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome. The term “secondary fibromyalgia” is sometimes used in these situations.

Some of the more common physical and psychological symptoms associated with fibromyalgia syndrome are listed in Table 8.1.

A full examination must therefore be undertaken at presentation or at referral. There should be no “red flags” (such as unexplained weight loss) potentially signalling serious underlying conditions. There may well be “yellow flags”, which suggest psychosocial problems, although they may not be apparent initially.

Limited investigations to exclude other causes of widespread pain are usually undertaken at presentation (thyroid function tests, full blood count, inflammatory markers, serum calcium and alkaline phosphatase, biochemical profile, creatine kinase, random blood glucose). The emphasis has to be on the biopsychosocial perspective, and any subsequent tests may well increase levels of anxiety. It is important to make a positive diagnosis of fibromyalgia after initial examination of the patient and explain to the patient that the blood tests are simply to ensure there is no underlying condition. They need to know there is no diagnostic test for fibromyalgia. It is useful at this stage to discuss what fibromyalgia is and possible models for causation with the patient in order to prepare them for the normal results of investigations. A well-informed patient will then not feel rejected.

**Clinical picture**

The typical patient will tend to be female, aged 30–50 years, with long-standing diffuse pain. She will often have a history of physical or psychological trauma, and this may have been related to previous abuse. She will describe a fatigue on waking. The symptoms are always present but are exacerbated by other stressors in her life. She may have experienced rejection by other doctors who investigated but did not find an organic cause of the symptoms. This rejection can lead to more anxiety and hence intensification of the symptoms. The patient may have also become depressed if her symptoms have not been helped by previous interventions.

The examination of such a patient reveals tender hyperalgesic sites and the patient visibly winces when they are pressed.

**Cause**

No single pathophysiological causative mechanism has been identified (Box 8.2), and the evidence to date suggests that fibromyalgia is a multifactorial syndrome characterized by abnormal processing of pain, known as central sensitization. In this process neuronal pain pathways originally activated from an identifiable noxious source later become activated in the absence of a clear stimulus. Neuroendocrine abnormalities have also been identified, but their clinical significance is not understood.
Fibromyalgia Syndrome

Management of fibromyalgia

The experience of pain is influenced by physical, psychological and social factors, which may mitigate or enhance the pain experience (Figures 8.3 and 8.4). Therefore as part of the assessment process it is important to identify any psychological (emotional distress, anxiety, difficult life predicaments, identifiable stressors) or social (family history, work issues) influences on the pain, as these will need to be addressed as quickly as possible to facilitate behavioural change.

The goals of management are twofold to assist the patient in the development of self-management skills and to improve the patient’s physical and psychological function.

Education

The patient will often need guidance, support and motivation from a health professional before feeling able to take an active role in the management of their symptoms. Physical inactivity, unrestorative sleep and emotional stress can increase the intensity of pain, and these areas need to be addressed. Patient-centred management goals need to be realistic to prevent failure and increased feelings of helplessness. A review of the evidence from multidisciplinary rehabilitation in fibromyalgia advocates the use of behavioural strategies (graded exercise, pacing, cognitive behavioural therapy, goal setting and relaxation) and stress-management techniques. Some of these strategies are covered in chronic-disease-management programmes such as the Expert Patient Programme.

Graded exercise

Many patients become physically de-conditioned and are fearful that exercise will induce damage to the joints or increase the pain and fatigue. The aim of graded exercise (that is, gradually increasing activity over a period of time) is to improve the patient’s general level of physical fitness by increasing muscle strength, stamina and flexibility. Through improving fitness levels the patient will be able to increase their general level of activity and experience a positive effect on well-being and sleep. Several sessions of supervised exercise may be needed at first to provide reassurance and feedback.

Pacing activities

Pacing involves breaking down everyday activities into achievable components. Patients tend to exert themselves on a “good day” and under-exert on a “poor day”. Pacing removes the “all-or-nothing” mentality that is not helpful in this condition. If patients can plan their activities, e.g. cleaning one room in the house a day instead of doing all the rooms in one go, they will still achieve the desired outcome and be able to remain active every day instead of continuously entering the “boom-and-bust” cycle. Patients should be encouraged to remain in the workplace and where possible apply the principles of pacing in their work situation.

Relaxation

Relaxation can reduce muscle tension, muscle pain, general feelings of anxiety, improve sleep and foster a sense of control over the condition.

Developing a sleep routine

Patients often develop an erratic sleep pattern and feel unrefreshed on waking. This increases the perception of pain, leads to poor
cognitive functioning and low mood state and reduces the ability to cope with everyday events. Self-help measures can improve the quality of a person's sleep. These include avoiding daytime sleeping, going to bed at the same time each night, carrying out relaxation techniques to clear the mind prior to settling, avoiding stimulants such as coffee and providing a quiet, well-ventilated environment.

**Drug therapy**
Pharmacological treatments are not particularly successful. Tricyclics such as amitriptyline may be helpful in improving sleep disturbance. Amitriptyline is prescribed in small incremental doses in general ranging from 10–50 mg (some patients are sensitive to side effects and need only 5 mg) and should be taken 2 hours prior to settling at night. The decision to increase the dose will be based on efficacy and side effects. Even with low doses side effects are common, albeit usually minor. Tricyclics should help improve sleep within 2 weeks, but a longer trial of 3–4 months is required to assess efficacy on pain. Serotonin-uptake inhibitors can improve energy and provide pain relief but tend to lose their effectiveness over time. Duloxetine has also been shown to reduce pain in women with fibromyalgia. Pregabalin has been shown to be helpful in reducing pain and fatigue and improving sleep. Simple analgesia, such as paracetamol, may be prescribed, but there is little evidence to support the use of strong narcotics.

**Complementary/alternative medicine**
Although few studies have examined the benefits of complementary/alternative medicine, patients often use numerous types of such treatments, including massage therapy, chiropractic and acupuncture.

In conclusion, a biopsychosocial approach to the assessment and management of patients with fibromyalgia is required, with an emphasis on assisting patients to develop coping strategies.

**Further reading**
Introduction

Osteoarthritis (OA) is the most common condition to affect synovial joints, the most important cause of locomotor disability, and a major challenge for health-care providers (Figure 9.1a). Because OA increases significantly with age (Figure 9.1b), it was long considered to be a degenerative disease that was an inevitable consequence of ageing and trauma. However, it is viewed now as a metabolically dynamic process characterized by an imbalance of joint breakdown in association with a maladaptive and insufficient repair process.

OA can result from abnormal biomechanical stresses (e.g. severe injury, repetitive excessive loading) superimposed on normal joint physiology, for example weakened cartilage due to a genetic mutation in collagen II (Figure 9.2). In fact, the genetic contribution to OA is equal to or greater than the genetic contribution to the most common inflammatory arthritis in women—rheumatoid arthritis (RA) (Figure 9.3). Moreover, the relative disability associated with these two forms of arthritis is similar (Figure 9.4). Thus, OA can be considered as the consequence or final common pathway of a number of interacting risk factors and processes, including genetic factors, gender, increasing age, excess weight, injury, joint deformity and occupational exposures. Risk factors may vary in importance according to the site of involvement (Table 9.1), and risk factors for development of OA may differ from risk factors for progression. For example, high bone density is a risk factor for development of knee, hip and hand OA, but low bone density is a risk factor for more rapid radiographic progression of hip and knee OA.

Presentation

OA is traditionally separated into two main categories: primary and secondary. Primary OA typically involves joints in characteristic locations (Figure 9.5a) and is likely to result mainly from genetic predisposition—the case of abnormal joint physiology as described above. Multiple Heberden’s nodes (bony enlargement of distal interphalangeal joints of the hand) (Figure 9.6) appear in middle age and are a strong marker for subsequent predisposition to knee OA and OA at other common target sites (“nodal generalized OA”). However, OA can occur in any joint. When OA occurs in atypical joints, such as the ankle, the presentation alone should trigger consideration of secondary OA. Typical aetiologies of secondary OA include joint trauma, previous fracture and preceding inflammatory arthropathy such as gout—the case of abnormal joint stressors as described above. The most common of these, joint trauma, can lead to OA 15–20 years after the joint insult and can be a cause of young-onset mono- or pauciarticular OA (Figure 9.7). When abnormal joint stressors and abnormal joint physiology occur together, the outcome is potentially even more severe. This is illustrated by the fact that severe meniscal damage to the knee is more likely to cause eventual knee OA in patients with hand OA (evidence for a genetic predisposition to OA) compared with patients without hand OA (Englund et al., 2004).

It is useful to contrast the distribution of OA joints with that of RA (Figure 9.5b). RA involves multiple joints in a symmetrical pattern, and spares the distal interphalangeal joints of the fingers. The radiographic manifestations of these two arthritides are distinct and can be used in their differential diagnosis as described below.

Despite the varying aetiologies, the presenting manifestations of OA are pain, loss of joint motion and function, minimal (<30 minutes) morning stiffness and short-lived stiffness after
Pathways to osteoarthritis

Abnormal stress
Normal joint physiology

Obesity
Trauma
Bone remodelling
Abnormal anatomy
Altered joint loading

Joint destruction pain disability

Ageing
Sepsis
Inflammation
Genetic factors
Biomaterial fatigue

Cell/matrix injury
Aberrant repair response
Enzymatic degradation
Proteoglycan loss
Mechanical failure

Pathways to osteoarthritis. Taken from Poole et al. 2007, with permission of Dr Farshid Guilak and the publisher, Lippincott Williams & Wilkins

Aetiology of osteoarthritis and rheumatoid arthritis

Genetic predisposition

Environmental/biomechanical triggers

Joint degeneration
non-autoimmune

Autoimmune disease

OA

RA

<45% 45-65% 50%

Joint destruction pain disability

Aetiologies of OA and RA

Figure 9.4 Relative work disability for OA and RA. Data taken from Pincus et al., 1989, based on 1978 US Social Security Survey of Disability and Work. In the original paper, OA and RA were referred to by their respective surrogates: asymmetric oligoarthritis and symmetric polyarthritis

Table 9.1 Important risk factors for osteoarthritis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Hand, knee and hip OA show strong heritability (40–60%); this probably results from combinations of multiple common polymorphisms rather than rare single genes with a large individual effect</td>
</tr>
<tr>
<td>Race</td>
<td>Knee OA is prevalent across the world, whereas hip OA is particularly prevalent in Caucasians</td>
</tr>
<tr>
<td>Age</td>
<td>Although not an inevitable consequence of ageing, OA is strongly age-related; this may reflect the cumulative effect of insults to the joint, aggravated by decline in neuromuscular function, or senescence of homeostatic repair mechanisms</td>
</tr>
<tr>
<td>Sex</td>
<td>Women have a higher prevalence and radiographic severity of OA at all joint sites apart from the hip. Women are also more likely to have symptoms if radiographic OA is present</td>
</tr>
<tr>
<td>Obesity</td>
<td>This is an important risk factor for knee OA, but a more modest risk factor for hip and hand OA</td>
</tr>
<tr>
<td>Bone density</td>
<td>High density is a risk factor for development of knee, hip and hand OA; low density is a risk factor for more rapid progression of knee and hip OA</td>
</tr>
<tr>
<td>Abnormal joint shape and alignment</td>
<td>Acetabular dysplasia is a recognized cause of hip OA, and distal femoral dysplasia (often overlooked) may contribute to knee OA; varus or valgus malalignment may be a risk for development and more rapid progression of knee OA—this can have a major interaction with obesity</td>
</tr>
<tr>
<td>Joint trauma and usage</td>
<td>Major joint injury is an important factor at the knee (especially if it causes subchondral fracture, meniscal injury or ligament rupture) and can cause OA at any site; recognized occupational hazards include farming (hip OA), underground mining (knee OA), professional soccer (knee OA) and some heavy manual jobs (hand OA)</td>
</tr>
</tbody>
</table>

resting ("gelling"), in the absence of systemic symptoms (fatigue, fever) or other system involvement. Joint stiffness arises, at least in part, from the accumulation of hyaluronan (a joint lubricant and the most abundant constituent of synovial fluid) and hyaluronan fragments in the deep layers of arthritic synovium during periods of rest, excluding water within the synovial tissue. Joint movement mobilizes hyaluronan from the tissue to the lymphatics and blood with attendant hydration of synovial tissue and improvement in joint stiffness symptoms (Engstrom-Laurent, 1987). The cartilage changes that accompany OA encourage deposition of crystals—both calcium crystals (calcium pyrophosphate and basic calcium phosphates), especially at the knee, and urate crystals. Patients with OA may therefore develop superadded acute pseudogout (mainly knees and wrists), and are at increased risk of secondary gout if they are on long-term diuretics or have chronic renal impairment (see Chapter 10).
Examination

The main clinical features of OA are symptoms, functional impairment and signs. Considerable discordance can exist between these three (Figure 9.8). Pain may arise from several sites in and around an osteoarthritic joint (Table 9.2). Suggested mechanisms include increased intra-capsular and intra-osseous pressure, subchondral microfracture and enthesopathy or bursitis secondary to muscle weakness and structural alteration. Severity of pain and functional impairment are greatly influenced by personality, anxiety, depression, daily activity and reduced muscle strength and proprioception (muscle performs an important proprioceptive role).

Table 9.2 Types of joint pain in OA

<table>
<thead>
<tr>
<th>Nature of pain</th>
<th>Probable aetiology of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain with use</td>
<td>Mechanical joint damage, enthesopathy from ligament or ligamentous attachments</td>
</tr>
<tr>
<td>Pain at rest</td>
<td>Inflammation with effusion and joint capsule distension</td>
</tr>
<tr>
<td>Pain at night</td>
<td>Intra-osseous hypertension</td>
</tr>
<tr>
<td>Sudden flare of pain</td>
<td>Crystal synovitis, torn meniscus, exacerbation of cartilage breakdown due to abnormal stressor with secondary synovitis from pro-inflammatory cascade due to release of cartilage matrix fragments; consider sepsis as a rare possibility</td>
</tr>
</tbody>
</table>

Figure 9.5 Pattern of joint distribution of primary OA and RA

Figure 9.6 Hands with Heberden’s nodes (bony enlargement of distal interphalangeal joints) and Bouchard’s nodes (bony enlargement of proximal interphalangeal joints)

Figure 9.7 Prevalence of knee OA after injury compared with baseline risk. Taken from Roos, 2005, with permission of Dr Ewa Roos and the publisher, Lippincott Williams & Wilkins
Osteoarthritis progression. See Box 9.1 for European and US guidelines on management of OA.

Symptoms of OA often are episodic. It is therefore advisable to provide the patient with an armamentarium of treatment options to choose from during periods of relative quiescence and relative flare.

**Patient education and information access**

This is a professional responsibility, but education also improves outcome and is a treatment in its own right. The myth that OA is a progressive wearing-out of joints due to old age still persists; this invariably leads to inappropriate reductions in activity. A major contribution to managing OA has been the finding that a patient’s psychological status (anxiety, depression and social support) is an important determinant of symptomatic and functional outcome. Good evidence supports the use of educational programmes to help patients understand OA and develop self-management strategies.

Crepitus, bony enlargement, deformity, instability and restricted movement may occur together and predominantly reflect structural changes. Varying degrees of synovitis (warmth, effusion and synovial thickening) may be superimposed, especially noticeable in knees, and muscle weakness or wasting is extremely common.

Assessment aims to establish the source of symptoms in each patient. When diffuse and generalized tender points are identified at tendon insertion sites, then the co-occurrence of fibromyalgia should be considered and attention to improving sleep be included in the management considerations. Only an adequate history and examination can determine how much structural and inflammatory change is present and how much these contribute to a patient’s problems.

**Diagnosis**

Typical OA can be diagnosed by history and examination alone. Currently the main investigation that can help confirm OA is the plain X-ray, with demonstration of characteristic structural abnormalities—focal joint-space narrowing (due to cartilage loss), marginal osteophyte or “spur” formation and subchondral sclerosis of bone (Figure 9.9). It is increasingly recognized that biochemical abnormalities of the joint precede radiographic abnormalities by as much as decades. For this reason, much effort is currently being put into identifying more sensitive imaging modalities, such as magnetic resonance imaging, bone scintigraphy and ultrasound, along with biochemical indicators in blood, urine or synovial fluid, that might identify and quantify OA more precisely and earlier than by X-ray.

**Management**

The goals of medical management of OA (summarized in Figure 9.10) are to: (a) provide patient education and information access; (b) relieve pain; (c) optimize function; and (d) minimize disease progression. See Box 9.1 for European and US guidelines on management of OA.

Symptoms of OA often are episodic. It is therefore advisable to provide the patient with an armamentarium of treatment options to choose from during periods of relative quiescence and relative flare.

**Box 9.1 European and US Guidelines for management of OA**

- The management plan must be individualized, taking into account the site and severity of OA symptoms, any co-morbidity, concurrent medications and patient acceptability
- Non-pharmacological treatments are central—drug treatments are adjuncts
- A core and option approach is required—all patients should be offered education, an exercise programme, advice to reduce adverse mechanical factors and paracetamol as the first oral analgesic to try; there is a wide range of other treatment options from which to select additional treatments, as required
Figure 9.9 Radiographic OA: representative images of a hand (a), a hip (b) and a knee (c) with radiographic OA.
Exercise
Local quadriceps-strengthening exercise can reduce pain and disability and improve the physiological accompaniments of knee OA (muscle weakness, impaired proprioception and balance, tendency to fall). Aerobic activity also reduces pain and disability from OA, improves well-being and sleep quality, and is beneficial for common comorbidities. Both forms of exercise need to be prescribed. Increased activity and exercise can be accomplished in a variety of ways (e.g. home exercise, group classes), tailored to the patient’s wishes and lifestyle. Pool exercise, wherein people weigh just one-eighth what they weigh on land, can mitigate negative effects of excessive joint loading due to obesity and allow freedom of joint movement and aerobic training for individuals with lower extremity OA.

Reduction of adverse biomechanical factors
Spreading physically hard jobs (e.g. housework, mowing the lawn) at intervals through the day, with breaks in between (“pacing”), can reduce sustained mechanical loading. Weight reduction can improve function and reduce pain in obese and overweight patients and may slow progression of knee and hip OA. Appropriate footwear (thick soft sole, no raised heel, broad forefoot and deep soft uppers) can reduce impact loading in people with knee and hip OA, and wedged insoles can counteract knee varus deformity. Walking sticks and other walking aids reduce loading across OA joints.

Pharmacological treatments
The high prevalence of OA, especially in the elderly, means that co-morbid conditions often exist, and management of OA must take into account these conditions and potential for drug interactions.

Pain is the main reason patients seek help. Long term, the non-pharmacological lifestyle measures mentioned above can all reduce pain, but drugs are often helpful adjuncts to help quickly reduce pain during exacerbations of symptoms. Paracetamol should be the first oral analgesic to try, based on its excellent safety and reasonable efficacy. Topical non-steroidal anti-inflammatory drugs (NSAIDs) and topical capsaicin are also safe and are particularly useful for hand and knee OA.

Oral NSAIDs, including highly selective COX inhibitors, and weak opioids (e.g. codeine, tramadol) may be considered for those patients who obtain insufficient relief from paracetamol and/or topical agents. The increased risk of gastrointestinal ulceration and bleeding from traditional NSAIDs can be decreased by concomitant prescription of a proton pump inhibitor or misoprostol. The highly selective COX inhibitors, although safer on the gut, may increase the risk of myocardial infarction and stroke, as indeed may many of the traditional NSAIDs. Traditional NSAIDs also cause adverse effects on renal function, especially in the elderly, and have multiple potential drug interactions. Oral NSAIDs and selective COX inhibitors therefore should be given at the lowest effective dose on an as-required, rather than regular, basis. Weak opioids, either alone or in combination with paracetamol, may provide good pain relief, but central nervous system side effects (e.g. constipation, headache, confusion) often limit their usefulness.

Nutraceuticals provide an alternative in older, high-risk patients with co-morbidity because they have no associated renal or gastrointestinal side effects and are very popular with patients. Glucosamine is contraindicated in patients with shellfish allergy. The initiation and use of either glucosamine or chondroitin sulphate requires monitoring of glucose in diabetics, as these agents are associated with mild insulin resistance in animals.

Intra-articular corticosteroid injection is a valuable treatment that often gives quick effective relief of pain that may last just a few weeks to a few months. It is particularly useful to tide a patient over an important event (e.g. family wedding, holiday) and to improve pain during initiation of other interventions such as an exercise programme. A variety of hyaluronan preparations are also available, given as a single injection or a course of one per week for 3–5 weeks. Although a modest, relatively prolonged (several months) improvement in pain may result, the cost and logistics of this treatment are limiting.

Surgical
The success of prosthetic joint replacements has greatly advanced management of end-stage hip and knee OA. Surgery is also used increasingly now at the shoulder, elbow, and thumb base. Although issues of funding, waiting times, choice of prosthesis and revision have to be faced, there is no doubt that such surgery can transform a patient’s life. Other surgical approaches (osteotomy, arthrodesis or joint fusion) may also be useful in specific circumstances. Arthroscopic debridement and lavage is indicated if a patient with OA describes mechanical locking. Symptomatic improvement following joint lavage alone can last several months.

The criteria for referral for consideration of joint replacement are not universally agreed upon, but include uncontrolled pain and severe impairment of function despite conservative treatment. Age,
in itself, is not a contraindication. Autologous chondrocyte transplantation is a procedure that is currently typically reserved for young patients with severe chondral defects.

In summary, OA is a condition of increasing prevalence characterized by a phasic progression with periods of relative quiescence and flare. An individualized and holistic approach to management is essential as the best means for relieving pain, minimizing disability and improving quality of life.

References


Further reading


Acknowledgements

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CHAPTER 10

Gout, Hyperuricaemia and Crystal Arthritis

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Overview

- Asymptomatic hyperuricaemia does not need treating.
- Steroids, non-steroidal anti-inflammatory drugs (NSAIDs), or colchicine can be used to treat acute gout; oral steroids might provide the best balance of risks and benefits.
- Patients with recurrent gout twice or more a year should be offered urate-lowering medication.
- Target serum urate for patients on urate-lowering drugs is <0.30 or <0.36 mmol/l.
- Dose of urate-lowering medication should be titrated according to response; many patients with recurrent gout get inadequate doses of urate-lowering drugs.

Gout and hyperuricaemia

Gout is a common metabolic disorder, typically presenting as an acute monoarthritis, most commonly of the first metatarsal phalangeal joint. The term “gout” includes an acute attack, the propensity for repeated episodes and also for chronic gouty arthritis. The underlying problem is a build-up of urate, a purine breakdown product. Humans, and some primates, lack uricase, which in other mammals oxidizes urate to allantoin, which is readily soluble. Both an increased dietary purine intake and an increased breakdown of endogenous proteins (e.g. cancer treatment or haematological malignancy) can increase urate levels.

Urate excretion is mainly renal. The rate of renal excretion is affected by urine flow, pH and competition for renal tubular exchange (e.g. diuretics). Patients whose problems are primarily due to increased purine turnover will have a high urinary urate, and those whose problems are primarily renal will have a low urinary urate. This distinction is rarely of clinical importance. For uric acid crystals to form, the serum needs to be saturated with urate, i.e. >0.42 mmol/l (7.0 mg/dl). This is, coincidentally, the upper limit of the normal range in men and postmenopausal women in many laboratories. For premenopausal women, the upper limit of the normal range for serum urate is 0.36 mmol/l (>6.0 mg/dl).

Epidemiology

Prevalence is probably around 1% in white populations. Gout is rare in premenopausal women. However, there are few reliable data on how many people are affected each year, or how many people are taking prophylactic drugs. As gout is associated with increasing age and obesity, it is likely to become commoner. Some non-white populations are more prone to gout/hyperuricaemia; e.g. the prevalence of gout is 6.4% and 3.6%, respectively, in New Zealanders of Maori and European origin. There is generally a higher prevalence of gout in indigenous ethnic groups around the Pacific Rim. In Malaysia, the three largest ethnic groups are Malay, Chinese and Tamil. All have higher mean levels of uric acid in serum than most white populations. Environmental factors also play a part; for example, changes to from a traditional island lifestyle to a more Westernized diet increased prevalence of gout 9-fold, to Maori levels, in Tokelauan islanders who migrated to New Zealand. The prevalence of gout may also be higher in black Afro-Caribbean ethnic groups. In sub-Saharan Africa gout is particularly associated with high alcohol intake in all socio-economic groups. A particular problem for some groups in sub-Saharan Africa is saturnine gout due to the effects of lead, absorbed from containers used for homemade alcoholic drinks, on renal tubular function.

Risk factors

Age and sex—Gout becomes commoner with increasing age (Figure 10.1). In men the reported prevalence ranges from <0.5% in those aged under 35 to over 7% in those aged over 75. It is rare in premenopausal women but increases to 2.5–3.0% in those aged over 75. The later age of onset in women may relate to the uricosuric effects of oestrogens.

Obesity—Relative risk of gout increases with increasing body mass index (BMI). Compared to people with a BMI of 21–25, those with BMI of >35 are four times as likely to develop gout (Figure 10.2).

Diet—Each additional daily portion of meat per day increases the risk of gout by 20%. Purine-rich vegetables do not appear to increase the risk of gout, while consuming more dairy products reduces the risk of developing the disease (Table 10.1).

ABC of Rheumatology, 4th edn. Edited by Ade Adebajo.
©2010 Blackwell Publishing Ltd. 9781405170680.
Dietary fructose may also increase the risk of developing gout. This occurs naturally and is also present in high-fructose corn syrup (HFCS), which is commonly used as a sweetener for soft drinks and other foods in the USA. The use of HFCS is uncommon outside the USA.

**Drugs**—A number of drugs can increase serum urate; this is most commonly due to diuretics. Aspirin and salicylates at low doses decrease urate excretion, but at high doses (4–6 g/day) they have a uricosuric effect.

**Alcohol**—Compared to non-drinkers, people consuming >50 g alcohol per day are 2.5 times as likely to develop gout (Figure 10.3). While there is a strong relationship between beer intake and gout, there is only a weak relationship between intake of spirits and gout. There does not appear to be a relationship between wine intake and gout. Alcohol is catabolized to ketones that compete with urate for excretion by the renal tubule. Beer typically contains substantial amounts of purines, from yeast, which are catabolized to urate by gut bacteria. Alcohol may also increase the dose of allopurinol needed by decreasing the conversion of allopurinol to its effective metabolite, oxipurinol.

**Relationship between gout and hyperuricaemia**

Hyperuricaemia is necessary for the development of gout. Crystal deposition can only occur when the serum is saturated with urate: ≥0.42 mmol/l. This may be different from some laboratories’ normal ranges, which are based on population norms. Only a minority of people with hyperuricaemia develop gout. For example, the annual incidence of gout is only 6% in people with a urate of 0.60 mmol/l (Figure 10.4). Serum urate can fall during an acute
attack, and patients on urate-lowering medication can still be affected until crystal deposits have cleared from the joints. Thus, demonstrating a raised serum urate is not an essential prerequisite for diagnosing gout.

**Hyperuricaemia and cardiovascular disease**

There is a well-recognized association between hyperuricaemia and cardiovascular disease. It is not clear whether hyperuricaemia is an independent risk factor for cardiovascular disease. Thus, screening for hyperuricaemia in those with a high cardiovascular risk is not indicated. However, assessing cardiovascular risk in people presenting with gout is worthwhile.

**Clinical features**

**Acute gout**

Typically gout presents as a rapid onset of a monoarthritis associated with severe pain and inflammation classically affecting the first metatarsophalangeal joint (podagra). Low-grade fever, general malaise and anorexia may accompany the joint symptoms. Onset may follow a drinking bout, or local trauma. Untreated, acute gout usually resolves spontaneously within 7–10 days but can on occasion last several weeks. The other most commonly affected areas are the other joints in the foot, ankle, knee, wrist, finger and elbow. The affected joint is warm, tender and swollen, and in most cases, the overlying skin is erythematous. The predilection for peripheral joints is probably because crystals are more likely to form in cooler joints. Typically, the attack occurs during the night. After the acute attack patients may be symptom-free for months or years.

**Diagnosis**—The diagnosis of acute gout is usually clinical. The European League Against Rheumatism (EULAR) recommendations for gout suggest that:

‘the rapid development of severe pain, swelling and tenderness that reaches its maximum within just 6–12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation though not specific for gout’

The gold standard is demonstrating urate crystals in synovial fluid. However, few generalists (or their patients) will relish aspirating an acutely inflamed first metatarsophalangeal joint. Urate crystals are strongly negatively birefringent on polarizing microscopy. Pyrophosphate crystals, which are weakly positively birefringent under polarized light, are found in pseudogout. Both types of crystals coexist in about 10% of crystal-associated synovial effusions. In the acute situation the important differential diagnosis is septic arthritis. If septic arthritis is suspected, then urgent specialist assessment is needed. Bursitis of the first metatarsophalangeal joint can mimic podagra and is often mislabelled and mistreated as gout, especially in young women.

Investigations—All patients with a suspected first episode of gout should be investigated to obtain some confirmatory evidence to support the diagnosis, to look for underlying causes and to identify associated co-morbidities (Table 10.2). X-rays are not helpful in the diagnosis of acute gout.

**Chronic gout**

Chronic, poly- or oligoarticular gout can cause inflammatory arthritis in older people, especially those on diuretics. No diagnostic pattern exists, although lower-limb-joint involvement is

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**Table 10.2** Investigation of patients with gout

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Causes</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urate</td>
<td>May fall during an attack</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Joint aspiration</td>
<td>Consider if diagnosis uncertain; will enable the alternative diagnosis of pseudogout to be made if pyrophosphate crystals are present; note, however, that both types of crystals may coexist</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>Possible alcohol abuse</td>
<td>Blood sugar</td>
</tr>
<tr>
<td>Renal function</td>
<td>Drug doses might need adjusting if renal function is poor</td>
<td>Thyroid function</td>
</tr>
<tr>
<td>Drug doses might need adjusting if renal function is poor</td>
<td>Review medication</td>
<td>Urac acid excretion</td>
</tr>
<tr>
<td>Calcium, magnesium, ferritin, thyroid function</td>
<td>Investigations if pseudogout suspected</td>
<td>Consider if there is a strong family history of gout, or if onset under age 25 or if renal stones are present.</td>
</tr>
</tbody>
</table>
common. Crystal deposits (tophi) can develop around hands, feet, elbows and ears; they are particularly common in older women with secondary, diuretic-induced gout, in whom they may develop without a history of acute gout. Tophi are chalky deposits of urate embedded in a matrix of lipid, protein and calcific debris. They are usually subcutaneous, but may occur in bone and other organs, including heart valves and the eye. Tophi can contribute to a destructive arthropathy and secondary osteoarthritis. This picture can also develop in patients with recurrent acute gout.

Diagnosis—Urate crystals can be demonstrated in aspirate from tophi. These can be seen radiographically as soft-tissue swellings (occasionally with associated calcification) and there are characteristic X-ray changes of subcortical cysts without erosions and geodes (punched-out type erosions with sclerotic margins and overhanging edges).

Urate stones
One in five patients with gout over-excrete urate and may develop urate stones. Around 5% renal stones are pure urate. However, urinary urate may co-precipitate in calcium oxalate or phosphate stones. Serum urate should be measured in patients with a history of renal colic. Uricosuric drugs should be avoided in patients with history of urate containing renal stones. Patients with ileostomies are prone to urate stones as a consequence of producing concentrated acidic urine.

Inherited metabolic disorders
Gout in childhood may be a manifestation of one of the several rare inherited disorders of metabolism, such as Lesch–Nyhan syndrome and G6PD deficiency and should be investigated in detail. Adults with new onset gout may be heterozygous for one of these conditions, but investigations should be restricted to those with indicative family histories.

Treatment
There are few robust data to inform the management of gout. Recommendations for the treatment are largely based on clinical experience rather than randomized controlled trial evidence. There are now some suggested quality standards for the management of gout/hyperuricaemia that can be used to audit practice (Box 10.1), and the British Society of Rheumatology has produced guidelines for the management of gout.

Acute gout
The choice of drug treatment is dependent on the balance of risks and benefits. Our view, backed by some empirical data, is that for many patients with acute gout a short course of oral steroids often provides the best balance of benefits and risks.

Non-steroidal anti-inflammatory drugs (NSAIDs)—There is one small randomized controlled trial of NSAIDs compared to placebo for acute gout. Decades of clinical experience attest to the efficacy of these drugs for acute gout. Typically, high-dose NSAIDs, e.g. indometacin 50mg three times a day, are recommended, although there are no empirical data to support this. The only firm conclusion from comparative studies of NSAIDs is that pain reduction with indometacin or etoricoxib are equivalent. If NSAIDs or COX-2 inhibitors are used, a co-prescription of a proton pump inhibitor is usually indicated.

Colchicine—There is one small controlled trial of colchicine compared to placebo for acute gout; everyone taking colchicine developed diarrhoea and vomiting, frequently before pain relief. Severe diarrhoea when immobilized with acute gout can be an unpleasant experience. Other adverse reactions include bone marrow and neuromuscular dysfunction. Traditionally high doses of colchicine are recommended; however, a lower dose of 0.5 mg three times a day is less toxic and can be adequately effective.
Allopurinol hypersensitivity may occur in up to 2% of patients; this dose should be titrated according to response, up to 900 mg/day. Typical dose of 300 mg/day achieve a target urate of 0.36 mmol/l. Its recurrent gout is unclear. Only a minority of patients taking the Allopurinol oxidase inhibitor, febuxostat, has been developed.

Allopurinol has been available for over 40 years. A new xanthine and hypoxanthine being converted into urate. Xanthine oxidase inhibitors—These prevent the purine breakdown and avoid beer; increase intake of low-fat dairy products. Reduce the amount of meat and fish eaten; reduce alcohol intake known to increase serum urate.

— Consider stopping diuretics or any other drugs prescribed for the first 3 months.

Steroids/adrenocorticotropic hormone (ACTH)—There are no controlled trials comparing steroids/ACTH with placebo for acute gout. One trial, in a Hong Kong emergency department, compared indomethacin 150 mg/day with prednisolone 30 mg per day for 5 days. Prednisolone was at least as effective as indomethacin. Among the patients that received indomethacin, 5% had a gastrointestinal haemorrhage and 11% were admitted to hospital for treatment of a serious adverse effect. No one in the control group had a haemorrhage or was admitted to hospital. A second trial, in Dutch primary care, compared naproxen 1 g/day with prednisolone 35 mg per day and found effectiveness to be equivalent and a similar incidence of adverse effects.

Clinical experience supports the use of intra-articular steroids, but septic arthritis must be positively excluded. Intra-articular injections in acute gout can be difficult and very painful, particularly in smaller joints.

Analgesics—Gout is painful. Patients may need potent analgesic in addition to specific treatments. For some frail patients, just using analgesics may be appropriate.

Other treatments—Experience and some controlled trial evidence suggest that some non-drug pain-relief modalities such as the use of ice packs may give additional pain relief.

Intercritical and chronic gout
The mainstay of treatment for prevention of recurrent acute gout and chronic gout is reducing serum urate enough to allow crystals to clear. Different authorities suggest <0.30 mmol/l or <0.36 mmol/l as the therapeutic target. Asymptomatic hyperuricaemia does not require treatment.

Patients with two or more attacks of gout per year should be offered urate-lowering medication. Starting urate-lowering drugs during an attack may delay resolution and should be avoided as lowering serum urate can trigger acute gout. An NSAID, probably with a proton pump inhibitor, or colchicine should be co-prescribed for the first 3 months.

Medication review—Consider stopping diuretics or any other drugs known to increase serum urate.

Lifestyle interventions—Patients should be advised to: lose weight; reduce the amount of meat and fish eaten; reduce alcohol intake and avoid beer; increase intake of low-fat dairy products.

Xanthine oxidase inhibitors—These prevent the purine breakdown products xanthine and hypoxanthine being converted into urate. Allopurinol has been available for over 40 years. A new xanthine oxidase inhibitor, febuxostat, has been developed.

Allopurinol—Allopurinol reduces serum urate, but its effect on recurrent gout is unclear. Only a minority of patients taking the typical dose of 300 mg/day achieve a target urate of 0.36 mmol/l. Its dose should be titrated according to response, up to 900 mg/day. Allopurinol hypersensitivity may occur in up to 2% of patients; this can be severe or even fatal. Desensitizing regimens of allopurinol can be tried in milder cases of hypersensitivity.

Febuxostat—Over half of patients taking febuxostat 80 mg achieve a urate of <0.36 mmol/l compared to one in five of those taking allopurinol 300 mg. However, febuxostat does not appear to be more effective at reducing recurrent gout over 1 year. It may have a role in patients who cannot take allopurinol, either because of intolerance or because it is contraindicated.

Uricosuric drugs—Uricosuric drugs lower serum urate by inhibiting its tubular reabsorption. There is no randomized controlled trial evidence supporting their use for prevention of recurrent gout. Only sulfinpyrazone is generally available for the treatment of gout. Benz bromarone can also be used, but it is not universally available, and there are concerns about it causing liver problems. Historically, probenecid has also been used. One should consider measuring urinary urate before starting uricosurics.

NSAIDs and colchicine—Both regular NSAIDs and colchicine can be used to prevent recurrent gouty attacks but have no effect on serum urate.

Uricase drugs—Uricase drugs work by oxidizing uric acid to the more soluble allantoin. A number of these are currently under investigation. Their role, if any, in the management of gout is unclear.

Other drugs—Several other drugs have, coincidentally, been found to have urate-lowering effects. These include losartan, fenofibrate, atorvastatin and amlodipine. Although they are not licensed for the treatment of gout, they may have a role if other drugs cannot be tolerated or if they are otherwise indicated for patients with multiple pathology.

Pseudogout
Pseudogout, which can be easily confused with gout, is caused by deposition of calcium pyrophosphate crystals. It most commonly affects knees, wrists, shoulders, ankles, elbows or hands. Typically it produces an episodic monoarthritis, but it can also have a clinical picture similar to osteoarthritis or rheumatoid arthritis. Its prevalence increases from 3% in people in their 60s to half of those in their 90s. It can be associated with hypothyroidism, hypercalcemia, haemochromatosis or hypomagnesaemia.

Diagnosis is based on identifying pyrophosphate crystals or chondrocalkinos seen on X-ray. Acute episodes can be treated with NSAIDs or intra-articular steroids. Long-term NSAIDs or colchicine can be used to try and prevent recurrence.

Other crystal diseases
A number of other crystals can produce acute musculoskeletal inflammation. Most common are hydroxyapatite crystals, which typically deposit in tendons, periarticular soft tissue and synovium. Hydroxyapatite deposition may be asymptomatic but can on occasion lead to significant joint destruction. Involvement of the
shoulder is sometimes called Milwaukee shoulder, but virtually any joint may be affected. Identifying and correcting an underlying cause of hypophosphataemia or hypercalcaemia may reduce the risk of future attacks. Calcium oxalate may also cause acute arthritis. Its identification in joint fluid requires special staining with Alizarin Red dye. Treatments for acute attacks include NSAIDs and intra-articular steroids.

**Reference**


**Further reading**


Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue that results in a high risk of fracture. Currently, the diagnosis is generally based on bone mineral density (BMD) thresholds measured by dual X-ray absorptiometry (DXA—see below), whereby an individual’s bone mineral density is compared with the mean (peak bone mass) for a young adult, as a standard deviation score (T score) (Table 11.1).

These thresholds were developed for measurements of BMDs of the spine, hip or forearm made with X-ray-based techniques in postmenopausal women. It is probably appropriate to use the same thresholds for BMD measurements made in men and premenopausal women after attainment of peak bone mass, but they should not be used for children or adolescents.

Pathophysiology

The human skeleton is composed of approximately 20% trabecular bone and 80% cortical bone. Bone undergoes a continual process of resorption and formation in discrete bone remodelling units. Approximately 10% of the adult skeleton is remodelled per year.

This turnover prevents fatigue damage and is important in maintaining calcium homeostasis. Irreversible bone loss results from an imbalance between the rates of resorption and formation. Trabecular bone is the more metabolically active type, and osteoporotic fractures are more common at sites that contain more than 50% trabecular bone.

Bone loss leads to thinning, and often perforation, of the trabecular plates (Figure 11.1). Trabecular perforation occurs particularly in situations of increased bone turnover, e.g. after the menopause, and the resulting loss of normal architecture leads to a disproportionate loss of strength for the amount of bone lost. Increased bone turnover is an independent predictor of fracture risk. This may reflect the increase in number of remodelling sites, which can act as a stress riser and increase bone fragility. As a result of accelerated bone loss caused by oestrogen deficiency, postmenopausal osteoporosis initially leads to predominant loss of trabecular bone and frequent trabecular perforation. This typically results in fractures of vertebral bodies and the distal forearm in the sixth and seventh decades of life. In later life, age-related reductions in bone due to remodelling imbalances predominate in both sexes in both cortical and trabecular bone, resulting in the typical manifestation of fracture of the proximal femur.

Epidemiology

The classical osteoporotic fractures are those of the spine, wrist and hip (Figure 11.2) but all fragility fractures in the elderly can be regarded as osteoporotic once pathological fracture (e.g. metastatic disease) has been excluded. Osteoporotic fractures cause considerable morbidity and mortality. Recent estimates suggest that the cost of managing such fractures in the UK is over £1.7 billion a year. One in two women and one in five men are likely to sustain a fracture related to osteoporosis by the age of 90 years. The incidence of osteoporotic fractures is increasing more than expected from the ageing of the population. This may reflect changing patterns of exercise or diet in recent decades.

Classification of osteoporosis

Traditionally, osteoporosis has been classified as primary (includes postmenopausal and age-related bone loss) or secondary (where bone loss is accelerated by the presence of an underlying disease) (Table 11.2). Secondary osteoporosis accounts for up to 40% of cases of osteoporosis in women and 60% of cases in men.
Table 11.1 The World Health Organization’s diagnostic thresholds for bone mineral density at the spine, hip or distal forearm

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Bone mineral density T score (SD units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≥−1</td>
</tr>
<tr>
<td>Osteopaenia (or low bone mass)</td>
<td>&lt;−1 but &gt;−2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤−2.5</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>≤−2.5 plus one or more fragility fractures</td>
</tr>
</tbody>
</table>

![Image](image1)

**Figure 11.1** Comparison of structure of trabecular bone from healthy (a) and osteoporotic (b) subjects, illustrating the architectural damage resulting from trabecular perforation

![Image](image2)

**Figure 11.2** Typical sites of osteoporotic fracture: wrist (a), vertebrae (b) and hip (c)

Table 11.2 Relatively common causes of secondary osteoporosis

<table>
<thead>
<tr>
<th>Endocrine</th>
<th>Gastrointestinal</th>
<th>Rheumatological</th>
<th>Malignancy</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotoxicosis</td>
<td>Malabsorption syndrome, e.g. coeliac</td>
<td>Rheumatoid arthritis</td>
<td>Multiple myeloma</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Primary hyper-parathyroidism</td>
<td>disease, partial gastrectomy</td>
<td></td>
<td></td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Inflammatory bowel disease</td>
<td></td>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td>Hypogonadism, including</td>
<td>Liver disease, e.g. primary biliary</td>
<td></td>
<td></td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td>anorexia nervosa</td>
<td>cirrhosis</td>
<td></td>
<td></td>
<td>Androgen-deprivation therapy</td>
</tr>
<tr>
<td>Diabetes type I</td>
<td></td>
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</tr>
</tbody>
</table>
Assessment of osteoporosis

This largely comprises the assessment of future fracture risk (determines the need for intervention) and the diagnosis or exclusion of underlying causes of osteoporosis.

Assessment of future fracture risk

Clinical risk factors—Several risk factors for fracture have been well established. Many of these risk factors impact on BMD but also contribute independently to future fracture risk. Clinicians frequently take account of these other risk factors in deciding whether treatment is required, and a number of algorithms have been developed to improve the prediction of fracture risk. Recently, the World Health Organization produced an algorithm (FRAX®) that estimates the probability of a major osteoporotic fracture (clinical vertebral, hip, wrist or proximal humerus) or hip fracture alone in the next 10 years (see http://www.shef.ac.uk/FRAX). The algorithm incorporates BMD as an additional, measurable risk factor to information gleaned from clinical risk factors and adds value to the prediction of risk. BMD is probably of most value in those deemed to be at intermediate or high risk. A history of prior low trauma fracture in adult life is a very important risk factor to identify and can usually be obtained by a good clinical history. In contrast, the suggestion of prior vertebral fracture requires spinal imaging for confirmation and appropriate management. The National Osteoporosis Guideline Group (NOGG) has recently published a new management guideline (Figure 11.3) that integrates FRAX with clinical management algorithms.

Spinal radiographs—Up to half of vertebral fractures are asymptomatic and may be suspected from height loss and the development of kyphosis. The latter features may also result from degenerative spinal disease, however, and radiographs of the thoracic and lumbar spine are important to differentiate fractures from degen-
The importance of vertebral fractures for future fracture risk cannot be overstated, and strategies in the near future will involve the assessment of patients by low-radiation-imaging DXA scans to identify prevalent fractures. In the absence of fractures, the assessment of bone mass on plain radiographs is unreliable, so radiological reports of osteopenia require confirmation by bone densitometry prior to any therapeutic decisions.

**Bone densitometry**—After age and prior fragility fracture, BMD is the next major determinant of a person’s risk of fracture. The predictive ability of bone density is comparable with that of blood pressure for determining the risk of cerebrovascular accident and of serum cholesterol for determining the risk of coronary thrombosis. The relative risk of fracture increases approximately 2-fold for each standard deviation decrease in bone density.

BMD is usually measured by DXA—a technique that uses extremely low doses of ionizing radiation to quantify BMD accurately and precisely. DXA of the spine and hip are the optimal clinical measurements for diagnosis. Measurement of bone density in peripheral skeletal sites with techniques such as quantitative ultrasound has useful predictive value for osteoporotic fractures, but appropriate intervention thresholds for these measurements remain uncertain, and they are probably not useful for monitoring responses to treatment.

Currently, no rationale exists for population screening of BMD. If access to bone densitometry is limited, it may be appropriate to treat individuals who have had previous low-trauma fractures or who have other strong risk factors for fracture, such as elderly people who need high-dose corticosteroid therapy. Otherwise, measurements should be targeted to individuals likely to be at increased risk of osteoporosis, where knowledge of BMD will influence management. Traditionally, this has meant the measurement of BMD in all patients with recognized risk factors, an approach encapsulated in the Royal College of Physician Guidelines published in 1999. This guidance has now been updated to incorporate the availability of the FRAX tool for assessing fracture risk (http://www.shef.ac.uk/NOGG). The National Institute for Health and Clinical Excellence (NICE) has also recently published guidance for the primary and secondary prevention of fracture in postmenopausal women (Table 11.3) (http://www.nice.org.uk).

### Identifying or excluding underlying causes of osteoporosis

Individuals with a low-trauma vertebral fracture or low BMD for age should be investigated for underlying causes of osteoporosis. In addition to a good clinical history, a small number of investigations can exclude the most common secondary causes of osteoporosis (Box 11.1). Treating the underlying cause often leads to at least partial recovery of bone mass.

### Reducing fracture risk

The ultimate goal of osteoporosis management is to reduce the future risk of fracture. This involves educating the patient about the nature of the disease, their fracture risk, lifestyle modification (Box 11.2) and, if necessary, the different types of therapy available.

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**Table 11.3** Clinical risk factors used for the assessment of fracture probability

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Low body mass index (&lt;19 kg/m²)</td>
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<tr>
<td>Previous fragility fracture, particularly of the hip, wrist and spine, including morphometric vertebral fracture</td>
<td></td>
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<tr>
<td>Parental history of hip fracture</td>
<td></td>
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<tr>
<td>Current glucocorticoid treatment (any dose, by mouth for 3 months or more)</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake of 3 or more units daily</td>
<td></td>
</tr>
</tbody>
</table>
In some patients, particularly those with recent vertebral fractures, additional approaches aim to reduce pain and improve mobility.

**Guidance**

In October 2008, NICE published two Technology Appraisal Guidance documents to address the primary (http://www.nice.org.uk/Guidance/TA160) and secondary (http://www.nice.org.uk/Guidance/TA161) prevention of osteoporotic fractures with alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide (secondary prevention only). While welcome, there a number of challenges to the implementation of these guidelines, particularly with regard to prescribing alternative treatments when generic alendronate is contraindicated or not tolerated. NICE plan to have clinical guidelines that will address some of the limitations with these approaches (such as not giving guidance for glucocorticoid-induced osteoporosis or men). In the meantime, a more pragmatic approach to treatment has been proposed by NOGG with the support of many professional and patient societies. This approach suggests that treatment should be considered when an individual’s probability of fracture is comparable to or exceeds that of a woman of the same age who has already sustained a low-trauma fracture.

**Antiresorptive agents**

**Bisphosphonates**—Alendronate and risedronate are available as once-weekly preparations with evidence for significant reductions in vertebral and non-vertebral fractures. These drugs have largely replaced the use of cyclical etidronate. Ibandronate, available as a once-monthly tablet or a three-monthly intravenous slow injection reduces vertebral fractures with indirect evidence for a reduction in non-vertebral fractures. More recently, zoledronate has become available as a once-yearly short infusion with good evidence of anti-fracture efficacy at all sites. Both NICE and NOGG recommend the use of generic alendronate as first-line therapy, although this may not be suitable for or tolerated by all. Poor absorption of these agents means they must be taken on an empty stomach before breakfast (30 minutes before for alendronate and risedronate; 60 minutes before for ibandronate) or on an empty stomach in the middle of a 4-hour fast (cyclical etidronate). The move away from oral daily dosing regimens to more convenient, less frequent dosing has improved adherence to the bisphosphonates.

**Hormone or oestrogen replacement therapy**—The use of hormone replacement therapy is no longer thought to be appropriate in the management of osteoporosis unless it is needed to control climacteric symptoms, or in women under 50 who have undergone an early menopause. The safety profile of oestrogen-only therapy appears somewhat better than combined oestrogen–progestogen therapy.

**Selective oestrogen receptor modulators**—These synthetic agents act as oestrogen agonists on bone and lipids, but without oestrogen-like stimulation of breast and endometrial tissues. Raloxifene reduces the risk of vertebral fracture but has not been shown to decrease the risk of non-vertebral fractures. Like hormone replacement therapy, raloxifene is associated with small increases in the number of thromboembolic events but conversely is associated with a significant reduction in the number of new cases of breast cancer. Other agents in this class will be available in the near future.

**Calcium (1000–1200 mg daily)**—This has a less marked effect on fracture reduction than the other antiresorptive agents. Adherence can be problematic, and several preparations are now available to aid patient choice and compliance.

**Vitamin D (800 units daily) and calcium (1000–1200 mg daily)**—This has been shown to reduce hip fracture risk in the frail elderly and should be considered in all elderly patients who are house-bound or in residential care. In patients at higher risk of fracture, it should be used as adjunctive therapy in combination with another antiresorptive agent.

**Calcitonin**—Calcitonin may be administered as subcutaneous injections or as a nasal preparation, which is associated with fewer side effects. Calcitonin has been shown to reduce the risk of vertebral fracture. This agent has analgesic properties that may be useful in the acute management of vertebral fracture.

**Formation-stimulating agents**

**Teriparatide and parathyroid hormone**—These agents have good evidence for their abilities to increase bone formation (and later bone resorption) with an improvement in bone mass and structure, particularly in trabecular bone such as the vertebralae, with reductions in spine fracture risk. A reduction in non-vertebral fractures has also been shown by recombinant teriparatide (PTH 1-34), possibly mediated by improvements in cortical bone width and/or thickness. They are expensive agents and their use is limited to patients with severe, progressive osteoporosis despite exposure to antiresorptive therapy. Teriparatide is licensed for use in men and women, whereas recombinant parathyroid hormone 1-84 is only licensed for postmenopausal women. Treatment is currently limited to 18–24 month durations and most patients will require treatment with antiresorptive agents after discontinuation to maintain the improvements in bone mass. Very recently, teriparatide has been shown to induce greater increases in spine and hip BMD than alendronate in patients with glucocorticoid-induced osteoporosis and is now licensed for use in this setting.

**Alternative agents**

**Strontium ranelate**—Strontium ranelate has been shown to significantly reduce vertebral and non-vertebral fracture risk in postmenopausal women. The precise mechanism(s) of action remains unclear, but treatment is associated with significant increases in BMD, partly mediated by the presence of strontium in bone, which impacts on the interpretation of changes in BMD. The change in BMD is therefore a potential marker of adherence to therapy, though it may also complicate future estimates of fracture risk.

**Pain relief**

Pain relief is frequently adequately achieved with analgesics, but physical measures—such as hydrotherapy or transcutaneous nerve stimulators—may be useful adjuncts to treatment. The pain-
modulating effects of low-dose antidepressants can be helpful, and many patients benefit from assessment at specialist pain clinics. The pain associated with fractures usually resolves within 6 months, but patients with vertebral fractures may need to be given long-term analgesia because of secondary degenerative disease. NICE has also approved techniques such as vertebroplasty (http://www.nice.org.uk/Guidance/IPG12) and kyphoplasty (http://www.nice.org.uk/Guidance/IPG166) for use in selected patients with recent vertebral fractures and persistent or severe pain. Both techniques give good pain relief. Kyphoplasty may also result in some restoration of vertebral height.

**Falls prevention**
Predisposing factors, such as postural hypotension or drowsiness due to drugs, should be eliminated where possible. Patients may benefit from physiotherapy to improve their balance and saving reflexes. Patients should be provided with appropriate walking aids, and an environmental assessment should be made of their accommodation to eliminate hazards such as loose rugs and cables. Hip protectors have a limited role to play. Visual assessment and treatment is also important. Assessment via specialized falls clinics may be appropriate, particularly in those individuals with features suggesting a medical cause for falls, such as palpitations or blackouts.

**Education**
An important part of the management of osteoporosis is education and support of the patient, their carers and their family. Groups such as the National Osteoporosis Society (Box 11.3) have a vital role in this area.

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**Box 11.3 National Osteoporosis Society (NOS)**

Camerton Bath BA2 0PJ
Tel.: 01761 471771 (for general enquiries); 0845 4500234 (for medical enquiries)

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**Monitoring of treatment**
The rationale for monitoring treatment response is that a proportion of patients fail to respond to treatment, commonly due to non-persistence with therapy, poor dosing compliance or, less commonly, due to underlying disease. The current standard measure used to monitor treatment response is spine DXA at 18–24 months after treatment initiation. Biochemical markers of bone turnover may offer a more rapid assessment of treatment response—within 3–6 months. The decrease in bone turnover in response to antiresorptive agents may be a superior predictor of the decrease in fracture risk.

**Further reading**
Pathogenesis

The cause of rheumatoid arthritis (RA) is not yet established; however, the postulate that remains popular is that an unknown antigen in a genetically predisposed individual is able to initiate a self-perpetuating immune response. The response has cross-reactivity with host tissue, initiating an autoimmune synovitis and subsequent hypertrophy. Synovial hypertrophy is the key factor that leads to cartilage and bone destruction, causing progressive joint damage and disability. Other tissues are affected through different mechanisms, accounting for the extra-articular manifestations.

Many cellular and chemical markers have been studied; the key effector cell still appears to be the T-cell, which orchestrates the immune response through a host of cytokines. The key cytokines involved in the pathogenesis of RA have been tumour necrosis factor-alpha (TNF-α) and interleukin-1. The advances in knowledge about RA pathogenesis have directed development of targeted therapy, which has led to major advances in the management of this disease.

Knowledge has advanced in genetics, and HLA-DR4 has been established as a marker of prevalence as well as severity in RA. However, other alleles have also been implicated, and this has been ascribed to a “shared epitope” on the hypervariable region of the human leukocyte antigen-DRB1 chain.

Clinical features

The objectives of clinical assessment for RA are mainly to: (a) establish the diagnosis; (b) evaluate the disease activity (is the disease active or quiescent?); (c) assess the disease severity (amount of damage and disability); and (d) look for extra-articular manifestations.

Usually the disease is insidious in nature, rarely occurring in men younger than 30 years, with gradually rising incidence with advancing age. In women the incidence steadily increases from the mid-20s to peak incidence between 45 and 75 years. In the classical presentation, which remains the more common variant, the disease affects the small joints of the hands and feet in a more symmetrical pattern. The joints predominantly affected are the metacarpophalangeal joints, the proximal interphalangeal joints and the wrists (Figure 12.1); in the feet the metatarsophalangeal joints and the forefoot joints are affected.

Less common forms of presentation are acute monoarticular, palindromic rheumatism and asymmetrical large joint arthritis. Theoretically all synovial joints can be affected; however, spine joints other than the cervical spine are very rarely involved in RA.

Extra-articular manifestations (Figure 12.2) are varied and also differ in different populations. They can affect almost any system of the body and are mediated by various mechanisms. Immune responses such as immune complex deposition, cytokine production and direct endothelial injury can produce distant and local effects. Also, mechanical causes such as synovial hypertrophy and subluxation of joints may cause entrapments of the nerves or vessels. The disability leads to disuse and abnormal mechanics, which leads to degenerative changes and osteoporosis.
in flexion (Figure 12.3) and extension and measuring the distance between the posterior margin of the atlas ring and the anterior surface of the odontoid process.

Amyloidosis—Renal deposition of amyloid (Figure 12.4) is a recognized feature of longstanding RA and should be suspected if the patient develops increasing leg oedema, proteinuria and worsening renal functions. Drug-related causes such as gold- or penicillamine-induced proteinuria need to be ruled out. A renal biopsy will conclude the diagnosis.

“Red flags”
A variety of complications of RA or its treatment can occur and require vigilance on the part of clinicians to pick them up early and intervene to prevent severe morbidity, and even mortality in certain cases; some of these are detailed below.

Atlanto-axial subluxation—This results from involvement of the atlanto-axial joint, which may be clinically asymptomatic until the subluxation develops. Development of pain around the occiput, radiating arm pain, numbness or weakness of the limbs and vertigo on neck movement are warning signs; if not picked up this may lead to sudden death, especially if patients undergo neck manipulation for endotracheal intubation during surgical procedures. It is advisable to actively look for it as part of pre-surgical evaluation. It can be picked up easily by doing lateral views of the cervical spine.
The diagnosis of RA is predominantly a clinical one; no diagnostic test has been shown to be foolproof, and both false-positive and false-negative results are seen with varying frequency.

**History**

A detailed history of the problem, its onset and progression with time, relieving and aggravating factors and the distribution of the symptoms are all important elements in the history. A progressive pattern of joint involvement, stiffness and increased pain after a period of inactivity and a history of joint swellings are indicative of inflammatory joint disorders. A family history of rheumatological disease can raise the suspicion further. The distribution of joint involvement helps in distinguishing other forms of arthritides such as spondyloarthritis and psoriatic arthritis.

**Clinical examination**

The objective of the clinical assessment is to identify signs of inflammatory arthritis, such as swelling, tenderness and restriction of movement of the joints. A symmetrical involvement of the hands, especially the metacarpophalangeal and proximal interphalangeal joints, with relative sparing of the axial skeleton, are some key elements that support the diagnosis of RA. Clinical evaluation may also pick up extra-articular findings that can support the diagnosis or refute it—for example, the presence of rheumatoid nodules and psoriatic skin patches, respectively. In early disease the classical signs of structural changes may be missing and subtle synovitis (Figure 12.6) may escape notice; however, tenderness and restriction without history of trauma should arouse suspicion.

**Laboratory evidence**

Active RA is associated with a variety of haematological responses. Acute-phase responses such as a high erythrocyte sedimentation rate or C-reactive protein, a high platelet count and high serum...
The American College of Rheumatology has formulated and modified classification criteria to aid in diagnosis of RA (Box 12.2); however, these criteria have poor sensitivity in picking up early rheumatoid disease.

**Differential diagnosis**

Other arthritides can be distinguished on the basis of joint-involvement pattern; however, atypical presentations may prove...
polyarticular gout. Malignant conditions such as leukaemias and lymphomas should be sought, especially in acute presentations in younger patients. In areas of high incidence, conditions such as hepatitis B and C and HIV need to be borne in mind.

As RA is a chronic disease that leads to significant morbidity and disability, the clinician has the vital responsibility of making an early diagnosis and commencing treatment early to prevent these problems from occurring. No laboratory tests are diagnostic, and ultimately the diagnosis relies on a clinical evaluation by the practitioner.

**Further reading**


Remarkable strides have been made in controlling clinical and radiological progression of rheumatoid arthritis (RA) in recent years. However, the usefulness of small molecules such as methotrexate has not been overshadowed by the current interest in biological-response modification. Our understanding of the molecular mechanisms responsible for the pathogenesis of RA has heralded a shift from empiricism to selective molecular targeting in immunomodulatory pharmacotherapeutics. While symptomatic control and reduction of the clinical signs of synovitis have been the foremost considerations in the past, modern pharmacotherapy has emphasized the need to slow down, if not halt, disease progression as well as to prevent the development of potential complications. It is now recognized that significant documented radiological damage can occur in this disease much earlier than previously thought, certainly within the first 2 years of disease onset. Disease-modifying therapy is therefore introduced early following confirmation of diagnosis, particularly in those with poor prognostic indicators, such as severe disease activity, radiological damage or anti-cyclic citrullinated peptide positivity. Some favour a more aggressive combination of drugs in early disease, with a possible “step-down” approach once the disease comes under control. The old “pyramidal” treatment approach has therefore been called into question, and new advances have dramatically improved the disease outlook for the RA patient.

**Non-steroidal anti-inflammatory drugs**

Non-steroidal anti-inflammatory drugs (NSAIDs) are inhibitors of cyclooxygenase, an enzyme that catalyses the conversion of arachidonic acid to prostanoids. The enzyme exists in two isoforms. Cyclooxygenase-1 is constitutively expressed in many tissues including platelets, blood vessels and the upper gastrointestinal (GI) mucosa, where production of prostaglandin E₂ mediates a protective mucosal effect that includes mucus secretion and diminution of acid production. Expression of cyclooxygenase-2 is induced at sites of inflammation, particularly on polymorphonuclear cells and macrophages. Thus, non-selective inhibition of both isoforms by traditional NSAIDs may ameliorate desirable gastroprotective effects mediated by cyclooxygenase-1, and reported hospitalization of RA patients as a result of upper GI complications may exceed 1% of patients treated per year. Selective inhibition of cyclooxygenase-2, however, has met with concerns over potential cardiovascular risks, although recent evidence suggests that this problem is also associated with several traditional NSAIDs. Despite these concerns, NSAIDs continue to be used for symptomatic control in RA, but it must be emphasized that they have little effect in limiting joint damage or radiological progression.

**Corticosteroids**

The demonstration of the anti-inflammatory efficacy of corticosteroids in RA resulted in the first Nobel Prize awarded for a clinical observation, and 70 years hence, these potent anti-inflammatory agents continue to have an important place in the management of RA. Furthermore, multiple routes of administration, including depot injections (methylprednisolone and triamcinolone acetonide) and local intra-articular injections offer a variety of therapeutic options. Given orally, the onset of action is quick and is therefore useful in relieving symptoms while awaiting the onset of DMARD activity. Lower oral doses have been favoured (prednisolone up to 10mg/day) owing to fear of suppression of the hypothalamus-pituitary–adrenal axis, and prevention of corticosteroid-induced osteoporosis must be considered in patients receiving these medications long term.
Disease-modifying antirheumatic drugs

Gold—Originally intended for the treatment of infectious diseases, gold is one of the oldest of the disease-modifying antirheumatic drugs (DMARDs) and has been in use for almost a century for the treatment of RA. An intramuscular drug of proven efficacy, radiological improvement with decrease in radiological damage bore evidence of its disease-modifying capacity. However, weekly injections may be cumbersome, and an oral form proved ineffective. This, together with the fact that over half of drug discontinuations were reported to be the result of toxicity (such as severe skin rash and nephrotoxicity), heralded a decline in its popularity over the years.

Methotrexate—A dihydrofolate reductase inhibitor originally used for its anti-proliferative effects in the treatment of cancer, methotrexate is now an anchor drug among DMARDs and a gold standard against which all emerging therapies are compared. An oral drug administered on a weekly basis, its anti-inflammatory mechanisms of action are thought to differ from its anti-malignant effects, and are largely related to its induction of adenosine release to the inflammatory environment. Compared with gold it has an excellent side-effect profile, the only frequent problem being post-doseage nausea, which frequently responds to folic acid (Box 13.1).

Sulfasalazine—Sulfasalazine, the first drug developed specifically for the treatment of RA, was first synthesized in the 1940s. It is composed of sulfapyridine and 5-aminosalicylic acid moieties and should be avoided in patients allergic to sulfa medications. Plasma half-life is greatly influenced by acetylation status, and slow acetylators are more likely to develop serious toxicities. While minor upper GI side effects and rashes are common, drug-induced hepatitis, cytopenias and Stevens–Johnson syndrome may also occur.

Hydroxychloroquine—Hydroxychloroquine is an antimalarial with proven efficacy in the treatment of RA, particularly in early and mild disease. Unlike its sister drug, chloroquine, occurrence of retinopathy is extremely rare. However, evidence for radiological protection has been unconvincing, and this benign medication in most often used in conjunction with other DMARDs in combination therapy rather than alone.

**Box 13.1 Side effects of methotrexate**

- Mucosal ulceration
- Alopeia
- Gastrointestinal—nausea and vomiting, oesophagitis, anorexia, diarrhoea, gingivitis, GI bleeding, GI perforation, pancreatitis, elevated transaminases, cirrhosis
- Bone marrow suppression—anaemia, leucopenia, thrombocytopenia, aplastic anaemia, malignancy—lymphoproliferative disorders
- Infections
- Interstitial pneumonitis
- Renal impairment
- Teratogenesis

**Box 13.2 Other DMARDs in use**

- Penicillamine
- Azathioprine
- Cyclophosphamide
- Ciclosporin
- Tacrolimus
- Mycophenolate mofetil
- Minocycline

**Leflunomide**—The youngest member among the DMARDs, leflunomide inhibits the de novo synthesis of pyrimidines by inhibiting dihydroorotate dehydrogenase, and this action principally affects lymphocytes which lack salvage pathways for pyrimidine synthesis. It may be useful in patients who have failed to respond to methotrexate, but can also be administered together with methotrexate to improve response. It has a long half-life, requiring a loading dose for 1–3 days. As a long washout period of up to 2 years is suggested prior to conception, careful planning is needed in premenopausal women.

Some of the other DMARDs in use are listed in Box 13.2.

**Combination therapy**

Although DMARDs represent a marked improvement over previous symptom-oriented therapies, response to monotherapy is often partial at best, and discontinuation, whether due to toxicity or lack of response, is commonplace. It has been suggested that using these medications with different but complementary mechanisms of action in combination not only allows for greater efficacy, but also limits effective required dosage and hence toxicity. Various combinations, including step-up and step-down regimens have been tried, often with the inclusion of methotrexate.

**Biological-response modifiers**

A major development in the treatment of RA in the last decade was the emergence of biological-response-modifying therapy. Previous attempts at drug development have largely been empirical efforts. Understanding of the molecular and cellular mechanisms that contribute to the generation and maintenance of the inflammatory processes that culminate in synovial inflammation and joint destruction has escalated astronomically in recent decades. These fundamental elements of the inflammatory cascade, whether it be a cytokine or an inflammatory cell subset, have become the targets of new treatment modalities. These drugs are administered parenterally, and the onset of action, unlike DMARDs, is rapid.

**Tumour necrosis factor antagonists**

Tumour necrosis factor (TNF) is a pivotal cytokine released in excess in RA, and is a major contributor to synovial inflammation and cartilage destruction. Blockade of its actions by the human TNF receptor 2–immunoglobulin constant region fusion protein, etanercept, resulted in the first success of biological-
response-modifying therapy in RA. Since then, monoclonal antibodies to human TNF have come into use, whether chimeric (infliximab) or fully humanized (adalimumab). These agents have been demonstrated to be efficacious in the treatment of RA on clinical, radiological and laboratory measures, particularly when used in combination with methotrexate.

Anakinra

The next cytokine to be targeted for therapeutic use was interleukin-1 (IL-1) and anakinra is a recombinant human IL-1 receptor antagonist. Its short half-life means that subcutaneous injections have to be given on a daily basis. Used alone or in combination with methotrexate, anakinra produces significant if modest clinical improvement in RA. Radiological improvement, including rates of progression of joint-space narrowing and erosion, have been more striking, however.

Rituximab

The B-lymphocyte is not only the source of inflammatory cytokines and antibodies important to the pathogenesis of the disease such as rheumatoid factor and anti-cyclic citrullinated peptide; B-cell help is a vital contributor to T-cell activation and antigen presentation. It is therefore little surprise that the B-lymphocyte may be a suitable target for RA therapy, despite previous dogma that RA is predominantly a T-cell-mediated disease. Rituximab targets the B-cell surface marker, CD20, which is expressed from the pre-B-cell stage through to the mature memory B-cell. Binding of this chimeric monoclonal antibody depletes CD20+ B-cells in a transient manner. Rituximab, whether alone or in combination with methotrexate, is effective at suppressing inflammatory parameters and limiting structural joint damage in RA, although seronegative patients have responded less well. While the risk of infection cannot be overlooked. Advances in orthopaedic surgery have also furthered situations such as atlanto-axial subluxation, arthroplasty and tendon transfer and repair surgeries.

Further reading


Chan ESL, Cronstein BN. Drugs that modulate the immune response. In: Samter’s Immunologic Diseases, 6th edn. Lippincott Williams & Wilkins 2001: 1213–1223.


The spondyloarthritides (SpA) comprise a group of syndromes that are distinct from rheumatoid arthritis and are characterized by inflammation of the spine in many, but not all, cases. Other key features include asymmetric oligoarthritis, enthesitis, psoriatic skin and mucosal lesions and overt or covert inflammatory bowel disease.

Tests for rheumatoid factor, anti-cyclic citrullinated peptide antibody and other autoantibodies are negative, but there is a strong association with the human leukocyte antigen (HLA) B27.

Spondyloarthritides occur in both adults and children, although spinal involvement is rare in children. A working definition has been provided by the European Spondyloarthritis Study Group (Box 14.1). A diagnosis of SpA requires one or two of the entry criteria plus one other. Skin, eye and bowel disease may become apparent only with the passage of time.

The classical forms of spondyloarthritis (also called “spondyloarthropathies”) and the key physical features are listed in Table 14.1.

<table>
<thead>
<tr>
<th>OVERVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Spondyloarthritides as a group occur with a similar prevalence to rheumatoid arthritis.</td>
</tr>
<tr>
<td>• The various spondyloarthritic syndromes share common clinical lesions, especially enthesitis, oligoarthritis, sacroiliitis, iritis, psoriasiform skin and mucosal lesions and overt or covert inflammatory bowel disease.</td>
</tr>
<tr>
<td>• Inheritance of HLA-B27 and other genes is common to all spondyloarthritides, the prevalence of these disorders varying with the local prevalence of HLA-B27.</td>
</tr>
<tr>
<td>• Diagnosis of ankylosing spondylitis is often long delayed; identification of inflammatory back pain is a key determinant in making the diagnosis early.</td>
</tr>
<tr>
<td>• Use of anti-tumour necrosis factor biologic drugs has revolutionized the treatment of severe ankylosing spondylitis.</td>
</tr>
</tbody>
</table>

Box 14.1 The European Spondyloarthropathy Study Group Criteria for Spondyloarthropathy

- Inflammatory spinal pain (defined as low back pain with morning stiffness, better on exercise, in patients <40 years old) or
- Asymmetric or predominantly lower limb synovitis plus
- Any one or more of the following: psoriasis, inflammatory bowel disease, alternating buttock pain, enthesopathy, sacroiliitis

Together, spondylarthritides are roughly as common as rheumatoid arthritis in Europe and North America, although their prevalence varies in other areas, generally reflecting the prevalence of HLA-B27 in that population. Their prevalence and that of associated conditions is presented in Table 14.2.

Ankylosing spondylitis

Ankylosing spondylitis (AS) is an aseptic inflammatory condition of the joints and entheses of the spine. AS occurs in 0.2% of the general population, in 2% of the B27-positive population and in 20% of B27-positive individuals with an affected family member. Males predominate with a male:female ratio ranging from 2.5:1 to 5:1. AS typically begins in young adulthood, but symptoms may arise in adolescence or earlier. Up to 15% of children with juvenile idiopathic arthritis are classified as having juvenile-onset spondyloarthritis. Such children present with pauciarticular peripheral arthritis with a predilection for the tarsal joints; axial complaints, with the development of radiographic sacroiliitis, tend only to develop in late teenage years or later.

The first symptom of AS is usually inflammatory back pain—the insidious onset of low back pain and/or buttock pain that persists for more than 3 months, awakens the patient from sleep, is accompanied by early morning stiffness and is typically improved by exercise. Fatigue often accompanies inflammatory back pain, although it may also be present in fibromyalgia and other conditions. Inadequately controlled inflammation leads to persistent stiffness and progressive loss of spinal mobility.
ABC of Rheumatology

Involvement of the hip can occur at any point in the course of AS and may be highly destructive. Enthesitis— inflammation at attachments of tendon or ligament to bone—is also a characteristic feature of AS. Enthesitis at the calcaneal attachments of the Achilles tendon, usually accompanied by Achilles tendon bursitis (Figure 14.3) and plantar fascia, producing sometimes disabling heel pain, is highly characteristic of AS, although it also occurs in other SpAs. Dactylitis, usually affecting a toe (“sausage toe”) (Figure 14.4), is also strongly suggestive of an SpA.

Ocular inflammation, usually acute anterior uveitis (iritis), occurs at some time in up to 40% of AS patients. Acute anterior uveitis typically causes pain, photophobia and, if untreated, impairment in visual acuity. Typically, it is unilateral and recurrent. Uncommon extra-articular manifestations of AS include aortic insufficiency, cardiac conduction defects and pulmonary fibrosis.

Table 14.1 Examples of spondyloarthropathies

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>Sacroilitis</td>
</tr>
<tr>
<td></td>
<td>Enthesitis</td>
</tr>
<tr>
<td></td>
<td>Spondylitis</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Oligoarthritis</td>
</tr>
<tr>
<td></td>
<td>Dactylitis</td>
</tr>
<tr>
<td></td>
<td>Skin and mucous membrane inflammation</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Reactive arthritis (Reiter’s syndrome)</td>
<td>Genito-urinary inflammation, iritis</td>
</tr>
<tr>
<td></td>
<td>Small and large bowel inflammation</td>
</tr>
<tr>
<td>Enteropathic arthritis</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated spondyloarthritis</td>
<td>Possible infectious trigger</td>
</tr>
<tr>
<td>Childhood spondyloarthritis</td>
<td>Associated with HLA-B27</td>
</tr>
</tbody>
</table>

Table 14.2 Prevalence of spondyloarthropathies

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%) per 100,000</th>
<th>male:female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>0.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>2000</td>
<td>1.0</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>20 – 100</td>
<td>1.3</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>16</td>
<td>3.0</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>30 – 75</td>
<td>1.0</td>
</tr>
<tr>
<td>Ulcerative disease</td>
<td>50 – 100</td>
<td>0.8</td>
</tr>
<tr>
<td>Enteropathic arthritis</td>
<td>1–20% of inflammatory bowel disease</td>
<td>*</td>
</tr>
</tbody>
</table>

*Peripheral arthritis occurs more in women; sacroilitis and spondylitis more often affect men

Box 14.2 The modified New York criteria for ankylosing spondylitis (1984)

A. Diagnosis
   1. Clinical criteria
      a. Low back pain and stiffness >3 months with improvement on exercise, not relieved by rest
      b. Limitation of spinal motion in both sagittal and frontal planes
      c. Limitation of chest expansion
   2. Radiologic criteria
      Sacroilitis: Grade ≥2 bilaterally or Grade 3–4 unilaterally

B. Grading
   1. Definite ankylosing spondylitis if the radiologic criterion is associated with >1 clinical criterion
   2. Probable ankylosing spondylitis if:
      a. the three clinical criteria are present
      b. the radiologic criterion is present without any signs or symptoms satisfying the clinical criteria

Box 14.3 Characteristics of inflammatory back pain (in patients <50 years old)

- Morning stiffness >30 minutes duration
- Improvement in back pain with exercise but not with rest
- Awakening because of back pain during the second half of the night only
- Alternating buttock pain

If none of four parameters present post-test probability of AS 1.3%
If one of four parameters present post-test probability of AS 2.6%
If two of four parameters present post-test probability of AS 10.8%
If three or more parameters present post-test probability of AS 39.4%, with sensitivity of 33.6% and specificity of 97.3%
(See Rudwaleit et al.)

The diagnosis is based on the modified New York criteria (Box 14.2). Radiographic assessment is a key element of these criteria: classical changes in the sacroiliac joints include erosions in the joint line, pseudowidening, subchondral sclerosis and finally ankylosis, reflected as obliteration of the sacroiliac joint. Radiographs of the spine may reveal squaring and “shiny corners” of the vertebral bodies and, later, syndesmophytes and facet-joint fusion (Figure 14.1). As radiographic sacroilitis often develops late, early diagnosis may be based on symptoms of inflammatory back pain (Box 14.3) combined with magnetic resonance imaging (MRI) evidence of sacroilitis (Figure 14.2).

HLA-B27 is rarely the definitive factor for diagnosis, but when the clinical suspicion is high, the test has reasonably high sensitivity and specificity.

Up to 30% of patients with AS also develop peripheral arthritis. Typically this is asymmetrical oligoarthritis affecting leg joints, most commonly the knee. Involvement of the hip can occur at any point in the course of AS and may be highly destructive. Enthesitis—inflammation at attachments of tendon or ligament to bone—is also a characteristic feature of AS. Enthesitis at the calcaneal attachments of the Achilles tendon, usually accompanied by Achilles tendon bursitis (Figure 14.3) and plantar fascia, producing sometimes disabling heel pain, is highly characteristic of AS, although it also occurs in other SpAs. Dactylitis, usually affecting a toe (“sausage toe”) (Figure 14.4), is also strongly suggestive of an SpA.
Assessment of ankylosing spondylitis

In recent years several instruments have been devised for measuring disease activity, overall function, severity and progression of AS. Those most widely used are detailed below.

**Disease Activity**—Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). A patient-completed set of six visual analogue scales assessing symptoms. The erythrocyte sedimentation rate and C-reactive protein are typically elevated, but levels do not usefully indicate inflammatory activity of spinal disease.

**Overall patient function**—Bath Ankylosing Spondylitis Functional Index (BASFI). A similar patient-completed set of 10 visual analogue scales assessing normal daily activities.

**Spinal mobility**—Bath Ankylosing Spondylitis Metrology Index (BASMI). A composite score derived from measurements of spinal mobility.

**Radiologic progression**—Modified Stoke AS Spinal Score (mSASSS). This uses lateral radiographs of the cervical and lumbosacral spine and can detect change over 2 years. It evaluates the anterior part of the lumbar spine and cervical spine and assesses chronic changes at each level with a score of 0 to 3 (0 = normal; 1 = erosion, sclerosis or squaring; 2 = syndesmophyte; 3 = bridging syndesmophyte).
Psoriasis occurs in 5% of most white populations, and 5–15% of sufferers develop one or another form of associated arthritis. In a small minority of patients arthritis precedes the onset of psoriasis.

Typical psoriatic nail changes such as pitting, onycholysis and hyperkeratosis are seen in over 80% of patients with psoriatic arthritis, although skin lesions may be subtle and should be sought specifically in the scalp and natal cleft. Arthritis is characteristically oligoarticular and asymmetrical and may be associated with dactylytis of fingers or toes, often described as a “sausage digit” (Figure 14.4). Distal interphalangeal joint involvement at the fingers is uncommon but highly characteristic (Figure 14.5). Enthesitis plays a role in dactylytis but may also occur at more typical sites around the patella or around the heel at the Achilles tendon or plantar fascia insertion. Twenty per cent of patients with psoriatic arthritis develop low back pain with sacroiliitis and may develop typical or atypical spondylitis. Conjunctivitis and anterior uveitis may occur but less commonly than in AS.

Psoriatic arthritis

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis, usually with negative tests for rheumatoid factor. It is not a homogeneous clinical entity. In common with other spondyloarthritides, the key features are seronegative arthritis, enthesitis and, in a minority, sacroiliitis or spondylitis. It is the only SpA in which small joints of the hand are frequently affected. Five patterns of joint involvement are recognized (Box 14.4), although many patients have overlapping patterns of disease.

<table>
<thead>
<tr>
<th>Box 14.4 Patterns of psoriatic arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Asymmetrical oligoarthritis (50%); involvement of one to five joints</td>
</tr>
<tr>
<td>• Predominantly distal interphalangeal joint disease (5–10%); distinctive but unusual form of psoriatic arthritis</td>
</tr>
<tr>
<td>• Rheumatoid pattern (25%); symmetrical small-joint arthritis particularly affecting metacarpophalangeal, wrist and proximal interphalangeal joints; may be indistinguishable from rheumatoid arthritis</td>
</tr>
<tr>
<td>• Arthritis mutilans (1–5%); osteolysis results in destruction of the small joints of the digits with shortening</td>
</tr>
<tr>
<td>• Spondyloarthritis (20%); may be isolated sacroiliitis, atypical or typical AS</td>
</tr>
</tbody>
</table>

The clinical course and disease severity of AS are highly variable. Inflammatory back pain and stiffness dominate the picture in the early stages, whereas chronic pain and deformity may develop over time. Osteoporosis tends to develop early in the disease, predisposing to spinal fractures later. One-third of AS sufferers give up work before retirement age because of their disease.
Reactive arthritis

Reactive arthritis (ReA) is aseptic arthritis that occurs subsequent to an extra-articular infection, typically of the gastrointestinal (GI) or genito-urinary (GU) tract. The key GI pathogens are *Salmonella typhimurium*, *Yersinia enterocolitica*, *Shigella flexneri* and *Campylobacter jejuni*; the commonest GU pathogen is *Chlamydia trachomatis*. The true incidence and prevalence of ReA are not well defined. In epidemics involving *Salmonella* or *Yersinia*, ReA develops in up to 7% of infected individuals, but in as many as 20% of B27-positive individuals. In such epidemic studies, B27 confers risk not only for the onset of arthritis but also for axial involvement and chronicity. Typically, arthritis begins 1 to 3 weeks after the GI or GU infection.

As with other SpA syndromes, the pattern of joint involvement in ReA is one of asymmetrical oligoarthritis mainly affecting joints of the leg. As in AS, enthesitis may arise as Achilles tendonitis or plantar fascitis, and dactylitis may occur at one or more toes. Sacroilitis, with buttock pain, may occur in the acute phase, but radiographic changes are seen largely in the patients with a chronic course.

When ReA is accompanied by urethritis, conjunctivitis or mucocutaneous lesions, the term “Reiter’s syndrome” may be applied, but increasingly ReA is used to refer to this symptom complex. Urethritis may be manifest as dysuria or discharge and psoriasiform skin, and mucosal lesions include circinate balanitis and keratinoderma blennorrhagicum (Figure 14.6), a painless papulosquamous eruption on the palms or soles. Painless lingual or oral ulcers may also be seen. Conjunctivitis is usually bilateral and painful. Acute anterior uveitis is usually unilateral and may not be synchronous with the acute episode but may be clinically indistinguishable from conjunctivitis.

The most important differential diagnosis for ReA is septic arthritis, so appropriate culture of synovial fluid should precede the diagnosis of ReA whenever possible. The course of ReA is variable, and few prognostic markers are available for the clinician to predict the course in any individual case. The majority of patients have an initial episode lasting 2 to 3 months, but synovitis may persist for a year or longer. In patients with chronic disease a significant minority develop some degree of functional disability.

Enteropathic arthritis

Enteropathic arthritis is an inflammatory arthritis associated with inflammatory bowel disease (IBD), particularly ulcerative colitis and Crohn’s disease. Two patterns of peripheral joint involvement are recognized, designated type 1 and type 2. Usually bowel and joint symptoms occur independently, and arthritis may wax and wane over many years. Non-specific arthralgia and myalgia without an inflammatory component, similar to that seen in fibromyalgia, is not uncommon in people with IBD.

Type 1 arthropathy affects approximately 5% of patients with IBD. Typically the peripheral arthritis is oligoarticular and principally affects the knees. It is usually self-limiting without leading to joint deformities. Joint symptoms can occur early in the course of bowel disease and may precede the onset of bowel symptoms. Enthesitis of the Achilles tendon and plantar fascia and dactylitis may also occur.

Type 2 arthropathy affects approximately 3% of patients with IBD. Arthritis is usually polyarticular, principally affecting the metacarpophalangeal joints, although the knees, ankles, elbows, shoulders, wrists, proximal interphalangeal joints and metatarsophalangeal joints may also be affected, sometimes in a migratory fashion.

Sacroilitis and spondylitis occur in up to 20% of patients with either form of IBD. The course of spinal involvement is completely independent of the course of the IBD and may precede by years the first manifestations of bowel disease.

Undifferentiated spondyloarthritis

The development of inflammatory back pain or peripheral large joint arthritis, often in individuals who are positive for HLA-B27, with or without other features of the seronegative SpA but without fulfilling criteria for any particular subtype, is referred to as undifferentiated SpA. Most patients are young adults, although children may be affected; a proportion of cases will evolve over time to into a classifiable subset, particularly ankylosing spondylitis.

It is not unusual for the first feature of a spondyloarthritis to be an enthesitis, especially at the Achilles tendon or plantar fascia. These lesions may also occur independently of any arthritic conditions, especially in athletes. In spondyloarthritis, Achilles tendinitis typically affects the actual entheseal junction, often with marked
bone oedema visible on MRI scanning and sometimes with Achilles tendon bursitis; in athletes pain and tendon swelling occur higher up in the tendon close to the muscle belly. Plantar fasciitis is not so easily differentiated, although it often occurs in overweight older adults.

There are no diagnostic criteria for undifferentiated SpA per se; however, the European Spondyloarthritis Study Group (ESSG) has set out criteria, as in Box 14.1.

**Treatment**

The goals of treatment are to relieve symptoms, improve function and delay or prevent structural damage. To some extent treatment of spinal inflammation differs from that of peripheral joint synovitis and enthesitis, so treatment must be tailored to the actual problems in the individual patient at the time.

**Sacroilitis and spondylitis**

*First-line treatment*—Regular physiotherapy and encouragement to exercise regularly; use of non-steroidal anti-inflammatory drugs (NSAIDS), such as naproxen or diclofenac, or COX-2 inhibitors such as etoricoxib or celecoxib.

*Second-line treatment*—Oral and intramuscular corticosteroids may control spinal symptoms, but long-term use should be avoided; local corticosteroid injections into one or both sacroiliac joints under radiographic imaging may be helpful.

*Third-line treatment*—Anti-tumour necrosis factor agents have been proven significantly to reduce spinal pain and stiffness and to increase spinal movement and patient function; reduction of spinal inflammation has been demonstrated by MRI scanning.

*Adjunctive treatment*—Bisphosphonates, calcium and vitamin D may improve bone density, although fracture reduction has not been demonstrated in AS; low-dose amitriptyline at night may improve sleep and reduce pain and fatigue.

**Oligoarthritis and/or enthesitis**

*First-line treatment*—Analgesics such as paracetamol/acetaminophen or codeine-based drugs may be helpful; intra-articular or intra-lesional corticosteroid injection can be useful for single peripheral joint involvement or enthesitis; injections into weight-bearing tendons should be avoided; NSAIDs may provide symptomatic relief (they must be used with caution in patients with IBD, as they may exacerbate the gut disease); orthotics, including heel pads, and carefully chosen footwear, including suitable trainer/running shoes, may provide the best symptomatic relief for arthritis or enthesitis affecting the feet; in patients with ReA, genital tract infection should be treated as in uncomplicated infection, with treatment of sexual contacts; antimicrobial treatment of gut infection is not usually indicated, and there is no clear evidence for long-term antimicrobial treatment of established arthritis.

*Second-line therapy*—Disease-modifying anti-rheumatoid drugs (DMARDs) may be effective for those patients with aggressive, erosive or polyarticular disease, as in the treatment of rheumatoid arthritis; methotrexate may be effective for both skin and joint disease, although the published evidence is scant; in individuals with enteropathic arthritis, sulphasalazine may be effective for both joint and bowel disease; rigorous monitoring of DMARD therapy, according to established practice guidelines, should be undertaken; oral or intramuscular corticosteroid treatment may be effective, especially in those with marked systemic features; in psoriatic arthritis, steroid therapy carries a risk of an exacerbation of skin disease on steroid withdrawal.

*Third-line treatment*—In those patients who have an inadequate response to conventional DMARDs and in whom the diagnosis is well established, anti-tumour necrosis factor therapy with etanercept, infliximab or adalimumab may be dramatically effective in the control of joint and skin disease; etanercept has not been shown to be effective for IBD.

**Further reading**


Introduction

The diagnosis of arthritis or other rheumatic conditions in children requires an awareness of the age-dependent manifestations of such conditions, skill in history taking, a meticulous approach to physical examination and judicious use of investigations. Such conditions may present with relatively common, non-specific, “constitutional” paediatric symptoms such as fever, rash, fatigue, weakness, anorexia and pain. Individually, or in combination, these are most likely to be features of common, insignificant, transient illnesses. Rheumatic diseases usually have additional clues, albeit subtle ones, that should alert the clinician to a possible rheumatic diagnosis. In arthritic disorders, joint swelling is the pivotal feature, but others include characteristic “rheumatic patterns” of fever, rash, weakness, diurnal variation or disease progression despite simple measures.

The key signs on physical examination may also be subtle, requiring experience and skill to discern and interpret them. A thorough physical examination (including detailed musculoskeletal assessment) of any child with potential rheumatic symptoms is essential. Joint swelling and pain with movement usually confirm the presence of arthritis (note that isolated joint pain/joint tenderness without swelling are features of arthralgia). Investigations, especially during the first few weeks of illness, are aimed at ruling out the long list of conditions that comprise the differential diagnosis of childhood arthritis.

Juvenile idiopathic arthritis (JIA) is the most likely diagnosis in children with persistent symptoms and clinical features of arthritis for at least 6 weeks (Box 15.1), as most other illnesses either resolve or are treated and referred to other specialists during this time period. For the experienced paediatric rheumatologist, the child with arthritis or other chronic rheumatic illness presents with an almost instantly recognizable pattern of symptoms. The lack of timely detection of childhood inflammatory disease and delay in treatment may adversely affect the course and outcome of JIA. There are also dangers inherent in trying to make the diagnosis of JIA too precipitously, without ruling out other rare but important disorders, such as septic arthritis or malignancy. Diagnostic imaging and laboratory investigation must always be carefully considered, but there is no pathognomonic test for JIA. Disproportionate over-investigation may increase child and family anxiety without adding value to the diagnostic process. The overzealous investigator may even exacerbate the severity of some conditions, such as chronic idiopathic pain syndromes.

This chapter aims to give an overview of JIA, including clinical features, differential diagnosis, investigations, natural history and principles of treatment. No substitute exists, however, for actual clinical experience, and the reader is strongly recommended to practise the skills of paediatric musculoskeletal examination at every appropriate opportunity. An appreciation of the range of normality in children and young people is an absolute prerequisite to the detection of abnormality.
Clinical features of JIA

JIA is one of the most common physically disabling conditions of childhood, with a prevalence of approximately one in a thousand children under the age of 16 years (surveys suggest that this may be higher, even as many as 4 in 1000 children; 10,000–40,000 affected children in the UK and up to 300,000 in the USA). The incidence of JIA is 1 in 10,000. In typical general practice, however, JIA is rare; one new case may be seen every 20 years. It is difficult to maintain a high index of suspicion for JIA in the face of this degree of rarity.

Most affected children are in their preschool or early school years, and often have difficulty describing their symptoms. Parents may notice joint swelling if one or more large peripheral joints are involved, such as the knee (the most common joint affected), ankle or wrist. It is rarer for children to present with isolated small joint (finger or toe) arthritis or axial joint involvement (such as the shoulder, hip, spine or temporomandibular joints), and parents are also less likely to notice swelling in these joints. Diurnal variation of symptoms, such as early morning joint stiffness or exacerbation after prolonged rest (joint “gelling”) are characteristic. Stiffness improves with movement and may be helped by a warm bath or shower. Duration of morning stiffness may provide an index of improvement with treatment. Joint dysfunction may be manifest by limping, difficulty with writing or inability to carry out other activities of daily living (Table 15.1).

There is accumulating evidence that the natural history of JIA may not be as benign as first thought; between a third and a half of symptoms, such as early morning joint stiffness or exacerbation after prolonged rest (joint “gelling”) are characteristic. Stiffness improves with movement and may be helped by a warm bath or shower. Duration of morning stiffness may provide an index of improvement with treatment. Joint dysfunction may be manifest by limping, difficulty with writing or inability to carry out other activities of daily living (Table 15.1).

Table 15.1 Typical symptoms of juvenile idiopathic arthritis

<table>
<thead>
<tr>
<th>Present in all forms of JIA</th>
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</thead>
<tbody>
<tr>
<td>Joint symptoms (pain, dysfunction, stiffness), particularly after sleep or prolonged sitting</td>
</tr>
<tr>
<td>Persistent joint swelling, particularly of the knee, ankle, wrist and small joints of the hand</td>
</tr>
<tr>
<td>Difficulty chewing, asymmetric mouth opening and micrognathia</td>
</tr>
<tr>
<td>Muscle atrophy</td>
</tr>
<tr>
<td>Flexion contracture deformity</td>
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<tr>
<td>Synovial hypertrophy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Constitutional symptoms (dramatic in children with systemic arthritis but mild in polyarthritis and ERA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (high and frequent in systemic arthritis, low grade in polyarthritis, no pattern in ERA)</td>
</tr>
<tr>
<td>Rash (maculopapular, recurrent in systemic arthritis, nodules in polyarthritis, rheumatoid factor+, psoriasis and nail pitting in psoriatic arthritis)</td>
</tr>
<tr>
<td>Growth failure (almost always severe in systemic arthritis, mild in polyarthritis and localized to specific bones in oligoarthritis)</td>
</tr>
</tbody>
</table>

ERA = enthesitis-related arthritis

induce early disease remission, an approach that has been complemented recently by a wider therapeutic armamentarium. Several targeted biologic drugs have been shown to be beneficial in JIA.

Physical findings in JIA

Peripheral joint arthritis in children is usually accompanied by joint swelling. In the knee, this may be demonstrated by ballotting synovial fluid, palpating a fluid thrill on joint movement, eliciting a positive patella tap, or occasionally finding a Baker’s cyst in the popliteal fossa. Swelling of the ankle may distort the contours of medial or lateral malleoli. When the ankle is dorsiflexed, the usually prominent anterior tendon surface markings may be obscured by arthritis, although this may be difficult to see in infants and overweight children. Other relevant observations include muscle wasting, particularly of the vastus medialis and gastrocnemius, and leg length discrepancy, which often indicates accelerated growth around affected joints.

Wrist arthritis may be best appreciated by asking the child to press the palms of their hands together in the “prayer” position; a dorsal bulge and reduced range of movement, especially if it is asymmetrical, are consistent features of synovitis. Swelling of the elbow can be palpated on either side of the olecranon and usually results in a flexion deformity of the elbow. Elbow swelling obscures the posterior dimple created when the elbow is fully extended.

The small joints of the hands and feet should be inspected and palpated individually; reliable signs of synovitis are the presence of joint margin tenderness, restricted movement, swelling and purplish discoloration, incomplete fist closure and diminished grip strength. Cervical spine involvement may be detected by inability to rotate the head laterally to place the chin on each shoulder and by reduced cervical extension. Temporomandibular synovitis is often missed; it may prevent full and symmetrical opening of the mouth. Involvement of sacroiliac joints and low back in patients with enthesitis-related arthritis (ERA) can be documented by a limited modified Schober test (less than 6 cm expansion of lumbar spine with forward bending) and documentation of tenderness of sacroiliac joints to direct palpation. Enthesopathy, a hallmark of ERA, is found at tendon insertions into bones, most frequently where the Achilles tendon inserts into the calcaneus. Careful observation of gait allows the examiner to evaluate the function of lower limb joints.

Children with JIA have a variety of extra-articular physical findings that help establish the diagnosis. For example, children with systemic arthritis may have little in the way of articular signs initially, but other characteristic features may be prominent, including a pink, macular, truncal rash (which may be pruritic and exhibit Koebner’s phenomenon), lymphadenopathy, hepatosplenomegaly and myalgia. Children with oligoarthritis tend to appear very healthy and have few findings aside from arthritis (most frequently the knee). If asymptomatic chronic anterior uveitis has preceded the onset of arthritis, posterior synechiae and/or band keratopathy may be visible with a hand-held ophthalmoscope focused on the lens.

Once the presence of arthritis is confirmed objectively, it is vital to exclude conditions that may mimic JIA. Most serious among
these are infection-related conditions (septic arthritis, osteomyelitis), trauma (including non-accidental injury), neoplasia (particularly acute lymphoblastic leukaemia and neuroblastoma), hidden inflammatory disorders (Crohn’s disease and ulcerative colitis), acute inflammatory conditions (such as Kawasaki disease and Henoch–Schönlein purpura [HSP]), and other childhood rheumatic conditions such as reactive post-infectious arthritis, systemic lupus erythematosus (SLE) and its variants (mixed connective tissue disease [MCTD]), SLE for antiphospholipid antibodies [APLA], subacute cutaneous lupus erythematosus [SCLE]), dermatomyositis (DMS), vasculitis syndromes and systemic sclerosis. Differentiating mechanical disorders and pain amplification syndromes from arthritis represents one of the greatest challenges in paediatric rheumatology.

An explanation of terms

“Juvenile idiopathic arthritis” is an umbrella term that has replaced previous nomenclatures, including juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA). The hallmark of JIA is persistent joint swelling in the absence of any defined cause in someone who is 16 years old or younger. Under the umbrella of JIA, children with at least seven unique types of arthritis can be classified both clinically and biologically, including the previously described onset subtypes of JRA/JCA (systemic-onset JRA/JCA, now called systemic arthritis; polyarticular-onset JRA/JCA, renamed polyarthritis; and pauciarticular-onset JRA/JCA, replaced by oligoarthritis), psoriatic arthritis (previously an illness separate from JRA) and enthesitis-related arthritis (ERA), which includes all of the conditions previously called (undifferentiated) spondyloarthropathy syndromes, seronegative arthritis and enthesopathy (SEA) syndrome and HLA-B27-related arthritis syndromes. In total, 95% of children and adolescents with JIA have a disease that is clinically and immunogenetically unique, and only 3–5% have features in common with rheumatoid arthritis (RA) of adulthood. The term adult-onset Still’s disease is used when a patient older than 16 years of age develops systemic arthritis.

Differential diagnosis of JIA

Many common conditions of childhood present with musculoskeletal symptoms (Table 15.2; Box 15.2). The most frequent of these are mechanical disorders such as hypermobility and trauma, (including non-accidental trauma), followed by infectious and post-infectious illnesses, malignancies, acute and chronic inflammatory disorders and the idiopathic amplification pain syndromes. In young patients it is important to consider genetic disorders of inborn errors of metabolism, and in children with recurrent fevers the auto-inflammatory disorders need to be ruled out.

Mechanical disorders

Joint pain secondary to hypermobility is the most common non-inflammatory cause of pain in children newly referred to a paediatric rheumatologist (Box 15.3). In general, younger children are more flexible than older adolescents (babies and toddlers’ joints are extremely mobile, and the finding of flat feet in children of this age is normal), girls are more flexible than boys, and black children are more flexible than their white peers. These children may complain of pain after physical activity and in the evenings, unlike patients with JIA who feel worse in the mornings and with rest and better as the day progresses. The physical examination demonstrates an extra 10–15° degrees if motion in lax joints. Hypermobility may be localized or diffuse. Much of the musculoskeletal pain is confined to the lower limbs and low back. Lower limb findings may be improved by the use of custom-moulded semi-rigid insoles with shock-absorbing posts (as indeed may other postural abnormalities of the feet) that aim to support the longitudinal foot arch and stabilize the ankle. To be successful, such insoles need specialized

Table 15.2 Differential diagnosis of juvenile idiopathic arthritis

<table>
<thead>
<tr>
<th>Presenting with a single inflamed joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile idiopathic arthritis: oligoarthritis, psoriatic arthritis or ERA</td>
</tr>
<tr>
<td>Septic arthritis: bacterial or tubercular: osteomyelitis</td>
</tr>
<tr>
<td>Lyme disease</td>
</tr>
<tr>
<td>Reactive arthritis: secondary to bacterial or viral infections</td>
</tr>
<tr>
<td>Haemarthrosis: secondary to trauma (including non-accidental) or bleeding disorder</td>
</tr>
<tr>
<td>Malignancy: leukaemia or neuroblastoma most common</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting with more than one inflamed joint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile idiopathic arthritis: polyarthritis (RF-positive or -negative), psoriatic, ERA or systemic arthritis</td>
</tr>
<tr>
<td>Other connective tissue diseases: SLE, juvenile dermatomyositis, sarcoidosis, Sjögren’s syndrome, MCTD</td>
</tr>
<tr>
<td>Reactive arthritis: secondary to bacterial or viral infections</td>
</tr>
<tr>
<td>Lyme disease</td>
</tr>
<tr>
<td>Malignancy: leukaemia or neuroblastoma most common</td>
</tr>
<tr>
<td>Immunodeficiency state-associated arthritis</td>
</tr>
<tr>
<td>Inflammatory bowel disease-associated arthritis</td>
</tr>
<tr>
<td>Other: chronic recurrent multifocal osteomyelitis, CINCA (also known as NOMID) and auto-inflammatory disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presenting with systemic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arthritis</td>
</tr>
<tr>
<td>Other connective tissue diseases—SLE, MCTD, Kawasaki disease, chronic vasculitis syndromes</td>
</tr>
<tr>
<td>Infection: bacterial (streptococcal, including acute rheumatic fever, tuberculosis, Gonococcus, Lyme disease and Brucella), viral (Epstein–Barr virus and hepatitis B) or parasitic (malaria)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Auto-inflammatory disorders</td>
</tr>
<tr>
<td>CINCA (NOMID)</td>
</tr>
</tbody>
</table>

CINCA = chronic infantile neurological cutaneous and arthritis; ERA = enthesitis-related arthritis; MCTD = mixed connective tissue disease; NOMID = neonatal-onset multi-system inflammatory disease; RF = rheumatoid factor; SLE = systemic lupus erythematosus
Box 15.2 **Differential diagnosis of joint swelling in children and young people**

- Juvenile idiopathic arthritis
- Infection-related disorders of joints and bones:
  - septic arthritis, osteomyelitis
  - reactive arthritis
- Connective tissue diseases, including systemic lupus erythematosus, dermatomyositis, vasculitis, scleroderma
- Trauma, including non-accidental injury
- Malignancy, including leukaemia, lymphoma, neuroblastoma, bone neoplasia
- Inherited diseases, including haemaglobinopathies, storage diseases
- Auto-inflammatory diseases, including familial Mediterranean fever (FMF), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), chronic infantile neurological cutaneous and arthritis (CINCA)/neonatal-onset multi-system inflammatory disease (NOMID)

Box 15.3 **Common lower limb findings in the benign hypermobility syndrome**

- Pes planus
- Genu recurvatum
- Out-toeing gait
- Over-pronated feet (secondary to ankle hypermobility)

Box 15.4 **Infectious agents implicated in reactive arthritis**

- Enteric bacteria are implicated in many paediatric cases of reactive arthritis but are much more common in adults with reactive arthritis than children
- Almost any infectious agent, including viruses (influenza, herpes, coxsackie, parvovirus B19 and rubella) and other bacteria, including mycoplasma, have been implicated in children and less so in adults
- Rheumatic fever and post-streptococcal reactive arthritis are both rare in European children, but they frequently occur in other parts of the world, including the USA

Source of infection should be undertaken before antibiotics are started. Arthrocentesis has the added advantage, particularly in the hip, of reducing intra-articular pressure and minimizing the risk of compromised blood supply to the epiphysis. Intravenous antibiotics are usually advocated until 48 hours after defervescence, with oral antibiotics continued until the erythrocyte sedimentation rate (ESR) has normalized and all clinical signs have resolved.

**Osteomyelitis**—Most children present with fever, bone pain and signs of toxicity. They cannot ambulate and have extreme pain at the site of infection. If the infection is located near a joint, it may cause a sterile (sympathetic) effusion that may be mistaken for arthritis. Radiographs may be normal initially or show periostial reaction; a technetium bone scan helps establish bone infection and prevent chronic osteomyelitis.

**Chronic rheumatic conditions**

**Systemic lupus erythematosus**—SLE typically presents in an adolescent girl with malaise, fever and bone or joint pain. Multi-system inflammatory disease is characteristic, but clinical manifestations are protean. SLE is rare in prepubescent children. An erythematous, acneiform facial rash may be present, and the classic photosensitive malar rash is a frequent but not a uniform finding. Most children have hair loss, mouth sores, lymphadenopathy, organomegaly, other rashes and swollen joints. Elevated blood pressure suggests renal involvement. Tests for antinuclear antibodies (ANAs) are almost always positive, but auto-antibodies such as those to double-stranded DNA and Sm, are more specific for SLE and usually present along with complement consumption. Antibodies to SSA (Ro), SSB (La) and anti-cardiolipin are positive in less than 50% of paediatric patients but should be looked for because their presence is associated with particular complications (risk of neonatal lupus syndrome and risk of thrombosis, respectively). Lymphopenia, thrombocytopenia and Coombs’ positive anaemia are regular findings. Simple urinalysis demonstrates the presence of proteinuria and casts, reflecting renal disease, the major cause of long-term morbidity that is more frequent in childhood than in adult-onset SLE. Adolescents presenting with Raynaud’s phenomenon may have MCTD, whereas those whose cutaneous manifestations that overshadow major organ involvement may have SCLE, another variant of lupus. APLA represents the newest condition associated with thrombotic events and specific
autoimmune pattern (the presence of anti-cardiolipin antibodies, lupus anticoagulant and false-positive Venereal Disease Research Laboratory test).

**Juvenile dermatomyositis**—Children with juvenile DMS may present insidiously and are often labelled as malingerers before the true nature of the diagnosis is appreciated. Typical symptoms include malaise, progressive proximal muscle weakness and muscle pain or discomfort. Arthritis is found in 20% of the patients. Dermatological manifestations include heliotrope rash (purplish discoloration and oedema of the upper eyelids) (Figure 15.1) and malar rash travelling down the naso-labial folds (malar rash in SLE spares the naso-labial folds), Gottron’s papules over the metacarpophalanges, elbows and knees (often mistaken for eczema) and cuticle hyperaemia (due to distended nailfold capillaries) (Figure 15.2). The diagnosis of juvenile DMS is usually made on the basis of typical rash and the finding of symmetrical proximal muscle weakness. Elevated serum muscle enzymes (CPK, aldolase, AST, ALT, LDH) confirm the presence of muscle inflammation. If the child has a typical rash but normal strength and enzyme levels, magnetic resonance imaging (MRI) of a large muscle demonstrates otherwise subtle inflammation on T2 images. In very weak children, respiratory failure and aspiration pneumonia may be life-threatening.

**Localized scleroderma syndromes**—Most children with scleroderma have a localized disorder characterized by areas of oval (morphea) or linear lesions that traverse over joints, face (coup de sabre deformity) and trunk (Figure 15.3). Some children have frank arthritis and occasionally may develop extensive joint limitations that mimic polyarthritis but produce paucity of inflammatory signs, except morning stiffness.

Systemic vasculitis syndromes such Wegener’s granulomatosis, polyarteritis nodosa or Churg–Strauss syndrome are extremely rare in childhood, and arthritis is not a common feature.

**Acute inflammatory conditions**

**Henoch–Schönlein purpura**—HSP is the most common vasculitis of childhood, manifested by purpuric rash over the lower legs and buttocks (Figure 15.4), often associated with cramping abdominal pain, bloody stools, haematuria and occasionally with arthritis of the ankles or knees. Haematuria is virtually always present, and proteinuria may be found, but significant renal disease is extremely rare.

**Kawasaki disease**—Arthritis is an uncommon feature at presentation in this illness of infants and toddlers; however, atypical cases of Kawasaki disease with fever, rash and elevated inflammatory markers, but without red eyes, raises the suspicion of systemic arthritis (Figure 15.5).

**Malignancy**

**Acute lymphoblastic leukaemia**—This may present with bone pain in children (sometimes primarily at night) and even frank arthritis, which can affect one, or sometimes more, joint(s). These children appear toxic and have pain over the affected bone(s). When these children present to the paediatric rheumatologist, their complete blood counts are normal, and a high level of suspicion is required. There is usually anaemia and elevated ESR. Bone-marrow biopsy confirms the presence of immature cells.
Neuroblastoma—Neuroblastoma is a particularly concerning possibility in younger children who present with fever and joint pain. Early metastases to the bone cause pain that may be difficult for the doctor to localize.

Lymphoma—Lymphoma usually affects older children and may present with musculoskeletal symptoms.

Primary bone malignancies—These are rare and usually visible on plain X-ray radiographs (Figure 15.6).

Idiopathic pain syndromes
The most dramatic musculoskeletal pain in children is often found in the idiopathic pain syndromes. These may be localized (complex regional pain syndromes) or generalized (diffuse pain syndromes, also called fibromyalgia). Exogenous stress (including school pressures, bullying or other forms of abuse, and even parental pressure) is a common accompanying feature, although often unrecognized by the parents. These children and adolescents deserve meticulous physical examination and judicious investigation to rule out an underlying organic pathology. Too much investigation and vacillating doctor-to-patient communication, however, may perpetuate or exacerbate the clinical features of these disorders. Indeed, treatment should start while investigations are ongoing, because disability is common. Occasionally, an idiopathic pain syndrome may complicate a pre-existing condition, such as juvenile idiopathic arthritis. An individualized, intensive, multi-professional, rehabilitation regimen, either in the community or on an inpatient basis, is essential to restore function.

Complex regional pain syndromes—Previously called reflex sympathetic dystrophy, complex regional pain syndromes may begin after trauma (often minor) or without a clear precipitant. They are always associated with immobility, followed by increasing pain,
Juvenile Idiopathic Arthritis

Liver function tests, creatinine kinase, aldolase, LDH—To rule out dermatomyositis.

Urinalysis—To rule out renal disease of SLE and HSP.

Immunology

Antinuclear antibodies—Positive in low titre in most children with JIA (especially oligoarthritis), and in up to 15% of the general paediatric population. High positive ANAs are seen in virtually all children with SLE and MCTD.

Rheumatoid factor—Negative in 95% of children with JIA but present in 25% of children with SLE.

Immunoglobulins—One in 500 children with JIA has a low level of immunoglobulin A (IgA). IgG is highly elevated in SLE.

Antistreptolysin “O” titre and viral serology—To help with acute rheumatic fever, post-streptococcal arthritis, viral and post-viral conditions.

Borrelia burgdorferi serology—To rule out Lyme disease if there is a history of travel in endemic areas.

Synovial fluid analysis—This is mandatory in suspected septic arthritis, but does not help in other differential diagnoses. Children do not get gout.

Investigations in children with arthritis

JIA is a label for children who fulfil classification criteria made on clinical features alone, as no diagnostic tests exist. Investigations are thus aimed at excluding a wide range of differential diagnoses. However, certain classic patterns emerge as features of history and physical examination combine with typical laboratory and imaging findings, allowing the clinician to arrive at the correct diagnosis.

Haematology

Complete blood count—To look for leucopenia, Coombs’ positive anaemia and thrombocytopenia of SLE and MCTD, as well as the elevated white blood cell (WBC) count and anaemia of chronic inflammation of systemic arthritis. Malignancy may not be ruled out without bone-marrow biopsy.

Erythrocyte sedimentation rate—ESR is elevated in systemic arthritis and SLE but normal in up to half of patients with JIA and in most children with dermatomyositis.

Bone-marrow aspirate—To exclude malignancy, especially before instituting corticosteroid treatment.

Biochemistry

C-reactive protein—C-reactive protein (CRP) is elevated in systemic arthritis but normal in up to half of patients with JIA, as well as patients with SLE, MCTD and DMS.

Urinary catecholamines—To exclude neuroblastoma.

Box 15.5 Features of complex regional pain syndrome

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Severe pain out of proportion to physical findings</td>
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<tr>
<td>Hyperaesthesia</td>
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<tr>
<td>Allodynia</td>
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<tr>
<td>Immobility of affected limb, including adopting a bizarre posture or gait</td>
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<table>
<thead>
<tr>
<th>Occasional</th>
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<tbody>
<tr>
<td>Limb swelling</td>
</tr>
<tr>
<td>Mottling of skin</td>
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<tr>
<td>Cool pallor of skin</td>
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Box 15.6 International League of Associations for Rheumatology classification of juvenile idiopathic arthritis

<table>
<thead>
<tr>
<th>Classification</th>
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<tbody>
<tr>
<td>Systemic arthritis</td>
</tr>
<tr>
<td>Oligoarthritis—persistent</td>
</tr>
<tr>
<td>Oligoarthritis—extended</td>
</tr>
<tr>
<td>Polyarthritis—rheumatoid-factor negative</td>
</tr>
<tr>
<td>Polyarthritis—rheumatoid-factor positive</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>Enthesitis-related arthritis</td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
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</table>
Systemic arthritis
Systemic arthritis usually begins in early childhood (although it can occur at any age through to adulthood), with prominent extra-articular features of high quotidian fevers (Figure 15.7), rash (Figure 15.8), myalgia, arthralgia and irritability (Box 15.7). Laboratory studies show elevated WBC count, severe anaemia, thrombocytosis, high ESR, CRP, ferritin and positive d-dimers or fibrin split products. The systemic features usually resolve after a few months but may last indefinitely. The pattern of arthritis is variable, ranging from several swollen joints to a widespread polyarticular pattern that can be very difficult to control. These children have the worst prognosis of all, not only regarding erosions and loss of joint motion but also because of severe growth delay and sequelae of chronic corticosteroid use. Macrophage activation syndrome has been associated with systemic arthritis and carries a 10–15% mortality rate. Treatment with intravenous corticosteroids and cyclosporine is usually successful in reversing rapid deterioration and disseminated intravascular coagulation.

Oligoarthritis—persistent
The most common condition under the rubric of JIA, oligoarthritis accounts for over half of all cases of JIA. It mainly affects preschool girls, with a sex ratio of 5:1. The knee is the most frequently affected joint, followed by ankle and wrist (Figure 15.9). The hip is almost never affected. This group of otherwise healthy little girls is at the highest risk for the development of chronic asymptomatic anterior uveitis (20%). Chronic anterior uveitis is clinically silent and insidiously progressive; it produces visual loss and blindness if not detected by slit lamp examination and treated early (with recommended monitoring every 3 months). It is frequently associated with positive ANAs, but all other laboratory investigations are normal. Investigations have identified a complex genetic predisposition to both oligoarthritis and uveitis. Localized growth disturbances are common; the affected leg grows longer (presumably as a result of chronic hyperaemia and increased blood supply to the
Juvenile Idiopathic Arthritis

The pattern of articular involvement in psoriatic arthritis is often asymmetrical, and tends to affect both small and large joints in a similar pattern to extended oligoarthritis, except for the presence of characteristic extra-articular features of psoriasis in a first-degree relative. Family history of a first-degree relative with psoriasis establishes the diagnosis. Asymptomatic uveitis with the same risk of blindness as in oligoarthritis affects many children, although the exact incidence is not known. These children should have a slit lamp evaluation every 3 months (Figure 15.11).

Oligoarthritis—extended
One-third of children with oligoarthritis whose disease during the first 6 months affects less than four joints continue to develop arthritis in further joints thereafter; hence the nomenclature “extended.” Many of these children have anterior uveitis. These patients have a different immunogenetic background than patients with persistent oligoarthritis and carry a prognosis similar to those with polyarthritis.

Polyarthritis—rheumatoid-factor negative
Polyarthritis accounts for 25–30% of children with JIA and usually affects preschool girls with a predominantly symmetrical arthritis of upper and lower limbs. Chronic anterior uveitis and growth disturbance are important but rare potential complications. This illness lasts most of childhood, and many children go into adulthood with active disease. These children have mild anaemia and usually positive ANAs. ESR and CRP may be mildly elevated.

Polyarthritis—rheumatoid-factor positive
This condition is similar in features and prognosis to adult RA and the only one deserving the name JRA. It affects girls primarily and usually presents in late childhood or adolescence. It affects less than 5% of patients with JIA and can be rapidly progressive and destructive. Rheumatoid nodules are common and failure to thrive more frequent than in seronegative polyarthritis. ANAs are usually positive (Figure 15.10).

Psoriatic arthritis
Arthritis may pre-date the onset of the classical skin findings of psoriasis by many years and is not required for the diagnosis in a child. The pattern of articular involvement in psoriatic arthritis is often asymmetrical, and tends to affect both small and large joints in a similar pattern to extended oligoarthritis, except for the presence of characteristic extra-articular features of psoriasis in a first-degree relative. Family history of a first-degree relative with psoriasis establishes the diagnosis. Asymptomatic uveitis with the same risk of blindness as in oligoarthritis affects many children, although the exact incidence is not known. These children should have a slit lamp evaluation every 3 months (Figure 15.11).
**Enthesitis-related arthritis**

ERA, or related conditions under the umbrella of JIA, typically begins after the age of 6 years and affects boys more often than girls. It is characterized initially by lower limb arthritis often complicated by enthesitis (inflammation of the point where tendon, ligament or fascia inserts into bone). The most common sites of enthesitis are at the insertions of plantar fascia (calcaneum, the base of the fifth metatarsal and the metatarsal heads), the insertion of the Achilles tendon into the calcaneum, and around and below the patella. Symptoms of sacroiliitis and spinal arthritis are uncommon at presentation. Although it may be a precursor illness to ankylosing spondylitis (AS), it is not known how many children with ERA progress to AS during their adult years. Uveitis affects these patients as well, but it tends to be asymptomatic, presenting with red eyes, photophobia and pain. Some adolescent boys also complain of urethritis. A family history of similarly affected relatives is often positive, and HLA-B27 antigen may be found in 50% of patients, while ANA is usually negative.

**Treatment**

**General principles**

The aim of therapy is to maintain the child’s or adolescent’s quality of life while preserving joint function for as long as the disease is active. It helps to keep in mind that humans are living longer, and thus depending longer on the preservation of joint integrity. Second only to early recognition and referral, aggressive medical approach and timely physical interventions are of paramount importance. Whenever possible, the care of a child with JIA should be provided by an efficient, multidisciplinary team, a microsystem that prides itself on patient education and outreach (Boxes 15.8 and 15.9). The team should be led by a pediatric rheumatologist working in tandem with a team of people who are expert in the specifics of paediatric rehabilitation, disease education, clinical and drug monitoring, the ethical conduct of clinical trials, school advocacy, nutrition, family and social support, and psychology. In addition, the need for ready access to other pediatric specialties, such as ophthalmology, orthopaedics, maxillofacial surgery, psychiatry, nephrology, infectious disease and dermatology, underscores the complexity of optimal management required for these children. Lastly, to fully maximize quality of care, the paediatric rheumatologist should be a member of one of the established networks of paediatric rheumatology professionals (clinicians including allied health professionals, scientists and all trainees), who collaborate in clinical trials augmented and enriched by translational research (such as the paediatric rheumatology international trials organization in Europe (PRINTO) and childhood arthritis and rheumatology research alliance (CARRA in the USA and Canada).

Hospital admission is often considered in European centres, intended for efficient initial investigation and team assessment of all patients with arthritis, particularly if they are significantly disabled or have prominent systemic features. In the USA, however, most children with arthritis, including JIA, are managed in outpatient settings, by paediatric rheumatologists heading up a painstakingly assembled multidisciplinary team. Most often, this team becomes a well-respected component of a clinical network employed within a tertiary referral structure (including children’s hospitals and large academic, university-affiliated medical institutions), managing children with complex and chronic inflammatory diseases and evaluating youngsters with symptoms that prove too challenging for their primary care physicians. Ideally, this tertiary team communicates well with the local team led by the primary care provider, or school nurse, or physio- and occupational therapists, working in a variety of community settings. Computerized systems of care will ease communication among different providers.

Drug treatment of JIA usually starts with oral non-steroidal anti-inflammatory drugs (NSAIDs). However, most patients need better control than can be accomplished with NSAIDs alone. Within 4–12 weeks, slow-acting antirheumatic drugs such as methotrexate or sulfasalazine, can be considered if signs of inflammation persist even without disability (Table 15.3). Seventy per cent of children with polyarthritis improve (much fewer with systemic arthritis do so), but many continue to have radiologic progression and risk a lifetime of disability and decreased productivity. The addition of one of the new biologic agents, such as anti-tumour necrosis factor alpha (TNF-α) receptors and monoclonal antibodies, is considered quite early in the USA, especially in children threatened with long-term disability from both chronicity and aggressiveness of their inflammatory synovitis (as documented in children with polyarthritis, systemic arthritis and psoriatic arthritis). The use of these agents has revolutionized the approach to potentially disabling arthritis in both adults and children, and the resulting outcomes have dramatically altered natural history and stopped progression of disease in thousands of patients. No longer are children with JIA kept in wheelchairs. If the experience of the last 10 years holds, prognosis is now excellent for

**Box 15.8 Members of the local community-based care team**

- Primary care provider, the patient’s general practitioner
- Rheumatologist
- Paediatrician
- Community rehabilitation and support staff
- School nurse
- Special education instructor
- Counsellor

**Box 15.9 Members of the paediatric rheumatology care team**

- Paediatric rheumatologist
- Paediatric nurse clinician
- Paediatric physiotherapist
- Paediatric occupational therapist
- Social worker
- Psychologist, parent liaison, nutritionist
Table 15.3 Drug treatment

**Non-steroidal anti-inflammatory drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Ibuprofen</td>
<td>10 mg/kg/dose four times a day</td>
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<tr>
<td>Piroxicam</td>
<td>0.2–0.3 mg/kg/dose once a day</td>
</tr>
<tr>
<td>Naproxen</td>
<td>10 mg/kg/dose twice a day</td>
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**Intra-articular corticosteroids**

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Triamcinolone hexacetonide</td>
<td>1 mg/kg/joint for large joints</td>
</tr>
<tr>
<td></td>
<td>0.5 mg/kg/joint for medium joints</td>
</tr>
<tr>
<td></td>
<td>1–2.5 mg/joint for digits</td>
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<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>Triamcinolone acetonide</td>
<td>2 mg/kg/joint for large joints</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg/joint for medium joints</td>
</tr>
<tr>
<td></td>
<td>2–4 mg/joint for digits</td>
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**Methotrexate**

<table>
<thead>
<tr>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td>0.3–1 mg/kg/dose once weekly orally or subcutaneously</td>
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**Sulfasalazine**

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<tr>
<th>Dosage</th>
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<tr>
<td>25 mg/kg/dose twice daily</td>
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**Etanercept**

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<th>Dosage</th>
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<tbody>
<tr>
<td>0.4 mg/kg/dose twice weekly or 0.8 mg/kg once weekly, both subcutaneously</td>
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</table>

**Parenteral corticosteroids**

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylprednisolone</td>
<td>10–30 mg/kg/dose daily over 1–3 days</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.2–2 mg/kg/dose once a day</td>
</tr>
</tbody>
</table>

*Need regular monitoring with blood counts, chemistry and metabolic tests and urinalysis

**Non-steroidal anti-inflammatory drugs**

Treatment of children with arthritis usually begins with NSAIDs. These are used in higher doses, relative to body weight, than in adults because children have increased rates of metabolism and renal excretion. An individual NSAID, if free of significant adverse effects, could be continued for 4–8 weeks before a judgement about efficacy is made and the treatment is escalated. Adverse effects include abdominal pain (usually minimized by taking the NSAID with food and treated successfully with ranitidine, omeprazole or misoprostol), change in mood (usually transient) and rarely, bronchospasm (mild asthma is not a contraindication to the use of NSAIDs in children). Naproxen has the additional side effect of inducing pseudo-porphyria, particularly in children with reddish-blonde hair and fair complexions.

Selective COX-2 inhibitors were tested in paediatric trials and found as effective and safe as the widely used traditional NSAIDs. However, only one, celecoxib, is labelled for use in children with arthritis, owing to increased incidence of myocardial infarction in adults. Cessation of NSAIDs may be considered if the patient has been free of active disease for at least 6 months. The majority of patients with early JIA do not respond completely to NSAIDs and need more aggressive treatment. In children with single joint involvement, an intra-articular corticosteroid with a long half-life is often recommended after 6 weeks.

**Corticosteroids**

Intra-articular preparations are the most frequently used form of corticosteroids in JIA. Triamcinolone hexacetonide has the highest efficacy and longest duration of action, although drug supplies are unreliable and at times limited within the UK and the USA. In children with oligoarthritis, intra-articular injections have largely replaced other interventions, including NSAIDs. A single injection usually resolves all signs of inflammation for several months. In the UK, intra-articular medication in children is usually given under general anaesthesia and multiple injections are common, whereas in the USA, where usually no more than one or two joints are injected, local anaesthetic is acceptable for most children.

Systemic steroids must be avoided if possible, because of a nearly unacceptable range of adverse effects, including growth and immune suppression, cataract formation, diabetes, avascular necrosis of bone, vertebral collapse and the horrible and
predictable physical changes of Cushing’s stigmata, in virtually all patients. In some situations, however, large pulses of intravenous methylprednisolone help gain control of active and devastating features of systemic arthritis and may be lifesaving in the face of significant pericarditis with tamponade or rapidly progressive macrophage activation syndrome.

The use of oral prednisolone is limited to low-dose, preferably alternate-day administration, for children with severe polyarthritis or systemic arthritis who are unable to function in school or the community despite having taken all available steroid-sparing medications. "Steroid-sparing agents" refers to aggressive interventions, including chemotherapy, biologics and stem-cell replacement, which should only be tried by experts in childhood rheumatic diseases.

Short stature, a common and severe sequel of poorly controlled systemic arthritis, may be treated with daily injections of growth hormone. Most children, as reported in several studies, have a statistically improved rate of growth while receiving growth hormone. Most children, as reported in several studies, have a systemic arthritis, may be treated with daily injections of growth hormone. The disease should only be tried by experts in childhood rheumatic diseases.

Short stature, a common and severe sequel of poorly controlled systemic arthritis, may be treated with daily injections of growth hormone. Most children, as reported in several studies, have a statistically improved rate of growth while receiving growth hormone and seem to achieve higher ultimate height. Similarly, and often in addition to the above, short stature associated with chronic corticosteroid use also improves after the addition of growth hormone and appears well tolerated.

**Slow-acting antirheumatic drugs**

**Methotrexate**—Methotrexate is effective in approximately 70% of children with polyarthritis but much less in systemic arthritis. It should be considered for any child whose arthritis is not well controlled with a trial of NSAIDs and intra-articular steroids, alone, after 4–12 weeks. Initial doses of 0.3–0.5 mg/kg of methotrexate are usually given by mouth once a week (recommended 1 hour before food to improve absorption). For recalcitrant disease, subcutaneous methotrexate provides serum levels up to 40% higher than the oral route. Once methotrexate is started, efficacy may be determined after 1–3 months.

The most common adverse events associated with methotrexate are nausea, followed by mouth sores. Subcutaneous administration may be less of a problem in this regard than oral administration. Oral folate supplements or ondansetron may be helpful, and leucovorin rescue is often used if symptoms persist after 24 hours. Other side effects include abdominal pain; elevated liver enzymes; and rarely, hair loss and bone-marrow suppression. Patients taking methotrexate must have blood monitoring on a monthly basis to screen for abnormal liver function and bone-marrow suppression. Adolescents must refrain from drinking alcohol.

Recent trials with leflunomide have shown the same efficacy and less toxicity in children taking leflunomide than methotrexate. While very similar to methotrexate in mode of action, leflunomide seems better tolerated, particularly by patients who develop some of the more recalcitrant side effects (such as nausea before the drug is even administered) (Silverman et al., 2005).

**Sulfasalazine**—Sulfasalazine has been shown to be efficacious in oligoarthritis and polyarthritis, but seems particularly effective in ERA. It is usually well tolerated, but an erythematous rash may be an adverse event. There are rare reports of aplastic anaemia. The usual doses of 2–4 g per day are divided into two doses. It is not of value in systemic arthritis, with a poor clinical response and an increased incidence of side effects such as macrophage activation syndrome.

**Biologic agents**

Currently three TNF antagonists exist, and two have been studied well in children: etanercept and infliximab. Adalimumab, a fully humanized monoclonal antibody to TNF, is also available. There remain significant long-term concerns relating to the unknown effects of these agents, particularly in young children. Many years of practice are needed to identify potential disruption of immune surveillance in children; however, to date with over 10 years and millions of prescriptions worldwide, experience has been overwhelmingly positive.

**Etanercept**—Therapy with this anti-TNF-α receptor is approved for the treatment of children with JIA whose disease is not adequately controlled with methotrexate or who are intolerant of it. Large multicentre trials showed that children with severe, methotrexate-resistant polyarthritis demonstrated sustained clinical improvement with more than 2 years of continuous etanercept treatment. Etanercept was generally well tolerated, and there were no increases in the rates of adverse events over time (Lovell et al., 2003). Etanercept may be initiated if methotrexate fails to control signs of inflammation or if there are unacceptable adverse drug reactions. Regular (1–2 month) monitoring of blood counts and chemistry studies is recommended. Etanercept should be discontinued in the event of fever or other signs of significant infection. Methotrexate is often discontinued when etanercept is started, but may be continued indefinitely after initiation of etanercept if it is well tolerated. Combinations of medical interventions appear to have the best long-term outcome.

**Infliximab**—Infliximab is a biologic agent developed for the treatment of RA in adults and is a chimeric monoclonal antibody against TNF-α. It is highly effective but not yet labelled for use in JIA. It is approved for use in childhood Crohn’s disease and being increasingly used for children with JIA who fail etanercept or have associated uveitis. In adults, infliximab is now approved for treatment of seronegative spondyloarthropathies. It is used in combination with methotrexate to minimize the risk of immune reactions. A dose of 5 mg/kg/dose is usually associated with improvement in the majority of children. Reactions are common and infusions should be done in paediatric settings where staff is experienced in handling intravenous infusions.

**Other drugs**

**Hydroxychloroquine**—Hydroxychloroquine is a relatively safe antimalarial drug that has been used widely in adults with RA, mostly as adjunctive therapy. Studies in children do not support its use in JIA, and the availability of successful interventions has largely superseded its use. It does show efficacy in RA and thus is still advocated for adolescents with RF-positive polyarthritis.

**Cyclosporin A**—Cyclosporin A is a II-2 inhibitor that targets T-cells and is used (with falling frequency and in combination with meth-
otrexate) to control features of systemic arthritis. It is initially well tolerated but only anecdotal success rate. It has also been combined with methotrexate to treat uveitis. Side effects include gingival hyperplasia and hirsutism. Over time, cyclosporin A contributes to hypertension and progressive renal disease. It is still used routinely to treat macrophage activation syndrome associated with systemic arthritis either solo or in combination with high-dose methylprednisolone.

Cyclophosphamide—Borrowing from oncology, high doses of chemotherapy are sometimes advocated for patients unresponsive to all other available therapies, particularly children with severe refractory systemic arthritis whose quality of life is poor and for whom even the newest biologic therapies are not working.

Autologous stem-cell transplantation
A number of children with truly refractory systemic arthritis have been successfully transplanted in Europe, and the procedure is being investigated in the USA for JIA unresponsive to all other therapies. It is a high-risk procedure but seems to offer a reasonable chance of inducing disease remission.

Natural history
JIA is a diverse group of conditions, each unique but all associated with persistent arthritis. The spectrum of JIA varies from: mild to severe; smouldering to rapidly progressive; uniphasic and polyphasic to chronic and continuous; affecting one to affecting most joints; associated with no extra-articular symptoms to such severe extra-articular manifestations as to overshadow the presence of arthritis. Accordingly, few children may remit spontaneously (predictive factors for this are unknown), while another small fraction will have devastating disease, refractory to all, including experimental, treatments. For the remaining minority of children with JIA, however, long-term follow-up studies highlight a much poorer prognosis than previously believed (Foster et al., 2003). These studies show a profound impact on later productivity and on quality of life of adults diagnosed at a time when biologic therapies had not yet been found. It follows then that early diagnosis and rapid referral to an experienced paediatric rheumatology team would be associated with improved outcome and that the longer duration of inflammation, the higher the impact on quality of life, in particular on independence in activities of daily living.

Studies of large numbers of children with JIA followed longitudinally show that as many as 30% continue to have active arthritis into their adult years. These studies include children with persistent oligoarthritis whose natural history of illness has been well described and tends to be limited to an average of 2 years of monoarthritis. That leaves children with polyarthritis and systemic arthritis, in addition to 20% with extended oligoarthritis, comprising the group who continues to have disease into adulthood. Today, many of these young adults are left with the chronic sequelae of short stature, restricted joint movement, asymmetrical growth and extra-articular abnormalities. An appreciation of the true natural history of JIA and the availability of successful treatments have imparted great urgency to prompt referral, initiation of aggressive treatment regimens, improved access to clinical trials and renewed hope for children with arthritis. Over the next decade, new treatments will be developed and tested in children, while concomitant translational research, including studies in pharmacogenetics, will all result in custom-designed individualized and uniquely targeted therapies.

References

Further reading
CHAPTER 16

Musculoskeletal Disorders in Children and Adolescents

Helen Foster\(^1\) and Lori Tucker\(^2\)

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\(^2\)British Columbia’s Children’s Hospital, Vancouver, Canada

OVERVIEW

- Musculoskeletal complaints in children are common, often benign and self-limiting, but can be presenting features of significant, severe and potentially life-threatening conditions.
- Making a diagnosis rests on competent clinical skills, knowledge of normal variants, knowledge of common clinical scenarios, “red flags” to suggest severe conditions and judicious use and interpretation of investigations.
- Common clinical scenarios include the limping child, “growing pains”, back pain and knee pain.
- Knowledge of “red flags” to suggest infection, malignancy, multi-system disease and inflammatory joint disorders are important.
- The management of musculoskeletal conditions involves a multidisciplinary approach.
- Many chronic conditions that begin in childhood continue into adult life, and the process of transitional care to adult services starts in early adolescence.

Introduction

Musculoskeletal (MSK) presentations in childhood are common, with a spectrum of causes (Box 16.1), the majority of which are benign and self-limiting. It must be remembered, however, that severe, potentially life-threatening conditions such as malignancy, sepsis, vasculitis and non-accidental injury may also present with MSK complaints. Furthermore, MSK features are common in association with chronic conditions other than rheumatic disorders, such as inflammatory bowel disease and cystic fibrosis. Diagnosis relies on competent MSK clinical skills, with the minimum of a screening MSK examination (Foster et al., 2006), appropriate knowledge of normal variants (Box 16.2), “red flags” to raise suspicion of malignancy or sepsis and clinical scenarios at different ages (Box 16.3). The approach to MSK assessment in children is different to that of adults; as young children may have difficulty in localizing or describing symptoms, the history is often given by the parent/carer, and complaints may be non-specific, such as “my child is limping”. Clinical assessment usually distinguishes between mechanical and inflammatory problems and an approach to assess-

Box 16.1 Differential diagnosis of musculoskeletal pain

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

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

Joint pain with swelling
- Trauma
- Infection
  - Septic arthritis and osteomyelitis (viral, bacterial, mycobacterial)
  - Reactive arthritis (post-enteric, sexually acquired)
  - Infection related (rheumatic fever, post-vaccination)
- Juvenile idiopathic arthritis
- Arthritis related inflammatory bowel disease
- Connective tissue diseases (SLE, scleroderma, dermatomyositis, vasculitis)
- Sarcoidosis
- Metabolic (e.g. osteomalacia, cystic fibrosis)
- Haematological (e.g. haemophilia, haemoglobinopathy)
- Tumour (benign and malignant)
- Chromosomal (e.g. Downs related arthritis)
- Auto-inflammatory syndromes e.g. CINCA, (Figure 16.1) periodic syndromes, CRMO)
- Developmental/congenital (e.g. spondylo-epiphyseal dysplasia)
Table 16.1: A strategy for characterizing musculoskeletal pain in children

<table>
<thead>
<tr>
<th>Localized pain</th>
<th>Diffuse pain</th>
</tr>
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<tbody>
<tr>
<td>&quot;Well&quot; child</td>
<td>&quot;Unwell&quot;** child</td>
</tr>
<tr>
<td>Strains and sprains</td>
<td>Septic arthritis</td>
</tr>
<tr>
<td>Bone tumours</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>JIA (oligoarticular subtype)</td>
<td>Hypermobility</td>
</tr>
<tr>
<td>Localized idiopathic pain syndromes</td>
<td>Diffuse idiopathic pain syndromes</td>
</tr>
<tr>
<td>&quot;Growing pains&quot;</td>
<td></td>
</tr>
</tbody>
</table>

"Well" Child | "Unwell" Child

Leukaemia Neuroblastoma JIA (systemic and polyarticular onset subtypes) SLE Juvenile dermatomyositis Vasculitis

**Associated with one or more “red flags”, such as fever, anorexia, weight loss, malaise and raised inflammatory markers.

JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus

This table is adapted from Malleson and Beauchamp, 2001

Box 16.2: Normal variants in gait patterns and stance

- Intoeing can be due to:
  - Hip—persistent femoral anteversion—commonly between ages of 3–8 years
  - Lower leg—(internal tibial torsion)—commonly from onset of walking to 3 years
  - Feet—metatarsus adductus—most resolve by the age of 6 years
- Bow legs (varus)—birth to early toddler—most resolve by 3 years
- Knock knees (valgus)—most resolve by age of 7 years
- Flat feet—most resolve by 6 years, and normal arches are evident on tiptoeing
- Crooked toes—most resolve with weight bearing

Box 16.3: “Red flags” to warrant concern in children presenting with musculoskeletal symptoms

- Systemic upset (fever, malaise, anorexia, weight loss or raised inflammatory markers)
- Bone pain and/or night pain
- Regression of motor milestones
- Functional disability

Figure 16.1: Chronic infantile neurological cutaneous arthritis (CINCA) syndrome: widespread rash

Box 16.4: The "limping child"

This is a common presentation, with a spectrum of age-related
neurological symptoms suggestive of nerve-root entrapment or cord compression and systemic findings to suggest malignancy or sepsis. Inflammatory back pain may be a late feature of enthesitis-related arthritis (a subtype of JIA), often presenting in late adolescence and with a strong association with expression of HLA-B27.

Mechanical pain
Osteochondritis of the knee (Osgood–Schlatter disease) is common, especially in adolescent boys who are physically active (particularly those who play football or basketball). Sever’s disease (osteochondritis of the calcaneum) may present with a painful heel. Flat feet (Figure 16.3) are common, and standing on tiptoe should create a normal medial longitudinal arch; inability to do so or painful fixed flat feet warrant further investigation to exclude tarsal coalition. High fixed arches, or pes cavus, may suggest neurological disease. Non-specific mechanical MSK pain in children is often labelled as “growing pains”. Making a diagnosis of “growing pains” requires careful assessment, and Box 16.4 suggests when alternative diagnoses need to be sought. Many children and adolescents with non-

<table>
<thead>
<tr>
<th>Table 16.2 Common/significant causes of limping according to age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toddler/preschool</strong></td>
</tr>
<tr>
<td>Infection (septic arthritis, osteomyelitis—hip, spine)</td>
</tr>
<tr>
<td>Mechanical (trauma and non-accidental injury)</td>
</tr>
<tr>
<td>Congenital/developmental problems (e.g. hip dysplasia, talipes)</td>
</tr>
<tr>
<td>Neurological disease (e.g. cerebral palsy, hereditary syndromes)</td>
</tr>
<tr>
<td>Inflammatory arthritis (JIA)</td>
</tr>
<tr>
<td>Malignant disease (e.g. leukaemia, neuroblastoma)</td>
</tr>
<tr>
<td><strong>5–10 years</strong></td>
</tr>
<tr>
<td>Mechanical (trauma, overuse injuries, sport injuries)</td>
</tr>
<tr>
<td>Reactive arthritis/Transient synovitis—“irritable hip”</td>
</tr>
<tr>
<td>Perthes’ disease</td>
</tr>
<tr>
<td>Inflammatory arthritis (JIA)</td>
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<tr>
<td>Tarsal coalition</td>
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<tr>
<td>Idiopathic pain syndromes</td>
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<tr>
<td>Malignant disease</td>
</tr>
<tr>
<td><strong>10–17 years</strong></td>
</tr>
<tr>
<td>Mechanical (trauma, overuse injuries, sport injuries)</td>
</tr>
<tr>
<td>Slipped capital femoral epiphysis</td>
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<tr>
<td>Inflammatory arthritis (JIA)</td>
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<tr>
<td>Idiopathic pain syndromes</td>
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<tr>
<td>Osteochondritis dissecans</td>
</tr>
<tr>
<td>Tarsal coalition</td>
</tr>
<tr>
<td>Malignant disease (leukaemia, lymphoma, primary bone tumour)</td>
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</tbody>
</table>

JIA = juvenile idiopathic arthritis
Reproduced by kind permission of the Arthritis Research Campaign (www.arc.org.uk)
specific aches and pains, including growing pains, are found to have joint hypermobility, which is suggested by symmetrical hyperextension at the fingers, elbows and knees (genu recurvatum), and flat pronated feet. It is important, however, to consider and exclude “non-benign” causes of hypermobility (e.g., Marfan’s, Stickler’s and Ehlers–Danlos syndromes), which are rare but important, as these children are at risk of retinal and cardiac complications. Non-specific aches and pains are also a feature of idiopathic pain syndromes, which are mostly seen in older female children/adolescents; such patients are often markedly debilitated by their pain and fatigue—the pain can be incapacitating—but the child/adolescent is otherwise well, and physical examination is usually normal. Localized idiopathic pain syndromes most commonly affect the foot or hand, may be triggered by trauma (often mild) and are likened to reflex sympathetic dystrophy.

**Neoplasia**

It is important to differentiate joint pain from bone pain. Bone pain is a “red flag” and is a common feature of leukaemia, metastatic neuroblastoma and primary bone tumours (Figure 16.4). It is important to note that these malignancies may also present with frank arthritis. Osteoid osteomas (the most common benign bone tumour) are usually located in the femoral neck or posterior elements of the spine, and typically cause night pain that can be relieved by salicylates.

**Arthritis and infection**

Children with septic arthritis are usually febrile, appear unwell and have severe pain with joint movement. Septic arthritis usually occurs in large joints. Reactive arthritis is usually monoarticular or
oligoarticular and follows bacterial infection in the gut (Salmonella, Shigella, Campylobacter, Yersinia), although in the older child and adolescent it is important to consider sexually acquired infection (Chlamydia, gonorrhoea). Rheumatic fever (a form of reactive arthritis that follows pharyngeal streptococcal infection) is uncommon in the UK, but common in developing countries. Lyme disease following tick-transmitted infection with Borrelia burgdorferi is suggested by the presence of an oligoarthritis, erythema chronicum migrans, and a travel history to an endemic area.

**Chronic arthritis (JIA)**

In the absence of sepsis or trauma, JIA is the most likely cause of a single swollen joint in a child and is covered in more detail in Chapter 15.

**Connective tissue diseases**

**Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) may be confused with chronic arthritis, because some patients present with arthritis as the primary clinical finding. SLE is rare but is more common in non-white individuals, with a predominance of girls affected in the adolescent group and more boys affected in young children. The arthritis of SLE is usually polyarticular, non-deforming and non-erosive. Extra-articular features are variable, and a diagnosis is made with a combination of clinical and laboratory features (Table 16.3). It is worth considering drug-induced SLE, which can develop from the use of anti-convulsants, oral contraceptives or minocycline. The medical management of SLE is complex and requires specialist supervision, and many patients require corticosteroid and immunosuppressive medication. In addition, patients often require anti-hypertensives, anticoagulation (related to antiphospholipid syndrome), and medications to control dyslipidaemias and avoid osteoporosis.

**Juvenile dermatomyositis**

Juvenile dermatomyositis (JDM) may present at any age, with characteristic skin involvement (Figure 16.5), and proximal muscle weakness which can present acutely or indolently. JDM has a broad range of severity; contrary to adult-onset DM, there is no association with malignancy. Patients with JDM may develop calcinosis as a late complication of poorly controlled disease (Figure 16.6). Severe complications at the time of active disease include risk of aspiration pneumonia and interstitial lung disease. Diagnosis usually rests on clinical assessment, and elevated serum muscle enzymes; most children do not require electromyography or a muscle biopsy in the absence of atypical features. Magnetic resonance imaging of the muscles is very useful to demonstrate muscle involvement and monitor disease activity. Treatment of JDM requires rapid initiation of high-dose corticosteroids, frequently accompanied by methotrexate, although other medication such as intravenous immunoglobulin, cyclophosphamide or anti-cytokine agents are used in severe or refractory disease. Physical therapy input is essential to optimize outcome.

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**Table 16.3** SLE in children and adolescents

<table>
<thead>
<tr>
<th>Common presenting symptoms</th>
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<tbody>
<tr>
<td>Malar rash</td>
</tr>
<tr>
<td>Arthritis</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Fever</td>
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<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Oral ulcers</td>
</tr>
<tr>
<td>Alopecia</td>
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<tr>
<td>Pleuritis/pericarditis</td>
</tr>
<tr>
<td>Central nervous system findings</td>
</tr>
<tr>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Raynaud's phenomenon</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
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</table>

<table>
<thead>
<tr>
<th>Laboratory findings</th>
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<tbody>
<tr>
<td>Anaemia (may be haemolytic with positive red cell autoantibodies)</td>
</tr>
<tr>
<td>Leukopenia, lymphopenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
</tr>
<tr>
<td>Elevated kidney function tests (blood urea nitrogen, creatinine)</td>
</tr>
<tr>
<td>Decreased complement components C3 and C4</td>
</tr>
<tr>
<td>Positive antinuclear antibody</td>
</tr>
<tr>
<td>High titre positive anti-double-stranded DNA antibody</td>
</tr>
<tr>
<td>Positive autoantibodies to extractable antigens (anti-Ro (SSA); anti-La (SSB); anti-Sm; anti-RNP)</td>
</tr>
<tr>
<td>Positive antiphospholipid antibodies (anti-cardiolipin, lupus anticoagulant)</td>
</tr>
</tbody>
</table>

**Figure 16.5** Gottron’s rash over the knees in juvenile dermatomyositis
growth of a limb and subcutaneous tissues (of the face or a limb). Current practice advocates aggressive treatment regimes (corticos- teroid and methotrexate) to control disease and limit severe dis- figurement and disability. Systemic scleroderma is very rare in children and includes progressive diffuse fibrous changes of the skin and fibrous changes involving internal organs—most com- monly lungs, gastrointestinal tract, heart and kidneys—with a sig- nificant mortality. Systemic scleroderma is slowly progressive, has a guarded prognosis and requires potent immunosuppression, although clinical trials are lacking to guide practice.

**Sclerodermas**

Scleroderma in childhood is rare and heterogeneous, and subtypes are determined by the type and number of lesions, the area of involvement and serological abnormalities. Localized scleroderma (Figure 16.7) is the most common and can present at any age, with the appearance of a patch of abnormal skin, which when untreated, generally follows a course of active expanding disease, fibrosis and eventual softening with some “remission”. The functional and cosmetic impact can be profound, as the lesions may interfere with growth of a limb and subcutaneous tissues (of the face or a limb). Current practice advocates aggressive treatment regimes (corticos- teroid and methotrexate) to control disease and limit severe dis- figurement and disability. Systemic scleroderma is very rare in children and includes progressive diffuse fibrous changes of the skin and fibrous changes involving internal organs—most com- monly lungs, gastrointestinal tract, heart and kidneys—with a sig- nificant mortality. Systemic scleroderma is slowly progressive, has a guarded prognosis and requires potent immunosuppression, although clinical trials are lacking to guide practice.
Vasculitis

Vasculitis (Figure 16.8) is a heterogeneous group of disorders, most commonly classified by the size of involved blood vessels. A diagnosis may be suggested by multi-system clinical involvement and laboratory features (Table 16.4). The common childhood vasculitides Henoch–Schönlein purpura (HSP) and Kawasaki (KD) disease (Box 16.5) often have transient arthritis affecting large joints. HSP is characterized by palpable purpura (Figure 16.9) over the legs and buttocks, abdominal pain, haematuria and arthritis. In general, HSP resolves completely within 4 weeks of onset; however, some patients have recurrences of rash and gastrointestinal symptoms, and a small percentage of children who develop renal disease with HSP go on to renal failure. KD is an acute systemic vasculitis, predominantly in young children (less than 5 years); it is usually self-limiting but has the potential for causing severe long-term complications due to the involvement of coronary and other blood vessels with aneurysms. Prompt recognition of KD is essential in providing early treatment with intravenous immunoglobulin, which decreases the risk of developing coronary aneurysms significantly.

### Features of Kawasaki disease

- Fever for more than 5 days plus at least four of the following signs:
  - Bilateral conjunctival injection
  - Changes in the oropharyngeal membranes (swollen fissured lips, strawberry tongue, injected pharynx)
  - Changes in peripheral extremities (erythema and swelling of hands and feet followed by desquamation of the skin)
  - Polymorphous rash
  - Cervical lymphadenopathy (at least one node >1.5 cm)

### Vasculitides in childhood

<table>
<thead>
<tr>
<th>Type according to size of vessel</th>
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<tbody>
<tr>
<td><strong>Large-vessel vasculitis</strong></td>
<td></td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td></td>
</tr>
<tr>
<td>[Giant cell (temporal) arteritis—rarely seen in adolescents/children]</td>
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</tr>
<tr>
<td><strong>Medium-vessel vasculitis</strong></td>
<td></td>
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<tr>
<td>Polyarteritis nodosa</td>
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</tr>
<tr>
<td>Kawasaki disease</td>
<td></td>
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<tr>
<td><strong>Small-vessel vasculitis</strong></td>
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<tr>
<td>Wegener’s granulomatosis</td>
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<tr>
<td>Churg-Strauss syndrome</td>
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<tr>
<td>Microscopic polyangiitis</td>
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<tr>
<td>Henoch–Schönlein purpura</td>
<td></td>
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<tr>
<td>Cutaneous leukocytoclastic vasculitis</td>
<td></td>
</tr>
<tr>
<td>[Cryoglobulinaemic vasculitis—rarely seen in adolescents/children]</td>
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</table>

### Features suggesting a vasculitis in adolescents and children

<table>
<thead>
<tr>
<th>Clinical</th>
<th></th>
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<tbody>
<tr>
<td>Fever, weight loss, persistent fatigue</td>
<td></td>
</tr>
<tr>
<td>Skin rash: palpable purpura, vasculitic urticaria, nodules, ulcers</td>
<td></td>
</tr>
<tr>
<td>Neurologic signs: headache, mononeuritis multiplex, focal CNS lesions</td>
<td></td>
</tr>
<tr>
<td>Arthritis or arthralgia, myalgia or myositis</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>Pulmonary infiltrates or haemorrhage</td>
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<table>
<thead>
<tr>
<th>Laboratory</th>
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<tbody>
<tr>
<td>Increased acute-phase reactants (ESR, CRP)</td>
<td></td>
</tr>
<tr>
<td>Anaemia, leukocytosis</td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td></td>
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<tr>
<td>Antineutrophil cytoplasmic antibodies (ANCA)*</td>
<td></td>
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<tr>
<td>Elevated factor VIII-related antigen (von Willebrand factor)</td>
<td></td>
</tr>
<tr>
<td>Haematuria</td>
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</table>

*ANCA: cytoplasmic (c-ANCA) associates specifically with Wegener’s granulomatosis and perinuclear (p-ANCA) associates with microscopic polyangiitis and a variety of other vasculitides

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

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Rare inflammatory syndromes

Inherited auto-inflammatory syndromes
These syndromes (Box 16.6) are rare, and children may present with repeated unexplained bouts of fever with a variety of clinical findings associated with the fevers, which may include rash (Figure 16.1), MSK complaints, abdominal pain and ocular and neurologic complaints. There is often a broad range of severity among patients with the same genetic disorder, making diagnosis on clinical grounds often challenging. New treatment options have become available for some patients with periodic fever syndromes, and patients require specialist supervision.

Chronic recurrent multifocal osteomyelitis
Chronic recurrent multifocal osteomyelitis (CRMO) is a condition that presents similarly to bacterial osteomyelitis, but no organism can be isolated and there are often multiple involved sites with recurring episodes. Children or adolescents present with bone pain, sometimes accompanied by swelling; most common affected areas are long bones (tibia), but ribs, clavicle, vertebrae or mandible can be involved. Radiographs show osteolytic changes similar to osteomyelitis, and a bone scan may show lesions that are asymptomatic. Antibiotics are not effective, and many children with CRMO have good symptomatic relief with non-steroidal anti-inflammatory drugs. For those with persistent disease, bisphosphonates are often effective.

The role of the multidisciplinary team
The paediatric rheumatology multidisciplinary team (MDT) is highly skilled in the provision and coordination of comprehensive and often complex management regimes for the child and family, providing education and support, with other specialist services as well as community services, schools and health-care providers within shared care clinical networks. Many children with rheumatic diseases have continuing disease activity or relapses in adulthood, or sequelae from previous disease activity, which require ongoing medical treatment. Health-care transition, for youths with childhood-onset rheumatic diseases describes the movement of patients from child- and family-centred paediatric care to adult-oriented health-care systems. The MDT coordinate transitional care, addressing generic and disease-specific health issues (Table 16.5), and ultimately transfer to adult rheumatology services. Education and support are paramount, particularly with complex treatment regimes and the impact on adolescent behaviours, such as avoidance of pregnancy and excess alcohol in those taking methotrexate.
References


Further reading


McDonagh JE. Transition of care from adult to paediatric rheumatology. Archives of Disease in Childhood 2007; 97: 802–807.
Polymyalgia Rheumatica and Giant Cell Arteritis

Eric L Matteson¹ and Howard A Bird²

¹Mayo Clinic, Rochester, USA
²Chapel Allerton Hospital, Leeds, UK

OVERVIEW

- Patients with polymyalgia rheumatica are over 50 years of age, and on average over 70 years old.
- Hallmark symptoms of the disease are shoulder and hip girdle pain with marked stiffness.
- Giant cell arteritis may be present in at least 30% of patients.
- Treatment is with glucocorticosteroids, initially 15–20mg a day of prednisone equivalent. Treatment is often required for several years.

Polymyalgia rheumatica (PMR) is a clinical syndrome that affects older patients and comprises proximal muscle group stiffness, particularly in the shoulder, and systemic features such as fatigue and weight loss. It is associated with an increased erythrocyte sedimentation rate (ESR) and responds dramatically to relatively small doses of steroids.

Giant cell arteritis (GCA) is a systemic vasculitis that affects large- and medium-sized arteries. Although it may involve any artery, it has a propensity to affect the branches of the external carotid artery, particularly the posterior ciliary arteries that supply the optic nerve and the superficial temporal artery; hence its alternative (often interchangeable) name “temporal arteritis” (Figure 17.1).

There are clinical and pathogenetic links between temporal arteritis, GCA and PMR, which has led to the concept that they are manifestations of a disease spectrum that affects the same disease population (Box 17.1). The two entities may occur in the same patient simultaneously, at different time points, or independently. PMR has been observed in 40–60% of cases of GCA, and 30–80% of patients with PMR have GCA.

Causes

The cause of GCA or PMR is likely to be polygenic, with both genetic and environmental factors contributing to disease susceptibility and severity.

Environmental

Acute-onset prodromal events and synchronous variations in incidence of PMR and GCA suggest a possible environmental infectious trigger. Several studies have shown concurrence in the incidence of PMR and GCA with epidemics of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, parvovirus B19, respiratory syncytial virus and adenovirus. Despite this, no definite causative infectious agent has been identified.

Genetics

Racial differences in incidence and familial aggregation suggest a common genetic susceptibility factor. PMR and GCA are linked with human leukocyte antigen DR4 (HLA-DR4). Patients who are positive for HLA-DR4 and those who are negative for HLA-DR4 do not present differently. A conserved sequence within the second hypervariable region located in the antigen-binding groove of the HLA-DR molecule has been identified. Differential expression of genes responsible for inflammatory cytokine expression are likely to account for the variable disease manifestations.

Clinical features

In the absence of a specific diagnostic test, apart from biopsy of the temporal artery when GCA is also present, the diagnosis of PMR is based on clinical features (Table 17.1) and made by exclusion.

ABC of Rheumatology, 4th edn. Edited by Ade Adebajo. ©2010 Blackwell Publishing Ltd. 9781405170680.
GCA usually may be viewed as inflammation of the aorta and its major branches. Its clinical features are related to the affected arteries. The scalp is tender to the touch, and it may even hurt to wear spectacles. Jaw claudication may occur while chewing. Clinical signs (Table 17.1) vary according to the duration of the disease. In the early stages, the pulse is full and bounding, and the arteries tender. Later, fibrosis and repair may predominate, the artery may have a nodular indurated feel to it, and the pulse is almost absent. Diplopia, partial or complete loss of vision, and cranial nerve palsy.
Histopathology

Giant cell arteritis—The inflammatory features of GCA are typically described as illustrating the “skip” phenomenon due to the patchy or segmental involvement of the arteries. GCA is principally a disease driven by T-cells that is limited to vessels with an internal elastic component. Histologically, the lesions are characterized by a mainly lymphocytic and macrophage infiltrate with the presence of giant and epithelioid cells (Figure 17.3). The CD3+ and T-cell population comprises CD4+ or CD8+ subsets, of which CD4+ T-cells predominate. The initial immunological event—probably the induction of CD4+ T-cell proliferation by an unknown antigen—occurs in the outer vessel layer: the adventitia. These CD4 cells produce interferon-γ, which attracts macrophages to the arterial wall, where they fuse to form multinucleated giant cells in the intima-media junction (Figure 17.4). The giant cells produce express adhesion molecules, nitric oxide and collagenases to result in, for example, tissue injury and in situ thrombosis.

Polymyalgia rheumatica—The histopathological features of PMR are defined less clearly than for GCA. Biopsy of synovium, especially of shoulder-joint structures, have confirmed synovitis in about one-third of patients, which is nonerosive and self-limiting arthritis.

Box 17.5 Biopsy for giant cell arteritis

- Biopsy is most useful just before or within 24 hours of treatment initiation with steroids, but treatment should not be delayed for the sake of obtaining a biopsy
- Skip lesions occur, so a negative result does not exclude giant cell arteritis
- A positive result may resolve later doubt about diagnosis, particularly if the response to treatment is not rapid and classical
- It may not be possible to biopsy all patients; the decision depends on local resources
- One week after starting steroid treatment, the chance of obtaining positive biopsy falls to 10%, although the biopsy may still reveal evidence of inflammation >1 year after initiation of treatment

(Figure 17.2) may all occur if the condition remains untreated. Late complications of large-vessel involvement, including aortic aneurysm and stenosis, may complicate the disease course. Patients should be followed long term for aortic disease with computed tomography and aortic magnetic resonance imaging (MRI) and complemented by ultrasonography of the aortic root and abdominal aorta by clinical and imaging assessment, as aneurysmal rupture is a cause of premature mortality in these patients. The value of biopsy for GCA is discussed in Box 17.5.
Inflammation of the temporal artery may also be demonstrated even in patients without overt GCA. The characteristics of synovitis on biopsy confirm a predominance of CD4+ T-cells and macrophages. Similar to features described in GCA, the vascular infiltrate reveals CD4+ interferon-γ-positive cells in the adventitia; macrophages that produce interleukin-1β, interleukin-6 (IL-6), endothelial cell adhesion molecules with matrix metalloproteinases, and inducible nitric oxide are seen in the media intima.

Increasingly used in clinical evaluation, ultrasonography of the shoulders (Figure 17.5) and hips may reveal synovitis of the joints or bursa. MRI studies also give evidence of an inflammatory process affecting distal articular or extra-articular (tenosynovial) structures, or both (Figure 17.6). Although skeletal muscle is not considered to be a site of pathology, focal changes in muscle ultrastructure and mitochondria abnormalities have been noted, but their significance remains unclear. Muscle enzymes and biopsies are normal.

**Investigations**

ESR and/or CRP are the most accepted and easily available markers of active inflammation in PMR (Figure 17.7). They are initially elevated in over 90% of patients, although PMR and even blindness from GCA can occur in the presence of a normal ESR. The ESR and CRP fall with effective treatment; the CRP falls faster. With treatment, the normocytic normochromic anaemia corrects, and the slight increase in hepatic alkaline phosphatase sometimes noted in active disease is reduced.

In parallel, to these basic laboratory studies, additional investigations should be arranged to exclude conditions that cause diagnostic confusion, including thyroid function studies and age- and symptom-appropriate malignancy screening. Additionally, an evaluation should be performed in all patients to screen and follow common conditions of elderly patients, which may be induced or exacerbated by protracted corticosteroid use, including diabetes, osteoporosis and cardiovascular disease.

Vascular assessment with ultrasound, computed tomography/ MRI, or conventional angiography may be required to assess the activity and extent of vascular involvement (Figure 17.8). Ultrasound and MRI may reveal a characteristic “halo” around inflamed vessels, even of the caliber of the temporal arteries. Positron emission tomography may occasionally be useful in defining disease activity, but remains experimental.

The basic investigations described above are summarized in Box 17.6.
Figure 17.6 MRI of shoulder in polymyalgia rheumatica (T2 fat suppressed corona). Oblique MRI sequences shows modest synovial inflammation with substantial fluid in the subacromial bursa associated with diffuse capsular edema extending into the adjacent tendons and muscle bellies. Courtesy of Dr D. McGonagle and Dr H. Marzo-Ortega, Academic Unit of Musculoskeletal Disease, Leeds General Infirmary, Leeds, UK.

Figure 17.7 Improvement in erythrocyte sedimentation rate, C-reactive protein, and the patient’s perception of pain (measured on a visual analogue scale) in response to corticosteroid therapy in a group of 76 patients with polymyalgia rheumatica. Courtesy of Dr Burkhard Leeb, Lower Austria Centre for Rheumatology, Stockerau, Austria.

Figure 17.8 Arterial thrombosis complicating polymyalgia rheumatica, supporting a generalized vasculitic aetiology of this condition. Courtesy of Dr C. Pease, Academic Unit of Musculoskeletal Disease, Leeds General Infirmary, Leeds, UK.
Chapter 1

not rendered mobile, or if other risk factors are present (see necessary, particularly if treatment is of long duration and the patient is of co-morbidities including prophylaxis for osteoporosis is necessary, particularly if treatment is of long duration and the patient is not rendered mobile, or if other risk factors are present (see Chapter 1).

Box 17.6 Basic investigations

- Complete blood count with differential
- Alkaline phosphatase
- Blood glucose
- Acute-phase reactants (erythrocyte sedimentation rate and/or C-reactive protein)
- Creatinine
- Blood lipids
- Thyroid function studies
- Creatine phosphokinase
- Bone mineral density
- Tuberculosis testing (PPD skin test; QuantiFERON gold)

Polymyalgia rheumatica

- Ultrasonography of hip and shoulder (where available and appropriate)

Giant cell arteritis

- Temporal artery biopsy
- Large-vessel evaluation with echocardiography, ultrasound, computed tomography, magnetic resonance imaging of the vessel wall, and magnetic resonance or computed tomographic angiography, as appropriate to the vessels of interest
- Position emission tomography

Box 17.7 Treatment of polymyalgia rheumatica

- “Treat the patient, not the sedimentation rate”
- Initial dose of corticosteroid should be adjusted to patient’s size and weight
- Typically start prednisone, equivalent of 10–20 mg daily for 1 month
- After 1 month, aim to reduce the dose by 2.5 mg every 2–4 weeks, titrating against clinical response and level of acute-phase reactants, with the aim of reducing to 10 mg daily
- After 6 months, try a further cautious reduction in increments of 1 mg daily every month, in the hope of reducing to 5 mg daily, as long as symptoms do not recur; in general, symptoms are a better guide to the need for continued treatment than persistent modest elevation in the acute-phase reactants
- Most patients require treatment for 3 years, but withdrawal over a period of some 6 months can be attempted at 1–2 years, if the response has been good; the duration of treatment may range from about 9 months to over 9 years
- Relapsing symptoms with reduction of the corticosteroid dose is common; the need for protracted treatment is associated with increased risk of corticosteroid-related side effects, prompting interest in the use of corticosteroid-sparing agents

Box 17.8 Treatment of giant cell arteritis

- Doses of prednisone/prednisolone should be higher than for polymyalgia rheumatica and the period of treatment longer; the incentive to reduce is much less than with polymyalgia rheumatica because of the possibility of vascular compromise
- For headaches alone, the starting dose of prednisolone should be in the range of 20–40 mg daily; with clinical signs of vasculitis or visual symptoms, the dose should be in the range of 30–60 mg daily; for impending or recent blindness, 80 mg daily should be given, possibly with the addition of intravenous hydrocortisone
- Dosage reduction can then be at a rate of about 5 mg every 3 or 4 weeks until a maintenance level of 10 or 15 mg daily is achieved, depending on response
- At 1 year, an effort should be made to reduce the dose to 5 mg daily in 1-mg steps
- Maintenance therapy at this low dose is likely to last up to 5 years
- As with polymyalgia rheumatica, relapses are common, and extended treatment may be needed; persistently elevated acute-phase reactants in the face of clinically quiescent disease should alert the clinician to the possibility of subclinical disease; physicians should be vigilant for the development of large vascular disease and assess appropriately
- Addition of low-dose aspirin as 81–325 mg daily has potential ancillary benefit in control of inflammation as well as cardiovascular protective value

Response criteria

The European Collaborating Polymyalgia Rheumatica Group recently proposed response criteria (Box 17.9) that aim to compli-
Box 17.9 European Collaborating Polymyalgia Rheumatica Group’s response criteria

Clinical improvement in pain (on visual analogue scale) and three out of four from:

- Reduction in C-reactive protein or erythrocyte sedimentation rate, or both
- Improvement in morning stiffness
- Ability to raise shoulders
- Improvement of physicians’ global assessment on visual analogue scale

Further reading


Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease associated with genetic and environmental risk factors. SLE is most common in women and those from non-white ethnic backgrounds. Lupus nephritis occurs in up to 50% of SLE patients. SLE patients should receive pre-pregnancy counselling to ensure optimal disease control and drug therapy before conception. Premature cardiovascular disease is an increasing cause of death in SLE patients.

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease of unknown cause (Mok and Lau, 2003) with a wide variety of manifestations that is usually characterized by remissions and relapses. SLE is part of a spectrum of autoimmune diseases that also includes discoid lupus, drug-induced lupus, neonatal lupus, Sjögren’s syndrome, antiphospholipid antibody syndrome, dermatomyositis/polymyositis and overlap syndromes. Antiphospholipid antibody may occur as a primary disorder or secondary to SLE or another autoimmune condition, such as autoimmune hypothyroidism or chronic active hepatitis. As no cure exists for these conditions, life-long follow-up is needed, so it is important that the primary care physician, patient and hospital specialists are involved closely in the management of these diseases (Bertsias et al., 2008).

**Causes**

SLE is a multifactorial disease caused by a complex interplay of genetic and environmental factors that vary between individuals and are still not well understood (Mok and Lau, 2003) (Boxes 18.1 and 18.2). SLE is characterized by multiple immune abnormalities, including dendritic, B- and T-cell dysfunction resulting in the development of autoantibodies and autoreactive T-cells. Defective clearance of apoptotic cells and of immune complexes contributes to pathogenesis with the activation of complement playing a major role in tissue damage. There is increasing evidence that the cytokine interferon-alpha (IFN-α) plays a role in activating genes involved in the disease, and that interleukin-6 (IL-6) and IL-10 levels are increased in active disease. Antiphospholipid antibodies are a specific family of autoantibodies directed against anionic phospholipids located in cell membranes. The pathogenic mechanisms in antiphospholipid syndrome relate to the prothrombotic effects of these antibodies in vivo.
Epidemiology

There are significant disparities in the incidence and prevalence rates of SLE disease worldwide (Danchenko et al., 2006) (Table 18.1) and in the cumulative incidence of clinical features (Table 18.2). This variability may be due to true population differences or to dissimilar methods of case ascertainment. Nevertheless, the consistent trend reflects that the burden of disease is highest in women and higher among non-white ethnic groups.

Clinical presentations

Systemic lupus erythematosus

The American Rheumatology Association’s 1982 classification criteria (Tan et al., 1982) for SLE (Box 18.3) were revised in 1997 (Hochberg, 1997). These criteria were designed not for diagnosis but for classifying patients into studies and clinical trials. The diagnosis of SLE should be considered if a patient has characteristic features of lupus (Table 18.2), even if they do not fulfil four of the eleven criteria. For example, a 25-year-old woman with malar rash (Figure 18.1), positive antinuclear antibody and histologically proven glomerulonephritis obviously has SLE, despite fulfilling only three of the criteria (Box 18.3).
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Haematological manifestations
Leucopaenia may be an early clue to the diagnosis of SLE. Lymphopaenia is the most common manifestation of SLE other than positive antinuclear antibodies and, in untreated patients, is caused by lymphocytotoxic antibodies. Mild neutropenia is relatively common in black people even without SLE, but values <1.5 × 10^9/l are usually related to disease or drugs. Anaemia is the second most common haematological abnormality seen in lupus patients and may be multifactorial. The differential diagnosis of anaemia is shown in Box 18.4. Thrombocytopenia may occur as an immune-mediated condition associated with a risk of bleeding, as in idiopathic thrombocytopenic purpura, or as a milder abnormality with platelet counts >80 × 10^9/l associated with a risk of thrombosis in antiphospholipid syndrome (see below).

Renal manifestations
Renal disease is an important determinant of the outcome of SLE. Renal disease can occur in up to 50% of white patients and 75% of black patients. Studies have shown that renal disease is also more severe in non-white patients. Early nephritis is often asymptomatic, so regular urinalysis for protein, blood and casts is essential. Some patients present with nephrotic syndrome and a few with devastat-
ing accelerated hypertension and renal shutdown. Renal biopsy is helpful for assessing the severity, nature, extent and reversibility of the involvement and is an important guide to treatment and prognosis. For example, those with mesangial nephritis (class I) rarely progress to renal failure, in contrast to those with diffuse proliferative glomerulonephritis (class IV), who are at risk for end-stage renal disease.

**Nervous system manifestations**

SLE may affect the central and peripheral nervous systems. Definitions for these manifestations have been proposed by a consensus group (American College of Rheumatology, 1999) (Boxes 18.5 and 18.6). The most common manifestations are headache, seizures, aseptic meningitis and cerebrovascular accidents. Antiphospholipid antibodies (including anticardiolipin antibodies) have been implicated in cerebrovascular accidents and chorea. It often is hard to determine whether the depression and headaches are due to lupus itself; in many cases, they are related to psychosocial issues. Other possible causes such as sepsis, drugs, uremia, severe hypertension and other metabolic causes must be sought and treated. Steroids are often blamed for inducing psychosis, but if any doubt exists, patients should be given more, not less, steroid while under medical supervision, particularly if active lupus is evident in other systems.

### Box 18.5  Central nervous system manifestations of systemic lupus erythematosus

- Aseptic meningitis
- Cerebrovascular disease
- Demyelinating syndrome
- Headache (including migraine and benign intracranial hypertension)
- Movement disorders (including chorea)
- Myelopathy
- Seizure disorders
- Acute confusional state
- Anxiety disorder
- Cognitive dysfunction
- Mood disorder
- Psychosis

### Box 18.6  Peripheral nervous system manifestations of systemic lupus erythematosus

- Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)
- Autonomic disorder
- Mononeuropathy (single or multiplex)
- Myasthenia gravis
- Neuropathy, cranial
- Plexopathy
- Polyneuropathy

**Pulmonary and cardiovascular manifestations**

Pleurisy, often without physical signs, is common in SLE. Less common manifestations are lupus pneumonitis, pulmonary haemorrhage, pulmonary embolism and pulmonary hypertension. Pulmonary haemorrhage can be sudden and acute and has high mortality. Pulmonary hypertension is associated with a poor prognosis, especially in pregnancy. Pericarditis is common but often asymptomatic. Other cardiac manifestations are myocarditis, endocarditis and rarely pericardial tamponade. Coronary artery disease is occasionally caused by vasculitis, but more often results from premature atherosclerosis (Box 18.7).

**Gastrointestinal manifestations**

Abdominal pain, nausea, vomiting and diarrhoea occur in up to 50% of SLE patients at some stage of the disease. Although the presentation of greatest importance is mesenteric vasculitis, in which the patient presents with an acute abdomen and is at high risk of death, there have been recent reports of patients with subacute abdominal pain or aseptic peritonitis. This is usually associated with other serological signs of active disease and generally improves with steroid therapy. Other abdominal manifestations include subacute bowel obstruction, hepatitis, sclerosing cholangitis, protein-losing enteropathy, pancreatitis and ascites. Exclusion or treatment of infection is essential in patients with these conditions.

**Pregnancy and SLE**

No evidence suggests that SLE reduces fertility, but active disease and the presence of antiphospholipid antibody syndrome (see below) may increase the risk of intrauterine growth retardation, premature delivery, miscarriages and stillbirth (Gayed and Gordon, 2007). Doses of prednisolone >10 mg/day predispose to pre-eclampsia, isolated hypertension in pregnancy, premature rupture of membranes and maternal infection. No evidence shows that prednisolone crosses the placenta and causes fetal abnormalities in humans. Increasing evidence shows that azathioprine (<2 mg/kg/day) and hydroxychloroquine (200 mg daily) can be continued in pregnancy (Ostensen et al., 2006). If patients are on an angiotensin-converting enzyme (ACE) inhibitor or mycophenolate mofetil for renal disease, then medications must be discontinued due to their association with congenital malformations in exposed fetuses (Ostensen et al., 2006). Other anti-hypertensive medications such as methyldopa, labetalol and nifedipine are the most widely used to control blood pressure, and steroids and azathioprine can be added for lupus manifestations needing ongoing treatment.
ist advice, as they are at risk of systemic complications. Hydroxychloroquine and pilocarpine with other local symptomatic measures, such as artificial tears, are used to treat the condition.

### Overlap syndromes and other lupus-like conditions

Up to 25% of patients with connective tissue disorders do not fit into classical descriptions and present with overlapping clinical features. Some may evolve into well-defined connective tissue disorders, while others have manifestations of more than one definite connective tissue disorder—e.g. systemic sclerosis combined with SLE and inflammatory myositis (see Chapter 21). Raynaud’s phenomenon is often present and may occur in isolation as the first manifestation of a connective tissue disorder. Patients with mild undifferentiated connective tissue disorders may have inflammatory arthritis, oedema of hands and acrosclerosis. Generally prognosis is good as long as patients do not develop pulmonary hypertension.

### Polymyositis and dermatomyositis

Proximal muscle weakness, elevated muscle enzymes, myopathic changes on electromyography and inflammatory changes on muscle biopsy are diagnostic criteria for polymyositis. The presence of a characteristic rash in the presence of the above features defines dermatomyositis. These diagnoses are made by fulfilling these criteria in combination and excluding other potential aetiologies for these test abnormalities.

### Antiphospholipid syndrome

Antiphospholipid syndrome (Box 18.11) is an important cause of recurrent arterial and venous thrombosis and miscarriages that are associated with antiphospholipid antibodies (Box 18.12).

### Thrombosis

The most common presentation of antiphospholipid syndrome is venous thrombosis in the arms or legs, which is often recurrent, multiple and bilateral, with a propensity for pulmonary embolism. Arterial thrombosis is less common but most frequently manifested by features of ischaemia or infarction. The severity of presentation depends on the acuteness and extent of the occlusion. The brain is the most common site, where thrombosis presents as stroke and transient ischaemic attacks. Other sites for arterial occlusion are the coronary arteries, and subclavian, renal, retinal and pedal arteries.

### Obstetric syndromes

Recurrent pregnancy losses in the second or third trimester are typical (Box 18.11). Patients should be monitored for intrauterine growth restriction due to placental insufficiency and pre-eclampsia in a specialist unit. Planned early delivery is often required. (See below for treatment during pregnancy in the setting of antiphospholipid antibody syndrome.)
Box 18.11 Criteria for classification of antiphospholipid syndrome

Clinical features
- Thrombosis
  - Confirmed episode of arterial and/or venous thrombosis in any organ or tissue
- Morbidity in Pregnancy
  - Fetal death beyond 10 weeks’ gestation with confirmed normal fetal morphology
  - Three or more spontaneous abortions before 10 weeks’ gestation in the absence of other maternal causes
  - More than one premature birth due to presence of severe placental insufficiency, pre-eclampsia or eclampsia before 34 weeks’ gestation

Laboratory criteria
- Immunoglobulin G and/or immunoglobulin M anticardiolipin antibodies in medium-to-high titre on at least two different occasions more than 12 weeks apart (using a standard enzyme-linked immunosorbent assay for β2-glycoprotein-I-dependent anticardiolipin antibodies) (Miyakis et al., 2006)
- Lupus anticoagulant in plasma on two separate occasions at least 12 weeks apart

Antiphospholipid syndrome definitely is present if at least one of the clinical features and one of the laboratory criteria are met.

Box 18.12 Tests for antiphospholipid antibodies

- Anticardiolipin antibodies
- Antibodies against co-factors associated with anionic phospholipids, for example, β2-glycoprotein
- Lupus anticoagulant
- Biological false-positive serological tests for syphilis

Other manifestations
Other prominent features include thrombocytopenia (up to 50% of patients), haemolytic anaemia, livedo reticularis (Figure 18.4), chronic ulcers, typically near the medial malleolus, and cutaneous vasculitis.

Catastrophic antiphospholipid syndrome
This is an acute and devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body, which are often fatal. The kidney is affected most often, followed by the lungs, central nervous system, heart and skin.

Outcome of SLE and antiphospholipid syndrome
Although survival has improved substantially over the last 50 years (90% of patients survive at least 5 years and over 80% at least 10 years), awareness is increasing that these patients succumb to late complications of the disease or its therapy. In particular, hyperlipidaemia, hypertension, premature ischaemic heart disease, diabetes mellitus and osteoporotic fractures may develop. Compliance with medications, clinic visits and lifestyle modifications is essential to prevent or reduce the risk of these associated problems, which may be iatrogenic or disease-related in origin (Bertsias et al., 2008). The long-term prognosis of antiphospholipid syndrome is poor, with organ damage in about one-third and functional impairment in up to one-fifth of patients at the end of 10 years.

Investigations

Investigations in SLE
A full blood count with differential white count, urinalysis and serum creatinine should be done for diagnosis and monitoring of the activity of SLE. Creatinine clearance or other assessment of glomerular filtration rate is more reliable for detecting early impairment of renal function. Patients with proteinuria or haematuria, or both, on dipstick must have microscopy done to look for casts if infection, stones and menstrual blood loss have been excluded.

For diagnosis, antinuclear antibody and anti-extractable nuclear antigen tests (see Chapter 24) should be done. No value is gained by repeating these tests, unless a change in clinical features is noted. Anti-ribonucleoprotein is associated with mixed connective tissue disease. Anti-dsDNA antibodies are useful for predicting patients at risk of developing renal disease and for monitoring disease activity. Although levels usually rise before a disease flare, they may fall at the time of flare. Levels of C3 and C4 fall with disease activity because of complement consumption, particularly in patients with renal disease. Levels also relate to the rate of synthesis in the liver and may rise in infections and pregnancy. Measurement of complement degradation products (for example, C3d, C4d) is less widely available but is more reliable for monitoring disease activity, as these reflect complement consumption alone. In women who are planning pregnancy, it is important to check for anti-Ro and anti-La antibodies and for antiphospholipid antibodies.
Infections should be avoided and treated promptly if appropriate, as they can precipitate flares. Similarly, contraceptive pills that contain oestrogen may exacerbate lupus disease or thrombosis and should be used with caution. In general, barrier methods or progesterone-only contraception are preferred. Pregnancy should be planned, as the outcome is better, with fewer complications in both mother and fetus, if the mother has inactive disease at the time of conception. Drug therapy should be reviewed before conception.

Overlap and lupus-like conditions are managed in much the same way as mild SLE (Table 18.3; Box 18.14). Dry eyes should be managed by the frequent use of artificial tears. Dry mouth is best managed by taking sips of plain water, sucking ice cubes, or eating sugar-free sweets. Artificial saliva preparations are disappointing.

### Investigations in antiphospholipid syndrome

Overall, 80–90% of patients with antiphospholipid syndrome are positive for antibodies to a complex of anticardiolipin antibodies and β2-glycoprotein I. Lupus anticoagulant is only found in 20% of patients with antiphospholipid syndrome but is associated with a high risk of thrombosis. Low levels of antiphospholipid antibodies of no clinical consequence may develop transiently after infections (Boxes 18.12 and 18.13).

### Management

#### General measures

Patients must be educated about the nature of their disease and the need for therapy. Leaflets from patient support organizations and references to reliable internet websites are useful. More than just drug therapy is required (Table 18.3; Box 18.14). Patients with sun-induced rashes should use sunblock regularly for about 6 months over the summer. Other patients with SLE should be aware that sun exposure may precipitate a disease flare.

### Drug therapy in SLE

Milder cases with intermittent rashes, arthritis and other mucocutaneous features can usually be treated with steroid creams, short courses of non-steroidal anti-inflammatory drugs (NSAIDs) and hydroxychloroquine (<6.5 mg/kg/day). These drugs are also widely used in overlap syndromes, with the exception of NSAIDs, which are contraindicated in patients with features of systemic sclerosis or renal disease. More severe cases of SLE usually require oral corticosteroids. Patients who need 10 mg/day of prednisolone or more despite hydroxychloroquine, or those who present with more severe manifestations (such as nephritis, gastrointestinal vasculitis or central nervous system disease) that need higher initial doses of prednisolone (0.5–1 mg/kg/day) are likely to need azathioprine, methotrexate or cyclophosphamide as steroid-sparing immunosuppressive agents (Table 18.4; Box 18.15). Mycophenolate mofetil
is a promising alternative drug for the treatment of severe lupus; it has been best studied for lupus nephritis as an alternative to cyclophosphamide, but it is not licensed for SLE yet. Cyclosporin A, tacrolimus and leflunomide are sometimes used for patients intolerant or resistant to other immunosuppressive agents (Table 18.4). Steroids should always be reduced slowly.

In pregnancy, patients may be given prednisolone, hydroxychloroquine and/or azathioprine, as the advantages are now considered to outweigh the risks. During lactation, prednisolone and hydroxychloroquine are acceptable, and azathioprine rarely causes problems at low doses. Methotrexate, mycophenolate, leflunomide and cyclophosphamide are contraindicated in pregnancy and while breastfeeding. Cyclosporin A has been used in pregnancy in patients who have undergone transplants, but is not usually recommended during lactation.

Meticulous screening and treatment of blood pressure, diabetes, hyperlipidaemia and osteoporosis are essential. In general, calcium-channel blockers, ACE inhibitors and angiotensin receptor blockers are the preferred anti-hypertensive agents, as they are helpful in the management of Raynaud’s phenomenon and renal disease, and because β-blockers aggrivate Raynaud’s phenomenon (Box 18.16). Bisphosphonates are often required in postmenopausal women, but they should be used with great care in women who may want to become pregnant in the future. Bisphosphonates, statins, ACE inhibitors and angiotensin-receptor blockers should be stopped before a planned pregnancy. Calcium and vitamin D can be used in all age groups. Treatment with anticoagulation and anti-epileptic, antidepressant, or antipsychotic drugs should be considered early in the management of patients with neuropsychiatric disease.

Oestrogen-containing contraceptives and hormone replacement therapy should be used with care in women with stable mild/moderate lupus and should be avoided in women with antiphospholipid antibodies, especially those with a history of thrombosis or pregnancy loss. Progesterone-only contraception is acceptable but is associated with a theoretical increased osteoporotic risk. Intrauterine devices can be used in women in stable relationships with a low risk of infection.


CHAPTER 19

Raynaud’s Phenomenon and Scleroderma

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The scleroderma spectrum

Scleroderma, meaning “hard skin”, is a generic term used to describe a number of related connective tissue disorders. There is a spectrum from localized dermal sclerosis, through systemic conditions featuring cutaneous and internal organ fibrosis together with vascular dysfunction, to purely vascular disorders of Raynaud’s phenomenon (Table 19.1). These conditions overlap clinically and pathologically, and in approximately 20% of cases there are additional features of other connective tissue disorders such as lupus, myositis or inflammatory arthritis (overlap systemic sclerosis). Although there are other causes for skin sclerosis, including sclerodema/scleromyxoedema, amyloidosis and nephrogenic systemic fibrosis, most of the differential diagnoses lie within the scleroderma spectrum. Distinguishing localized forms of the disease from those in which internal organ complications may develop is central to management. Absence of antinuclear antibodies, altered nailfold capillaroscopy and Raynaud’s phenomenon all point towards localized scleroderma (see below).

Raynaud’s phenomenon

Episodic cold-induced vasospasm (Figure 19.1), triggered by cold or emotional stress, affects around 5% of the adult population, especially young females. In Primary Raynaud’s (90%) there are no other clinical or investigational abnormalities. Secondary Raynaud’s (10%) implies there are other features, usually an underlying autoimmune rheumatic disease. Investigation of Raynaud’s symptoms includes the identification of secondary causes (Box 19.1). Such causes of Raynaud’s, or acrocyanosis, include vibrating machine tools, thoracic-outlet obstruction, drugs such as β-blockers, and haematological abnormalities such as cryoglobulinaemia. Macrovascular arterial disease, embolization and systemic vasculitis, including Berger’s disease, are important but rare differential diagnoses. Some patients with isolated Raynaud’s
Raynaud’s phenomenon and connective tissue diseases

Many patients with a defined connective tissue disease have Raynaud’s phenomenon. For SSc this approaches 95% and emphasizes a likely central role for vascular abnormalities. In lupus or dermatomyositis the frequency of Raynaud’s is around 50%. It is less common in other rheumatic diseases, including Sjögren’s syndrome and rheumatoid arthritis. There are many patients with overlap syndromes who have Raynaud’s and also features such as arthralgia, malaise or photosensitivity but who do not fulfill classification criteria for a defined disease. These are best termed “undifferentiated connective tissue disease” cases, which may later evolve into more significant diseases (see also Chapters 18 and 21).

Systemic sclerosis

The most important disease within the scleroderma spectrum is SSc. This has high mortality, and approximately 60% of patients diagnosed with SSc will ultimately die from the disease. Most often this is due to cardio-respiratory complications. Nevertheless, there has been significant improvement in survival recently due to better treatment of organ-based complications, and the overall 5-year survival now approaches 80%. Cardinal features of SSc are the association of skin sclerosis with Raynaud’s phenomenon, which is almost always present, and with internal organ involvement, which varies in extent between patients.

The majority of cases fall into one of two major subsets (Table 19.1). The diffuse cutaneous subset (dcSSc) is determined by involvement of skin proximal to the knees and elbows and may actually be confused with an inflammatory arthropathy in its early stages. Most of the important complications develop within the first 3 years of dcSSc, and skin sclerosis tends to be maximal at...
phenomenon, oesophageal dysmotility, sclerodactyly and telangiectasia occur. It is probably better not to distinguish such cases, as these manifestations are not universal and under-emphasize the life-threatening complications that develop in a significant proportion of lcSSc patients. These include pulmonary arterial hypertension, severe midgut disease and interstitial pulmonary fibrosis. Other Sc cases include overlap syndromes with features of polyarthritis, myositis or systemic lupus erythematosus, and the small group of SSc sine scleroderma who have major visceral involvement, Raynaud’s phenomenon and a hallmark autoantibody—typically anti-topoisomerase 1. The term “MCTD” is probably best avoided, as most of the patients with this designation evolve into a defined overlap syndrome, often with prominent features of SSc or lupus.

around 18–30 months. Thereafter skin involvement tends to stabilize or improve. Despite stabilization or improvement in skin sclerosis, internal organ complications may develop at a later stage, and so long-term follow-up is mandatory. The characteristics of patients with each subset at different times in their disease are summarized in Boxes 19.2 and 19.3. Raynaud’s generally develops concurrently with the skin disease or shortly afterwards. The limited cutaneous subset of SSc (Figure 19.2) accounts for around 60% of cases in most North American or European series. Skin involvement is much less extensive and may be confined to the fingers (sclerodactyly), face or neck. Raynaud’s phenomenon is very prominent and may preceede development of SSc by several years. The designation “CREST syndrome” is popular in the USA, referring to a subgroup of lcSSc in whom calcinosis, Raynaud’s

**Box 19.2 Characteristic findings and suggested treatment for limited cutaneous scleroderma**

**Early stage (≤5 years after onset)**
- Constitutional symptoms—fatigue common
- Skin thickening—no or minimal progression
- Organs affected—Raynaud’s phenomenon, ulcers of digital tips, oesophageal symptoms
- Treatment—vascular treatment (oral or intravenous) with or without digital sympathectomy, removal of calcinosis, treat oesophageal problems

**Late stage (>10 years after onset)**
- Constitutional symptoms—fatigue common and aggravated by effects of vasculopathy and gut disease
- Skin thickening—stable or slow progression
- Organs affected—Raynaud’s phenomenon, ulcers of digital tips, calcinosis, oesophageal stricture, small bowel malabsorption, pulmonary arterial hypertension, lung fibrosis
- Treatment—vascular treatment (oral or intravenous) with or without digital sympathectomy, removal of calcinosis, treat oesophageal and midgut problems

**Box 19.3 Characteristic findings and suggested treatment for diffuse cutaneous scleroderma**

**Early stage (≤5 years after onset)**
- Constitutional symptoms—fatigue, weight loss, pruritis
- Skin thickening—rapid progression with peak involvement by 2 years typical
- Organs affected—risk of renal, cardiac, pulmonary fibrosis, gastrointestinal, articular and muscular damage
- Treatment—vascular therapy, physiotherapy and occupational therapy as appropriate; immunosuppression for lung fibrosis and severe or progressive skin involvement; low-dose corticosteroids

**Late stage (>5 years after onset)**
- Constitutional symptoms—generally diminished
- Skin thickening—stable or regression
- Organs affected—musculoskeletal deformities, progression of existing visceral diseases but reduced risk of new complications
- Treatment—treat complications, gradual withdrawal of immunosuppression

![Figure 19.2 Characteristic features of limited cutaneous scleroderma. (a) Puffy fingers, tight skin, Raynaud’s phenomenon, loss of distal digits and ulceration of tips of digits. (b) Microstomia and telangiectasia. (c) Hypopigmentation caused by diffuse cutaneous scleroderma.](image)
Figure 19.3 Common immunofluorescent patterns seen on testing for antinuclear antibodies. 
(a) Homogeneous—typical of antibodies to DNA, with or without histones. 
(b) Speckled—typical of antibodies to Ro, La, Sm and ribonucleotide protein. 
(c) Nucleolar—typical of scleroderma. 
(d) Centromere—mainly found with limited cutaneous scleroderma

**Autoantibody profiles**

The major hallmark autoantibodies associated with SSc are mutually exclusive (Figure 19.3). Thus, if a patient has anti-centromere antibodies they will almost never have anti-topoisomerase 1 or another reactivity associated with SSc. This appears to reflect the immunogenetic background of these individuals and may explain the clinical differences between patients with hallmark reactivity. The SSc-associated patterns of autoantibody reactivity are summarized in Table 19.2.

**Risk stratification in SSc**

The clinical heterogeneity of SSc and differences in natural history between the two major subsets and the life-threatening nature of some of the SSc-associated complications have led to attempts to risk-stratify patients at diagnosis and initial assessment. Abnormalities reflecting systemic inflammation (elevated erythrocyte sedimentation rate), pulmonary disease (impaired diffusion capacity, DLCO) or renal involvement (proteinuria) identifies patients with a poor 5-year survival. In addition, the clinical association of antibody profiles allows patients at increased risk of

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>60% lcSSc</td>
<td>Associated with typical CREST</td>
</tr>
<tr>
<td>Scl-70</td>
<td>40% dcSSc, 15% lcSSc</td>
<td>Predictive of interstitial lung involvement, especially in iSSc</td>
</tr>
<tr>
<td>RNApol</td>
<td>20% SSc</td>
<td>Anti-RNApol I or III associated with diffuse subset and renal disease</td>
</tr>
<tr>
<td>U1-RNP</td>
<td>10% SSc</td>
<td>Associated with overlap features</td>
</tr>
<tr>
<td>U3-RNP</td>
<td>5% SSc</td>
<td>Poor outcome and isolated PHT in dcSSc</td>
</tr>
<tr>
<td>PM-Scl</td>
<td>3% SSc</td>
<td>Myositis overlap</td>
</tr>
<tr>
<td>Th/To</td>
<td>5% SSc</td>
<td>Lung fibrosis in lcSSc</td>
</tr>
<tr>
<td>anti-M2</td>
<td>5–10% SSc</td>
<td>Especially in lcSSc with PBC</td>
</tr>
</tbody>
</table>

See also chapters 18 and 20
pulmonary or renal complications to be identified. In the future, such information is likely to direct management and screening. Antibodies can predict particular complications such as antitopoisomerase and lung fibrosis, anti-RNA polymerase and renal crisis or anti-Th/To and respiratory involvement in lcSSc. At present the strongest genetic associations relate to SSc-specific autoantibodies, but other genetic factors that determine the disease profile are being sought. Recently a genetic variant in connective tissue growth factor (CTGF) was associated with SSc (Fonseca et al., 2007).

Management of SSc

The principles of effective management of SSc are summarized in Box 19.4. Unfortunately at present there are no disease-modifying treatments of proven efficacy. Most patients benefit from vascular therapy, and a number of agents that suggest the potential for vascular remodelling have been used in trials (Table 19.3). Immunosuppressive treatment is generally reserved for patients with early and aggressive dcSSc or with a major organ-based complication such as interstitial lung disease or myositis. Cyclophosphamide has been demonstrated to have modest benefit in prospective clinical trials (Hoyles et al., 2006; Tashkin et al., 2007). A number of approaches are being evaluated in clinical trials. High-dose immunosuppression with autologous peripheral stem-cell rescue is currently being evaluated in clinical trials. There are currently no effective antifibrotic agents for established SSc, but a number are under development. They include biological therapies that neutralize key potential cytokines driving SSc, including transforming growth factor beta 1 (TGFβ1) and CTGF.

Organ-based complications

The outcome of SSc is largely determined by the extent and severity of organ-based complications. Some of these are almost universal, such as oesophageal reflux, while many of the severe complications occur in around 10–15% of cases overall.

Pulmonary hypertension—Pulmonary hypertension is the single largest cause of death directly attributable to SSc. The frequency of the complication is likely to be around 10% overall, although published prevalence studies have varied largely owing to differences in diagnostic methods and variation in study cohorts. It occurs in both limited and diffuse cutaneous subsets, although as an isolated complication it is most often seen in established lcSSc. Diagnosis can only be made robustly using right-heart catheterization and is determined by a mean pulmonary arterial pressure in excess of 25 mm Hg at rest, without elevated pulmonary capillary wedge pressure, but with increased pulmonary vascular resistance.

Distinction should be made between pulmonary arterial hypertension (PAH) and pulmonary hypertension secondary to severe interstitial lung fibrosis. The latter is uncommon in SSc, although some degree of lung fibrosis in association with PAH is frequent and may impact on survival. Historically the outcome in SSc-associated PAH was dismal, with a 2-year survival of 47%. With the advent of modern advanced therapies, including endothelin receptor antagonists (e.g. bosentan, sitaxentan) and selective phosphodiesterase inhibitors that promote nitric-oxide-induced vasodilatation (e.g. sildenafil) given in the context of a multidisciplinary pulmonary hypertension service, outcome for confirmed PAH has improved and currently survival of greater than 69% at 2 years has been demonstrated. Nevertheless, this is much inferior to outcome in idiopathic (previously primary) PAH using the same therapies, and so there is much scope for improvement.
Therefore new and better treatments are needed. It has been suggested that alveolar epithelial damage may be more important than inflammation in driving the fibrosis, and research data confirm that markers of epithelial injury or permeability such as serum KL-6 or DTPA clearance may provide predictive information about future decline in lung function. At present having determined the presence of fibrosis by HRCT, the cornerstone of management is serial pulmonary function testing. Progressive deterioration, even if gradual, is a clinical indicator for active treatment. At present immunosuppressive strategies are used. In severe advanced disease without major co-morbidity, single lung transplantation has been shown to be beneficial.

Scleroderma renal crisis (SRC)—There have been major advances in management of renal disease in SSc. The major problem is one of recognition, and education of both patients and physicians is important. SRC often presents non-specifically with headaches and visual disturbances before encephalopathy, cardiac failure or acute oliguric renal failure develop. Treatment with angiotensin-converting enzyme inhibition is mandatory. Patients should be admitted for blood pressure control and monitoring of renal function. Fifty per cent of cases require dialysis, which is temporary in many individuals. There may be significant recovery in renal function for up to 2 years after a renal crisis, and decisions regarding transplantation should be delayed until that time. There is no evidence that prophylactic administration of ACE inhibitors is helpful in preventing renal crisis or improving outcome, and the cornerstone of management is patient education, vigilant blood pressure monitoring, and avoidance of nephrotoxic drugs or high-dose corticosteroids with prompt initiation or appropriate therapy early in the course of the SRC.

Lung fibrosis—Interstitial lung fibrosis is a common internal organ manifestation of SSc (Figures 19.4 and 19.5). It is present in more than 30% of cases but may not be inexorably progressive. The anti-scl70 autoantibody provides a useful clinical marker and is generally associated with lung fibrosis in both SSc subsets. High-resolution computed tomography (HRCT) imaging is currently the gold-standard test to detect and determine the pattern and extent of disease. Bronchoalveolar lavage is favoured in some centres and certainly correlates with the extent of disease, but not always with activity. Lung biopsy is not routinely indicated, but histologically most cases of SSc-associated lung fibrosis are classified as non-specific interstitial pneumonia, rather than the usual interstitial pneumonia pattern of idiopathic lung fibrosis. This may explain the better outcome for most patients with SSc compared with idiopathic pulmonary fibrosis. Immunosuppressive treatment with cyclophosphamide has recently been shown to be superior to placebo in a large controlled clinical trial, but the effect was modest.

Scleroderma renal crisis (SRC)—There have been major advances in management of renal disease in SSc. The major problem is one of recognition, and education of both patients and physicians is important. SRC often presents non-specifically with headaches and visual disturbances before encephalopathy, cardiac failure or acute oliguric renal failure develop. Treatment with angiotensin-converting enzyme inhibition is mandatory. Patients should be admitted for blood pressure control and monitoring of renal function. Fifty per cent of cases require dialysis, which is temporary in many individuals. There may be significant recovery in renal function for up to 2 years after a renal crisis, and decisions regarding transplantation should be delayed until that time. There is no evidence that prophylactic administration of ACE inhibitors is helpful in preventing renal crisis or improving outcome, and the cornerstone of management is patient education, vigilant blood pressure monitoring, and avoidance of nephrotoxic drugs or high-dose corticosteroids with prompt initiation or appropriate therapy early in the course of the SRC.

Gut disease—The gastrointestinal tract is the most frequently affected organ in SSc. Up to 90% of patients demonstrate oesophageal dysmotility with reflux, and the proton pump inhibitors have dramatically improved symptomatic disease. Strictures are now relatively rare, although vigilance for Barrett’s metaplasia is required. Midgut disease with bacterial overgrowth may respond
to broad-spectrum antibiotics, although maintenance treatment may be required. Paradoxically, colonic involvement may lead to severe constipation, and anorectal incontinence is prevalent. It is important that acute abdominal complications of SSc are managed conservatively as far as possible, because major abdominal surgery is poorly tolerated owing to SSc-related co-morbidity, prolonged post-operative ileus and poor healing.

Patient Support organizations are listed in Box 19.5.

References


Further reading


CHAPTER 20

Reflex Sympathetic Dystrophy

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2 University of Alberta, Edmonton, Canada

Introduction

Reflex sympathetic (osteo)dystrophy (RSD) is a descriptive term for a condition mainly affecting the limbs, with severe pain, a preceding event that might be relatively trivial in traumatic terms, and abnormal blood flow and sweating in the affected area.

To have the “full house” clinically, the following should be present: (a) severe pain, usually starting peripherally, and working more proximally over time in a non-dermatomal fashion (allodynia)—the pain is disproportionate to the triggering event and clinical findings (hyperpathia); (b) usually a preceding event that might be relatively trivial in traumatic terms; (c) abnormal blood flow to the affected area (usually a limb), with colour changes (blues, whites and reds) and oedema; (d) abnormal sweating in the area; (e) changes in the motor system, with weakness and sometimes tremor; (f) eventual structural changes to superficial and deep structures leading to atrophic, shiny skin, contractures and patchy osteoporosis around joints on X-rays.

Although diagnostic criteria have been proposed, these have not been validated and are complicated by the fact that not all features may be present at the same time and may vary in their intensity. The condition tends to affect upper limbs more commonly than lower limbs. Usually one limb is affected, but it can become bilateral, or affect another limb. It is usually most evident distally (hand and wrist, or foot and ankle), but a whole limb can be affected, such as in “shoulder-hand syndrome”.

This chapter explores the following areas: What causes RSD? How is RSD diagnosed? What is the treatment of RSD?

What causes RSD?

The cause of RSD is far from understood, but it appears to involve an exaggeration of normal physiological responses and involves changes at multiple levels in the central and peripheral nervous systems. Some epidemiological features of RSD are shown in Table 20.1. Taking total knee arthroplasty as an example, a prevalence of between 0.8 and 1.2% of persistent RSD has been quoted. However, a recent prospective study suggested that 21% of patients fulfilled diagnostic criteria 1 month after operation, falling to 12.7% at 6 months, suggesting that symptoms and signs of RSD are not improved. The change in terminology has also failed to catch on, so that many specialists still refer to RSD, even though it is clear that the reflexes are not necessarily involved, and the sympathetic nervous system cannot be implicated in many patients (for example, sympathetic ganglia blockade only relieves the pain in some patients).

To have the “full house” clinically, the following should be present: (a) severe pain, usually starting peripherally, and working more proximally over time in a non-dermatomal fashion (allodynia)—the pain is disproportionate to the triggering event and clinical findings (hyperpathia); (b) usually a preceding event that might be relatively trivial in traumatic terms; (c) abnormal blood flow to the affected area (usually a limb), with colour changes (blues, whites and reds) and oedema; (d) abnormal sweating in the area; (e) changes in the motor system, with weakness and sometimes tremor; (f) eventual structural changes to superficial and deep structures leading to atrophic, shiny skin, contractures and patchy osteoporosis around joints on X-rays.
RSD, which are summarized below. A series of vicious circles that result in the characteristic features of inflammation with microvascular dysfunction. These interrelate in a number of theories have been propounded, but revolve around uneventful recovery, but a minority go onto develop RSD? A who suffer the potential triggers listed in Table 20.1 make a full and abnormalities may be a key driver. A crucial question that has not been satisfactorily answered is: Why do the majority of patients reported for Colles’ fracture and peripheral nerve injury, respectively. The pathology of RSD is bedevilled by the lack of tissue studies, either pre- or post-mortem. Limited histological investigations have suggested that microangiopathy or other vascular abnormalities may be a key driver. A crucial question that has not been satisfactorily answered is: Why do the majority of patients who suffer the potential triggers listed in Table 20.1 make a full and uneventful recovery, but a minority go onto develop RSD? A number of theories have been propounded, but revolve around peripheral mechanisms, central mechanisms and neurogenic inflammation with microvascular dysfunction. These interrelate in a series of vicious circles that result in the characteristic features of RSD, which are summarized below.

### Peripheral mechanisms
Trauma to C fibres and A\(^\text{\text{TM}}\) afferents is likely to be an initiating event. Many patients have sympathetically maintained pain, which may activate both mechanoreceptors and nociceptors. Some patients experience benefit from alpha blockade, supporting a role for \(\beta\)-adrenoceptors in the pathogenesis of RSD. These receptors become expressed on nociceptors in some cases of soft-tissue and nerve injury. Some patients demonstrate supersensitivity to catecholamines, consistent with increased \(\beta\)-adrenoceptor responsiveness.

### Central mechanisms
In RSD an initial activation of nociceptors may lead to alteration of central information processes, resulting in central sensitization. Patients exhibit normal thresholds for the detection of cold and heat, but reduced thresholds for cold-pain and heat-pain, suggest-

### Neurogenic inflammation
Release of vasoactive peptides, including substance P and calcitonin gene-related peptide, from afferent nerve fibres cause vasodilatation, with increased vascular permeability and protein leakage. Neuropeptides may also be released in response to impaired blood flow, oxygen deficiency and an increase in protons and skin lactate levels. This might explain why some of the early clinical features of RSD appear to be inflammatory.

### Microvascular dysfunction
A number of investigators have confirmed microvascular dysfunction in RSD, although it remains unknown whether these changes, reflected by colour and temperature changes, drive the disease process or are secondary to it.

Bringing these factors together, it has been suggested that RSD is initiated by trauma to C fibres and A\(^\text{\text{TM}}\) afferents in soft tissue or nerves, resulting in neurogenic inflammation. Signs of inflammation predominate in early disease, with redness, increased skin temperature due to inhibition of cutaneous vasoconstrictor neurons, with subsequent loss of function and pain. Early in the disease, the sympathetic nervous system plays a role, but when central sensitization takes over, with changes at the dorsal root ganglion level, the pain becomes independent of sympathetic nerves. There is a competition between the continued inhibition of vasoconstriction and supersensitivity of the peripheral vessels to circulating adrenaline. Late intractable disease can be characterized by a cold, painful limb with poor or no function, with disuse leading to immobility and contractures.

### How is RSD diagnosed?
In the early stages of RSD the limb is swollen and tender, and the diagnosis may not be straightforward, as it can mimic many other diseases, such as inflammatory arthritis, cellulitis, osteomyelitis, deep venous thrombosis, lymphatic obstruction and malignancy. In the late intractable disease, when the limb becomes cold, chronic arterial insufficiency needs to be considered.

There is no diagnostic test for RSD, and tests are only required to rule out the other causes of a painful swollen limb as listed above. Routine investigations, such as a full blood count and erythrocyte sedimentation rate should be normal, and if not an explanation should be sought. In terms of positive features supporting RSD

<table>
<thead>
<tr>
<th>Triggers</th>
<th>Usually some noxious event such as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist and tibial fractures (about 30% may demonstrate mild features, but only a minority go on to severe disease)</td>
<td></td>
</tr>
<tr>
<td>Trauma: mild or moderate</td>
<td></td>
</tr>
<tr>
<td>Rotator cuff tendinitis or subacromial bursitis</td>
<td></td>
</tr>
<tr>
<td>Surgery: carpal tunnel decompression, arthroscopy, arthroplasty, lumbar spine surgery</td>
<td></td>
</tr>
<tr>
<td>Central nervous system disorders: head injury, hemiplegia, spinal cord injury, neuropathy</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>Immobilization: in any of the above may be an important factor</td>
<td></td>
</tr>
</tbody>
</table>

| Sex | More common in women than men, with a ratio of 3:1 quoted |
| Age | Any age, although the mean in some studies is quoted as 52 years; now well recognized in children |

| Genetics | Some evidence to support a familial predisposition |
| Personality traits | No convincing evidence to support an association |
| Psychological factors | Some patients can have motor weakness and movement disorders relieved by placebo, nerve blocks or infusions |
Diagnostic criteria for RSD

1. The presence of an initiating noxious event, or a cause of immobilization
2. Continuing pain, allodynia or hyperalgesia, in which the pain is disproportionate to any inciting event
3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

Note: criteria 2–4 must be satisfied

(Table 20.2), X-rays may show patchy osteoporosis, especially in the juxta-articular region. Joint space is usually preserved, but may be lost in late disease with ankylosis. On bone scanning there is increased uptake in early disease, and reduced uptake in late disease. Patients with markedly increased uptake may have a better prognosis, possibly reflecting the fact that they have not yet progressed to late-stage disease. Thermography detects asymmetry in limb surface temperature, but is not widely available. Bone densitometry and magnetic resonance imaging (MRI) may show nonspecific changes, such as reduced bone density, soft-tissue swelling and bone-marrow oedema, but nothing specific to positively diagnose RSD. The greatest value of MRI is to rule out other causes of a painful swollen limb.

How is RSD treated?

Owing to our limited understanding of the aetiology and pathogenesis of RSD, much of the therapeutics is empirical, and what helps one patient may not help others. Because established RSD can be very challenging to treat, emphasis has been placed on prevention where possible and, failing that, early intervention. The main aims are to reduce pain and restore function. Early mobilization following predisposing conditions is important, and graded physiotherapy may be very helpful. A trial in 1999 showed that vitamin C, a powerful antioxidant, may prevent RSD, supporting the growing evidence for the role of oxygen-free radicals in RSD. This needs to be researched further.

Patients who are particularly vulnerable are patients with a previous history of RSD, particularly if they require surgery on the previously affected part. A controlled study found that the risk of RSD could be reduced by a stellate ganglion block after the operation. An uncontrolled study suggested pre-operative calcitonin may prevent recurrence.

Although many experts and committees have recommended physiotherapy, occupational therapy, vocational rehabilitation and behavioural therapy, the evidence base for these is weak or lacking. One study compared physiotherapy and occupational therapy with social work intervention as the control, and showed no differences in the three groups for pain at 12 months, with only small improvements in temperature and global impairment for the intervention arms of the trial. An algorithm of treatment has been proposed by Stanton-Hicks (2002) with a cautious start (heat, massage and gentle movement to restore normal sensory processing), then isometric exercises for strengthening, treatment of secondary myofascial pain syndrome, aerobic conditioning, through to complete functional rehabilitation. Because pain can be the main rate-limiting factor in rehabilitation, medical and psychological therapies often have to run side by side (Table 20.3).

The mainstay of drug interventions is analgesics and non-steroidal anti-inflammatories. Low-dose antidepressants and anticonvulsants are commonly used, but the evidence base is sparse. A systematic review of therapies concluded that the only trial data that consistently demonstrated analgesia was with oral corticosteroids. However, many clinicians have understandable concerns about using steroids for disease that has the potential to become chronic, and where the evidence base for ongoing inflammation driving the disease is limited. A plethora of other drugs have been tried in RSD, which is testimony to the difficulties in treating the condition. Intranasal calcitonin has shown conflicting results. Drugs that do show promise are the bisphosphonates, justified initially on osteoporosis being a significant feature of RSD. A controlled trial of alendronate showed improved bone mineral content of the affected limb, but only small benefits to pain management. By contrast, a trial of intravenous clodronate showed substantial improvements in pain management at 6 months, with highly significant pain reduction compared with placebo.

The role of sympathetic blockade is controversial. For paravertebral blockade, the stellate ganglion for upper limb RSD is blocked with a series of local anaesthetics, depending on response, and the lumbar sympathetic chain for lower limb RSD. Another technique is intravenous blockade, usually with guanethidine. However, a systematic review found this treatment to be ineffective, so its use may decline in future. Continuous blockade of the brachial or lumbar plexus has been advocated with drugs such as morphine, so that whenever the catheter is in place, the patient can take advantage of the pain relief to maximize their rehabilitation.
Intrathecal baclofen proved to be effective for the upper limb dystonias in six out of seven patients, but did not improve pain. Spinal-cord stimulation has been shown to be effective in relieving pain in controlled trials. The procedure is, however, not without risk, as it involves placing an electrode on the dorsal aspect of the spinal cord, and an electric current produces paraesthesias that block the pain in the affected area. However, the average improvement in pain is sustained but not substantial, and functional and quality-of-life benefits have not been demonstrated. This leaves the dilemma of whether invasive and costly interventions that provide modest pain relief are justified. Clearly these concerns and the risks involved mean that patients have to be carefully selected.

Further reading


Diagnosis of connective tissue diseases is often challenging because of the protean clinical features and the fact that no single symptom or sign is pathognomonic of a specific connective tissue disease. Classification criteria for the major connective tissue diseases (see Chapters 18 and 19) were developed primarily as a means of standardizing patient populations for clinical research rather than for diagnosis. In practice, they are extremely limited for early diagnosis of connective tissue diseases. In many patients attending connective disease clinics, it is not possible to make definitive diagnosis, especially early in the course of a systemic rheumatic illness. Many, but not all, of these patients eventually fulfill classification criteria for one or more of the major connective tissue disease entities, a process that may take 10–20 years.

A substantial proportion of these patients have non-specific symptoms or signs—most commonly either isolated Raynaud’s phenomenon, or an early inflammatory polyarthritis, or constitutional symptoms of fever, malaise and fatigue. Serological tests often show abnormalities that are suggestive of a connective tissue disease but not sufficiently specific to classify the patient as having one of the major connective tissue diseases. This has prompted the introduction of additional terms such as “overlap syndrome” and “undifferentiated connective tissue disease.”

From a management perspective, it is important not only to recognize and treat potentially aggressive disease, but also to avoid over-treatment in patients where either the diagnosis is unclear or the disease has a potentially benign course.

## Autoantibody profile in diagnosis

Antinuclear antibodies are a hallmark of connective tissue diseases. Serology is of particular value in situations in which clinical expression of the disease is incomplete, when the presence of a particular antinuclear antibody profile can be diagnostic. These antibodies can be found in a variety of clinical settings, however, and their occurrence does not necessarily indicate the presence of any specific disease. It is therefore imperative that requests for antinuclear antibody tests and the interpretation of results thereof be done in the light of the clinical findings.

The indirect immunofluorescence test, using the HEp-2 cell substrate, is the gold standard for detecting antinuclear antibodies. In both systemic lupus erythematosus and scleroderma, antinuclear antibodies can be detected in 95% or more of untreated patients with active disease by this method (Table 21.1). In cases suspected of having either of these diseases, the indirect immunofluorescence test is enough as a screening test for antinuclear antibodies, and it is not cost effective to test automatically for anti-nDNA or other antibody specificities. The individual antinuclear antibody fluorescent patterns are of limited diagnostic utility but may provide guidance to more specific immunological tests. In some instances, a false negative result may occur if either the antigen is outside the nucleus (for example, anti-Jo-1 and anti-ribosomal P-protein antibodies, both often categorized under the umbrella term “antinuclear antibodies”) or if it is present in a form not recognised by a particular autoantibody (for example, when anti-Ro is directed exclusively to determinants on the native Ro molecule not expressed in cultured HEp-2 cells). In such cases, the clinical picture dictates that specific autoantibody assays should be undertaken.

Once antinuclear antibodies have been detected with a screening test, it is important to determine their specificity. This is now part of the standard operating procedure of serology laboratories, but the process is greatly facilitated by the doctor giving sufficient clinical information when antinuclear antibody testing is requested.
Is it a Connective Tissue Disease?

Do not fulfil criteria for any one disorder (Figure 21.1). Although no universally agreed definition of “undifferentiated connective tissue disease” exists, this term should be distinguished from other commonly used terms such as “overlap syndrome,” in which patients meet the criteria for two or more connective tissue diseases or specific criteria for mixed connective tissue disease (Table 21.3) (see also Chapters 18 and 19). Other terms used in the literature that are synonymous with undifferentiated connective tissue disease include “lupus-like”, “pre-lupus,” “latent lupus” and “incomplete lupus.”

Long-term, prospective follow-up studies of outcome show that these patients represent a large proportion (25–50%) of patients presenting to connective tissue disease clinics. Only a minority of patients, about 30%, evolve clinically to fulfill classification criteria of a defined connective tissue disease, usually in the first few years of follow-up. Spontaneous remission occurs in 5–10% of patients, but in the majority the undifferentiated connective tissue disease state persists. Major organ involvement is rare in these patients. Serositis, alopecia, photosensitivity, discoid rash (Figure 21.2) and the presence of either anti-nDNA antibodies or anti-Sm antibodies are predictors of evolution to SLE.

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**Table 21.1** Antinuclear antibodies in various diseases detected by indirect immunofluorescence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency of antinuclear antibodies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune rheumatic disease</strong></td>
<td></td>
</tr>
<tr>
<td>• Drug-induced lupus</td>
<td>100</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
<td>98</td>
</tr>
<tr>
<td>• Systemic sclerosis (scleroderma)</td>
<td>95</td>
</tr>
<tr>
<td>• Sjögren’s syndrome</td>
<td>80</td>
</tr>
<tr>
<td>• Pauciarticular juvenile idiopathic arthritis</td>
<td>70</td>
</tr>
<tr>
<td>• Polymyositis or dermatomyositis</td>
<td>60</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td>50</td>
</tr>
<tr>
<td><strong>Organ-specific autoimmunity</strong></td>
<td></td>
</tr>
<tr>
<td>• Primary autoimmune cholangitis</td>
<td>100</td>
</tr>
<tr>
<td>• Autoimmune hepatitis</td>
<td>70</td>
</tr>
<tr>
<td>• Myasthenia gravis</td>
<td>50</td>
</tr>
<tr>
<td>• Autoimmune thyroid disease</td>
<td>45</td>
</tr>
<tr>
<td>• Idiopathic pulmonary hypertension</td>
<td>40</td>
</tr>
<tr>
<td><strong>Other conditions</strong></td>
<td></td>
</tr>
<tr>
<td>• Waldenström’s macroglobulinaemia</td>
<td>20</td>
</tr>
<tr>
<td>• Subacute bacterial endocarditis</td>
<td>20</td>
</tr>
<tr>
<td>• Infectious mononucleosis</td>
<td>15</td>
</tr>
<tr>
<td>• Leprosy</td>
<td>15</td>
</tr>
<tr>
<td>• HIV</td>
<td>10</td>
</tr>
<tr>
<td><strong>Normal population</strong></td>
<td></td>
</tr>
<tr>
<td>• Children</td>
<td>8</td>
</tr>
<tr>
<td>• Adults</td>
<td>15</td>
</tr>
</tbody>
</table>

Specific antinuclear antibody tests are often helpful in stratifying patients into clinical subsets, which may be useful in the further management of specific clinical manifestations and prognostication (Table 21.2). These autoantibodies are usually present from the beginning of the clinical presentation and are detectable throughout the course of the disease. In some instances, such as the anti-nDNA test, autoantibody titres may fluctuate with disease activity. Many serology laboratories these days use commercial kits to detect specific autoantibodies. Although these tests are less labour intensive, they vary in sensitivity, and sometimes produce false-positive results. This is especially the case with the anti-nDNA and anti-Sm assays.

**Undifferentiated connective tissue disease**

The term “undifferentiated connective tissue disease” was first coined in 1980 by LeRoy and colleagues (LeRoy et al., 1980). This was to counter the concept of mixed connective tissue disease being a distinct disease entity and to point out that many patients designated as having mixed connective tissue disease presented with an early phase of disease that later evolved into one of the “classic” connective tissue diseases, particularly scleroderma. Subsequently, undifferentiated connective tissue disease has been embraced by others and, rather than replacing mixed connective tissue disease, it has been used to describe patients with clinical and laboratory features of connective tissue disease (Box 21.1) who do not fulfil criteria for any one disorder (Figure 21.1). Although no universally agreed definition of “undifferentiated connective tissue disease” exists, this term should be distinguished from other commonly used terms such as “overlap syndrome,” in which patients meet the criteria for two or more connective tissue diseases or specific criteria for mixed connective tissue disease (Table 21.3) (see also Chapters 18 and 19). Other terms used in the literature that are synonymous with undifferentiated connective tissue disease include “lupus-like”, “pre-lupus,” “latent lupus” and “incomplete lupus.”

Long-term, prospective follow-up studies of outcome show that these patients represent a large proportion (25–50%) of patients presenting to connective tissue disease clinics. Only a minority of patients, about 30%, evolve clinically to fulfill classification criteria of a defined connective tissue disease, usually in the first few years of follow-up. Spontaneous remission occurs in 5–10% of patients, but in the majority the undifferentiated connective tissue disease state persists. Major organ involvement is rare in these patients. Serositis, alopecia, photosensitivity, discoid rash (Figure 21.2) and the presence of either anti-nDNA antibodies or anti-Sm antibodies are predictors of evolution to SLE.

---

**Box 21.1** Characteristics of undifferentiated connective tissue disease

- Common manifestations
  - Raynaud’s phenomenon
  - Arthralgia or myalgia
  - Rash
  - Sicca symptoms
  - Constitutional symptoms (fever, malaise, fatigue)
- One-third evolve into a defined connective tissue disease, usually within 5 years

---

**Figure 21.2** Swollen “puffy” fingers of patient with undifferentiated connective tissue disease
Table 21.2 Specificity of antinuclear antibodies in diagnosis and disease expression

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibody</th>
<th>Frequency (%)</th>
<th>Clinical association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematos</td>
<td>Anti-nDNA‡</td>
<td>70</td>
<td>• Lupus nephritis</td>
</tr>
<tr>
<td></td>
<td>Anti-nucleosome</td>
<td>70</td>
<td>• Early disease, lupus nephritis, drug-induced lupus</td>
</tr>
<tr>
<td></td>
<td>Anti-Sm</td>
<td>10–25*</td>
<td>• Vasculitis, central nervous system lupus</td>
</tr>
<tr>
<td></td>
<td>Anti-U1RNP</td>
<td>30–50*</td>
<td>• Raynaud’s phenomenon, swollen fingers, arthritis, myositis, mixed connective tissue disease</td>
</tr>
<tr>
<td></td>
<td>Anti-Ro</td>
<td>40</td>
<td>• Photosensitive rash, subacute cutaneous lupus erythematos, neonatal lupus, congenital heart block, Sjögren’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Anti-La</td>
<td>15</td>
<td>• As for anti-Ro</td>
</tr>
<tr>
<td></td>
<td>Anti-ribosomal P-protein</td>
<td>15</td>
<td>• Central nervous system lupus (psychosis or depression)</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Anti-Ro</td>
<td>60–90#</td>
<td>• Extraglandular disease, vasculitis, lymphoma</td>
</tr>
<tr>
<td></td>
<td>Anti-La</td>
<td>35–85#</td>
<td>• As for anti-Ro</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Anti-centromere</td>
<td>5–30*</td>
<td>• Limited cutaneous disease, microvascular or macrovascular disease, telangiectasia</td>
</tr>
<tr>
<td></td>
<td>Anti-ThRNP</td>
<td>4</td>
<td>• Limited cutaneous disease</td>
</tr>
<tr>
<td></td>
<td>Anti-topo-1</td>
<td>25</td>
<td>• Diffuse cutaneous disease, interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td>Anti-RNA polymerases</td>
<td>20</td>
<td>• Rapidly progressive diffuse cutaneous disease, scleroderma renal crisis</td>
</tr>
<tr>
<td></td>
<td>Anti-U3RNP</td>
<td>5–20*</td>
<td>• Diffuse cutaneous disease, pulmonary hypertension</td>
</tr>
<tr>
<td>Dermatomyositis and polymyositis</td>
<td>Anti-Jo-1</td>
<td>30</td>
<td>• Anti-synthetase syndrome: mechanic’s hands, interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td>(antibodies to other tRNA synthetases)</td>
<td>(3)</td>
<td>(anti-synthetase syndrome)</td>
</tr>
<tr>
<td></td>
<td>Anti-SRP</td>
<td>4</td>
<td>• Severe myositis</td>
</tr>
<tr>
<td></td>
<td>Anti-Mi2</td>
<td>10</td>
<td>• Dermatomyositis</td>
</tr>
</tbody>
</table>

‡Anti-double-stranded DNA antibody
*Higher frequency in people of African or Indian origin
#With sensitive enzyme-linked immunosorbent assays
†Low frequency in people of African origin

Table 21.3 Terminology

<table>
<thead>
<tr>
<th>Undifferentiated connective tissue disease</th>
<th>Patient has features seen in connective tissue disease but does not meet criteria for a defined connective tissue disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overlap syndrome</td>
<td>Patients meet criteria for two or more connective tissue diseases</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Overlap of rheumatoid arthritis-like arthritis, systemic lupus erythematos, scleroderma, and myositis with antibodies to U1RNP</td>
</tr>
</tbody>
</table>

Box 21.2 Raynaud’s phenomenon—features suggestive of an underlying connective tissue disease

- Onset in early childhood or later adult life
- Asymmetrical involvement of fingers
- Evidence of digital ischaemic damage
- Abnormal morphology of nailfold capillaries (including dilated, distorted capillaries and areas of capillary dropout)
- Presence of autoantibodies associated with connective tissue disease

Raynaud’s phenomenon
Raynaud’s phenomenon is often the presenting manifestation of connective tissue diseases, especially scleroderma (Box 21.2). It is common, however, in otherwise healthy people.

Which connective tissue disease?
Although clinical presentation in the early stage can be similar between connective tissue diseases, the evolution of typical clinical features over weeks or months is usually enough to distinguish the
characteristic patterns associated with the different diseases. Early diagnosis is aided by recognition of distinctive serological profiles that are generally present with the earliest clinical manifestations. Diagnosis can also be facilitated by typical laboratory abnormalities and histological changes in the tissues involved. For example, microscopic polyangiitis, which presents with weight loss, fever, polyarthritis and active urinary sediment, can be distinguished from lupus by an autoimmune response characterized by pANCA antibodies directed against myeloperoxidase and the typical histological picture of pauci-immune focal necrotizing glomerulonephritis. Similarly, dermatomyositis sine myositis, which presents with photosensitive eruptions on the face, arms, and hands and is associated with myalgia, can be distinguished from lupus by the distribution of the eruption, a raised serum creatine kinase, and typical changes on muscle biopsy, despite the absence of frank weakness (Figure 21.3).

Diagnosis is often complicated if lupus is part of an overlap syndrome and the patient fulfills classification criteria of more than one connective tissue disease (as opposed to undifferentiated connective tissue disease). The most common overlaps with systemic lupus erythematosus are patients who also have features of systemic sclerosis (Figure 21.4), polymyositis, or both, and patients with rheumatoid arthritis. Sometimes patients present with an overlap syndrome; at other times, the picture evolves sequentially. Development of Sjögren's syndrome during the course of systemic lupus erythematosus is well established, but occasionally patients with primary Sjögren's syndrome develop typical features of lupus, especially photosensitive eruptions typical of subacute cutaneous lupus erythematosus, after many years of disease.

Patients with an overlap of systemic lupus erythematosus and scleroderma or polymyositis, or both, often have a distinctive serological profile that includes high levels of antibodies to U1RNP. These patients have been suggested to have a distinctive connective tissue disease “mixed connective tissue disease.” This concept is very controversial, however, with critics and protagonists.

A number of series report patients who fulfill criteria for both systemic lupus erythematosus and rheumatoid arthritis. For these patients, the term “rhupus” has been coined. These patients are usually easier to recognize when the rheumatoid arthritis develops first, but they are characterized ultimately by typical rheumatoid features such as erosive arthritis, subcutaneous nodules and rheumatoid factor. These features are accompanied by cutaneous, renal, haematological and other clinical manifestations characteristic of systemic lupus erythematosus, but unusual for rheumatoid arthritis, with the presence of anti-nDNA antibodies.
**Differential diagnosis of connective tissue diseases**

A common clinical conundrum is the distinction of systemic lupus erythematosus from other connective tissue diseases (Table 21.4). All frequently present with a mixture of systemic symptoms, including fever and weight loss, and musculoskeletal and/or mucocutaneous involvement. The combination of a careful history and physical examination, urine analysis, chest X-ray, laboratory tests for an acute-phase response, blood count, serum biochemistry, complement levels, creatine kinase and serological profile, however, results in the correct diagnosis in a high proportion of cases.

**Drug-induced lupus**

A carefully elicited drug history is essential to exclude drug-induced lupus. The management of this is very straightforward, involving discontinuation of the offending agent and short-term anti-inflammatory treatment. Procainamide and hydralazine carry the highest risk of inducing a lupus-like syndrome but are now seldom prescribed in clinical practice. In more recent years, several cases of drug-induced lupus have been reported in association with minocycline, a drug is prescribed often for acne, and sulfasalazine, a disease-modifying antirheumatic drug in rheumatoid arthritis, although individual risk of drug-induced lupus is low with these agents. In the context of rheumatoid arthritis, the diagnosis is sometimes difficult to make, particularly as antinuclear antibodies are present in up to 50% of patients with the condition. Drug-induced lupus is rare in people of African origin. The clinical presentation is similar to that of idiopathic systemic lupus erythematosus, with systemic features including fever and weight loss, arthralgia or frank arthritis, and serositis (particularly common with procainamide). Major organ involvement, such as nephritis and central nervous system manifestations, is less common, although renal disease can rarely occur in sulfasalazine-induced lupus. A high level of antinuclear antibodies usually shows a homogeneous pattern from the earliest presentation, and the typical preponderANCE OF CONNECTIVE TISSUE DISEASES**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic rheumatic diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Prominent signs of synovitis; multisystem involvement uncommon at presentation; no autoantibodies associated with connective tissue disease</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Pronounced Raynaud’s phenomenon; scleroderma; characteristic serological profile</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Distinctive pattern of eruption; prominent muscle involvement; serological profile</td>
</tr>
<tr>
<td>Primary vasculitis</td>
<td>Distinctive renal involvement; neutrophilia (sometimes eosinophilia); serological profile</td>
</tr>
<tr>
<td>Behçet’s syndrome</td>
<td>Lack of typical serological features</td>
</tr>
<tr>
<td>Adult Still’s disease</td>
<td>Typical fever pattern; lack of typical serological features</td>
</tr>
<tr>
<td>Hereditary periodic fever syndromes (familial Mediterranean fever, TNF-associated periodic syndrome, hyperimmunoglobulin D, etc)</td>
<td>Intermittent manifestations; no autoantibodies associated with connective tissue disease</td>
</tr>
<tr>
<td><strong>Other systemic disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Typical liver involvement; absence of typical lupus features</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Typical histology; no autoantibodies associated with connective tissue disease</td>
</tr>
<tr>
<td>Histiocytic necrotizing lymphadenitis (Kikuchi–Fujimoto’s disease)</td>
<td>Typical histology; lymphadenopathy, fever, neutropenia and occasional antinuclear antibodies</td>
</tr>
<tr>
<td>Angioimmunoblastic lymphadenopathy</td>
<td>Typical histology; no autoantibodies associated with connective tissue disease</td>
</tr>
<tr>
<td><strong>Other causes of photosensitivity and red face</strong></td>
<td></td>
</tr>
<tr>
<td>Polymorphous light eruption</td>
<td>Lack of systemic features; different histology; absent autoantibodies</td>
</tr>
<tr>
<td>Rosacea</td>
<td>Papulopustular eruption; non-systemic; absent autoantibodies</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>Different morphology and histology; non-systemic, absent autoantibodies</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>History of allergen contact; pseudovesicle; no autoantibodies</td>
</tr>
<tr>
<td>Jessner’s benign lymphocytic infiltration</td>
<td>Typical histology; negative serology</td>
</tr>
<tr>
<td>Erythrohepatic protoporphyria</td>
<td>Vesicobullous lesions; urinary and plasma porphyrin profile; no antibodies associated with systemic lupus erythematosus</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Typical histology; diagnostic serology</td>
</tr>
<tr>
<td>Lupus vulgaris</td>
<td>Painful nodular cutaneous form of tuberculosis</td>
</tr>
<tr>
<td><strong>Other causes of fatigue and musculoskeletal pain</strong></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>No objective inflammation; no autoantibodies associated with connective tissue disease</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Little objective inflammation. May have Raynaud’s phenomenon and carpal tunnel syndrome</td>
</tr>
</tbody>
</table>
ance of anti-histone antibodies can be shown with specific assays. Antibodies to native DNA and "extractable nuclear antigens" commonly associated with idiopathic systemic lupus erythematosus are invariably negative, except in the case of minocycline-induced lupus. The gold standard for diagnosis of drug-induced lupus, however, is that it resolves after the drug is stopped; the symptoms improve within days to weeks, although the antinuclear antibodies may take a year or two to disappear.

The anti-TNF agents, mainly used in the treatment of rheumatoid arthritis, but also for Crohn's disease and ankylosing spondylitis, also induce antinuclear antibody and, specifically, anti-nDNA antibody production. This phenomenon has been observed with all of the anti-TNF agents currently on the market, although more often with infliximab than adalimumab or etanercept. Only a very small proportion of patients develop a lupus-like illness, manifesting mainly with skin rashes, worsening polyarthritis and serositis. In all cases the illness has been reported to be mild and has resolved on discontinuation of the anti-TNF agent. As in the case of sulfasalazine-induced lupus, diagnosis can be challenging in patients with rheumatoid arthritis who have pre-existing antinuclear antibodies.

**Other disorders of the skin**

One of the most common conundrums in the connective tissue disease clinic is the patient referred with a history of photosensitivity or red face in association with musculoskeletal symptoms and, perhaps, systemic features such as fatigue. Photosensitive eruptions are common in the normal female population or may be induced by, for example, non-steroidal anti-inflammatory drugs. About 10% of women develop polymorphous light eruption—a pruritic papular eruption that occurs within hours of sun exposure, typically on normally covered sites, that spares the face and hands, and that resolves within days without epidermal change (Figure 21.5). In contrast, photosensitivity in systemic lupus erythematosus also affects the face and hands. The latent period after sun exposure is usually longer, the skin is less pruritic, and the eruption persists longer.

Similarly, the facial erythematous rash that is seen typically in patients with systemic lupus erythematosus must be distinguished from other causes. Typical rosacea consists of papulopustular lesions on a background of telangiectasia (Figure 21.6). Sometimes, light exposure aggravates this condition and a biopsy is sometimes needed to distinguish atypical forms from lupus. Benign lymphocytic infiltration, such as Jessner's (Figure 21.7), may produce papular or annular lesions that are indistinguishable clinically from subacute cutaneous lupus erythematosus (Figure 21.8) and tumid (papular) lupus erythematosus. The typical histological appearance includes a dense dermal lymphocytic infiltrate without the characteristic epidermal changes of lupus. Seborrheic dermatitis may affect the cheeks and paranasal folds and is usually pruritic and associated with desquamation. Contact dermatitis, which may be caused by cosmetics, produces superficial erythema, pseudovesicles and sometimes eyelid swelling. Lupus vulgaris, a painful nodular cutaneous form of tuberculosis, often affects skin over the nose and ears.
Diabetic cheiropathy is seen especially in patients with long-standing, severe type 1 diabetes. It causes painless generalized puffiness and induration of the fingers, resembling scleroderma. An inability to fully extend the fingers produces the so-called “prayer sign”. Optimal glycaemic control and exercises may prevent worsening. Scleredema, another mimic of scleroderma in poorly controlled diabetes, presents as a thickened, indurated infiltrative skin disease. Unlike scleroderma, it occurs mostly on the upper back and is not associated with either Raynaud’s phenomenon or antinuclear antibodies. It often clears spontaneously with good glycaemic control.

**Is it infection?**

Some infections can mimic connective tissue disease, especially systemic lupus erythematosus; these include HIV, syphilis, tuberculosis and persistent Epstein–Barr virus and cytomegalovirus infections. They can present with mucocutaneous manifestations, fever, malaise, polyarthralgia, lymphadenopathy and serological abnormalities, such as positive tests for antinuclear antibodies and rheumatoid factor. Distinguishing systemic lupus erythematosus from HIV infection can be especially challenging because of the additional overlapping clinical features of neuropsychiatric complications, nephropathy and haematological abnormalities such as leucopenia and thrombocytopenia.

A common clinical conundrum is how to distinguish an acute infection from a disease flare in a patient with systemic lupus erythematosus. To complicate matters further acute infections not infrequently trigger a lupus flare. Both bacterial infections and tuberculosis occur more commonly in lupus patients than in matched controls. Even patients in remission have an increased risk of infection, and this risk is enhanced by corticosteroids and other immunosuppressive agents such as cyclophosphamide. Bacterial infections involve the commonly occurring pyogenic organisms such as *Staphylococcus* species and *Escherichia coli*. Opportunistic infections also occur, especially in patients who take high-dose corticosteroids and immunosuppressive agents.

Measurement of C-reactive protein (CRP) has been suggested as a way of distinguishing between infection and a lupus flare. CRP levels are higher in patients with infection compared with those with active lupus; levels of CRP >60 mg/l strongly indicate infection, whereas levels <30 mg/l make infection highly unlikely. Occasionally, high levels of CRP can be seen with lupus flares of arthritis or serositis in the absence of infection. Prospective longitudinal studies have, however, shown CRP to be an unreliable predictor of infection.

In the absence of useful surrogate markers of infection in systemic lupus erythematosus, exhaustive microbiological investigations and early and often repeated cultures, sometimes from affected tissues, are needed to make a definitive diagnosis.

**Reference**

Further reading


Introduction

Sports and Exercise Medicine addresses the prevention and management of sports- and activity-related medical complaints, and the use of exercise for health-related benefit. Rheumatologists are often faced with sports injuries and have many patients who will benefit from an exercise prescription.

Sports injuries

Introduction

The key to managing sports-related injury is having an understanding of the patient and their sport. As with any patient, it is important to consider the patient's ideas, expectations and concerns. Those with an "athletic psyche" may have high anxiety levels about their injury and its implications, unrealistic expectations for recovery goals and time frames and a tendency to "overcomply" with rehabilitation programmes. An insight into the mechanics, training and techniques of the sport involved is also important, as this allows the underlying cause of the injury to be addressed (Figure 22.1).

Assessment

When assessing sports injuries, it is helpful to consider intrinsic and extrinsic factors (Table 22.1).

Intrinsic factors encompass physical, physiological and psychological aspects of an individual that may contribute to injury. Importantly, what may be considered "abnormal"—for example, asymmetry of muscle development or joint range of motion—may be normal in relation to a trained athlete. Similarly, what is normal in the general population may be abnormal for an athlete—for example, average flexibility in a gymnast is likely to be abnormal.

Extrinsic factors play a significant role in the development of injury. Doing "too much, too soon, too often" is a common error in athletes of all levels. Other factors, such as inappropriate or recent change in equipment, environmental conditions and competing surfaces, also may play a role.

A central concept in the assessment of an athlete, in particular when considering injury, relates to the delicate balance that exists between optimal mobility of a joint or a series of joints, and optimal stability. Frequently this balance is disrupted in the development of injury and must be considered in diagnosis and treatment of any athletic complaint.

History—The history addresses the injury, training and competing habits, the potential role of other extrinsic factors, previous injury history and other medical issues. The mechanism of injury is important in elucidating the diagnosis, as it will implicate the structures involved and the severity of the injury.

Pain is most frequently the cardinal symptom and a usual pain history is taken: its site(s), radiation, timing of onset and subsequent temporal pattern, aggravating and relieving features and associated symptoms. The degree of swelling and its rapidity of onset after injury frequently correlate with the severity of injury. Instability or a feeling of "pre-instability" are highly relevant in sport and may indicate a true structural deficit or a lack of neuromuscular control. Clicking and clunking of a joint is relevant, particularly if new or painful. Neurological symptoms may be present and may indicate a true neurological deficit or, more frequently, neural irritation in association with a chronic soft-tissue injury.

A history of treatments used to date, a medication history (including vitamins and supplements) and a general medical background are all important. For example, underlying medical com-
Sports and Exercise Medicine

Assessment of asymmetry of muscle groups, flexibility and joint range of motion, is important but must be interpreted carefully. Core stability and control—the ability to control the body adequately during movement—should be assessed, as it is so often lacking in the injured athlete. Regional assessment of the injury follows the usual strategy of “look, feel, move and special tests”. Identification of the site(s) of tenderness, swelling, instability and neurovascular status follows.

Although assessment commences with examination of the patient at relative rest, it is very important to proceed to dynamic assessment where there is any doubt about the nature and cause of the injury (Figure 22.2). It may be necessary to evaluate the individual during or after a rigorous set of exercises in order to reproduce symptoms. Video analysis may be very informative in illustrating the underlying factors contributing to injury; input from a coach or technical expert is also often helpful.

Investigations—Investigations (imaging in particular) are frequently required in the assessment of the injury, but should be requested only after a clinical diagnosis is made and interpreted carefully. No imaging is foolproof, and it is vital to request the correct test for the suspected injury.

Imaging includes plain X-rays, diagnostic ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and isotope bone scans. Plain X-rays assess for fractures, myositis ossificans, loose bodies and underlying joint damage but are not sensitive to early stress injuries. Stress views may be necessary to assess for instability. Diagnostic ultrasound demonstrates soft-tissue anatomy and impingements and allows dynamic assessment of the joint in question. MRI provides further information of the surrounding anatomy, bone oedema and some soft-tissue injuries (Figure 22.3), but MR arthrography is necessary to evaluate the labra of shoulder and hip most accurately. CT scanning for loose bodies, and scintigraphy for stress injuries in particular, may be indicated. Laboratory investigations for underlying medical complaints may be necessary.

Compartment studies, involving measurement of muscle compartment pressures before, during and after exercise are important in the evaluation of individuals with possible chronic exertional compartment syndromes.

Other investigations, such as dual X-ray absorptiometry scanning for those with recurrent stress fractures may be warranted. The sites of low bone density in athletes may differ from the general population in view of the different patterns of skeletal loading; scanning of sites such as the forearm is often necessary.

Management

The management of sports related injuries commences with an accurate diagnosis and identification of all the contributing factors. Education and counselling in relation to the injury, and discussion and agreement on an appropriate management strategy are vital. Appropriate levels of compliance will be enhanced by ensuring the athlete has a clear understanding of the injury, its implications and treatment. Clear goals need to be set, and reviewed regularly. Pain

Table 22.1 Common extrinsic and intrinsic factors in sports injuries

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypermobility</td>
<td>Training: too much, too soon, too often</td>
</tr>
<tr>
<td>Muscle weakness/imbalance</td>
<td>Technique</td>
</tr>
<tr>
<td>Poor flexibility (local, general)</td>
<td>Equipment</td>
</tr>
<tr>
<td>Femoral anteversion</td>
<td>Surface</td>
</tr>
<tr>
<td>Tibia varum/valgum</td>
<td>Environment</td>
</tr>
<tr>
<td>Pes planus/cavus</td>
<td>Drugs (e.g. anabolic steroids/corticosteroids)</td>
</tr>
<tr>
<td>Presence of another injury</td>
<td>Poor nutrition</td>
</tr>
<tr>
<td>Chronic diseases (e.g. rheumatoid arthritis)</td>
<td></td>
</tr>
</tbody>
</table>
Pain control may be necessary in order to allow rehabilitation to proceed. This may be in the form of ice/heat modalities, simple analgesics or non-steroidal anti-inflammatory drugs. Injections may be useful. For example, local anaesthetic may be used to identify the source of pain, and corticosteroid for chronic injuries in which inflammation is ongoing. Injudicious loading under the influence of analgesia, and in particular corticosteroid, must be avoided.

Surgery may be required — either early, or if other management approaches fail. The decision to intervene operatively will depend upon the nature of the injury and the circumstances of the athlete. For example, elite athletes may choose to have surgical intervention in the hope it will speed recovery to promote a swift return to sport. Surgery is never an isolated treatment; rehabilitation remains an essential part of management.

Examples of indications for early surgical intervention include fractures, acute traumatic tendon ruptures, significant loose bodies and labral injuries, and exertional compartment syndromes.

Even when surgery is likely to be indicated, many injuries may be managed in the initial phases with rehabilitation (Figure 22.4). This may be termed ”pre-habilitation”: where strength and proprioception can be partly restored, enhancing the pace of post-operative recovery.

Box 22.1 Principles of management of sports injuries

- Early diagnosis, identify and correct the mechanism
- In the acute phase: PRICES
- Control pain in order to allow rehabilitation to proceed
- Rehabilitation addresses flexibility, strengthening, proprioception, sports-specific work such as agility, speed, power, technique
- Graduated return to sport

Figure 22.2 Gait analysis and shoe pressure measurement can be particularly helpful in the assessment of lower limb injuries

Figure 22.3 MRI of thighs showing left hamstrings muscle injury
complete rupture), the muscle or ligament affected (e.g. a straight-forward long head of biceps tear to the problematic hamstring) and the location within the muscle/tendon complex (a midsubstance tear compared with a tear at the musculotendinous junction). The impact of any injury is of course further complicated by the functional aspirations of the individual and their age, which will affect the site of injury and the potential for healing. The most common acute sports injury is undoubtedly the ankle sprain.

**Ankle sprain**—Inversion injuries to the lateral ligament complex of the ankle are one of the most common causes of long-term disability after injury. Injuries initially occur in plantar flexion and slight inversion, such as at push off (Figure 22.5). Recurrent injuries can occur with minimal trauma, e.g. slipping on a kerb, indicating instability: functional (muscle weakness, loss of proprioception) or mechanical (significant ligament disruption).

After the acute injury, the degree of soft-tissue damage can be estimated by the extent of the swelling, and the likelihood of bone injury by clinical features (Box 22.2). Ankle sprain can result in additional damage that may cause either ongoing instability or chronic pain (Box 22.3). Popping, clicking, locking and neuralgia may all be significant.

Clinical assessment includes assessment of balance and proprioception, mechanical stability, sites and degree of tenderness, and neurovascular status. Management of the acute injury should focus on early mobilization, range of motion and strengthening exercises (particularly the peroneals) and proprioceptive work. Use of an ankle brace may help in an earlier return to sport.

**Common sports injuries—the acute injury**

Sports injuries can be broadly divided into acute injury and chronic overuse injury. The most common acute injuries involve ligaments (sprain) or muscles (strain) and vary enormously in severity in terms of the extent of injury (from a simple sprain/strain to a

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**Figure 22.4** Rehabilitation involves progression from basic flexibility and strength exercises to sports-specific activities. Here, the athlete performs a single leg squat, a simple core stability exercise. Figure courtesy of Badminton England

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**Figure 22.5** An ankle sprain involves a tear to one or more of the lateral ligaments of the ankle (a) and usually occurs with the foot in plantar flexion in slight inversion (b).

---

**Box 22.2 Ottawa Ankle Rules: when to X-ray for bony injury after ankle sprain**

- Inability to bear weight and/or
- Bone tenderness at the posterior edge of the tibia or fibula or tip of either malleolus
Stress fractures—Stress injuries to bone are a common reaction to repetitive loading of the skeleton without adequate time for remodelling. Although most stress injuries are fatigue-related, the possibility of insufficiency fractures, particularly in lightweight athletes, must always be considered. Most stress fractures will respond to relative rest, support and correction of the underlying cause (training, biomechanics, equipment errors). However, certain stress fractures are associated with an increased risk of poor healing/completion, including the superior surface of the femoral neck, anterior tibial cortex and navicular. These are areas that are under tension (rather than compression) and/or have poor vascular supply. They are managed either by non-weight-bearing and close monitoring or early surgical intervention (Figure 22.6).

Exercise prescription

The benefits of exercise in the prevention and management of disease are well established. Many patients with rheumatological diseases should be given an exercise prescription, as many are at increased risk of medical complications such as osteoporosis and cardiovascular events. Current recommendations are that adults aged 18 to 65 years need moderate-intensity aerobic physical activity for a minimum of 30 minutes on 5 days each week or vigorous-intensity aerobic physical activity for a minimum of 20 minutes on 3 days each week and strengthening exercise two to three times weekly. This may need to be modified for those with diseases such as rheumatoid arthritis, but provides a target.

The exercise prescription has a number of components (Box 22.4), which are adjusted according to the individual’s needs, char-
acteristics (e.g. age) and preferences. Patients in moderate- to severe-cardiac-risk groups should be assessed with an exercise test before commencing a programme. Supervision of patients may be necessary. Compliance is enhanced by education and counselling, careful prescription in choice of activities, written information about the programme, goal setting and frequent follow up, which may be done by telephone.

**Summary**
The evidence supporting the benefits of exercise/an active lifestyle both in preserving and restoring health is irrefutable. An active lifestyle will inevitably result in occasional musculoskeletal "injury", and while sports and exercise medicine has now been recognized as a medical specialty and thus should have increased NHS provision, the rheumatologist will still have a valuable role in contributing to the wider impact of activity-related musculoskeletal injury. It is therefore important that rheumatologists are confident in the assessment and rehabilitation of the exercising individual.

**Further reading**
The vasculitides are a heterogeneous group of uncommon diseases characterized by inflammatory cell infiltration and necrosis of blood-vessel walls. Systemic necrotizing vasculitis can be rapidly life-threatening, so early accurate diagnosis and treatment is vital. Vasculitis may be primary (Wegener’s granulomatosis, Churg–Strauss syndrome, microscopic polyangiitis and polyarteritis nodosa) or secondary to established connective tissue disease (such as rheumatoid arthritis), infection or malignancy. The severity of vasculitis is related to the size and site of the vessels affected. Classification is based on vessel size and determines the treatment approach (Table 23.1; Box 23.1).

**Large-vessel vasculitis**

Large-vessel vasculitis includes giant cell arteritis and Takayasu’s arteritis. Giant cell arteritis is described elsewhere (Chapter 17). Takayasu’s arteritis is uncommon and affects young adults, who initially present with a non-specific illness and later with loss of pulse, claudication (especially of the upper limbs) and stroke.

**Medium-vessel vasculitis**

**Classical polyarteritis nodosa**

A multi-system vasculitis characterized by formation of microaneurysms in medium-sized arteries. Patients present with a consti-
Vasculitis and Related Rashes

Granulomatosis — disease without renal involvement — may have a better prognosis. Biopsy of affected organs shows a necrotizing arteritis, often with formation of granulomas (Figure 23.3).

Microscopic polyangiitis
This is characterized by a vasculitis that commonly affects the kidneys. Lung involvement usually presents with haemoptysis caused by pulmonary capillaritis and haemorrhage (pulmonary-renal syndrome).

Biopsy of the kidney shows a focal segmental necrotizing glomerulonephritis with few immune deposits (sometimes called pauci-immune vasculitis).

Medium- and small-vessel vasculitis
This group includes the major necrotizing vasculitides: microscopic polyangiitis, Wegener’s granulomatosis and Churg–Strauss syndrome, with involvement of both medium and small arteries. These may occur at any age, with the peak incidence at 60–70 years and are slightly more common in men. The annual incidence is about 20 cases per million people. The symptoms depend on the size and site of the vessel affected and on the individual diagnosis. They are associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA).

Wegener’s granulomatosis
This is characterized by a granulomatous vasculitis of the upper and lower respiratory tracts and glomerulonephritis, but almost any organ system can be affected (Figure 23.2). The lungs are affected in 45% of patients at diagnosis. Symptoms in the ear, nose and throat (such as epistaxis, crusting and deafness) are particularly associated with this condition, and they should be sought in all patients with suspected vasculitis. Patients with limited Wegener’s granulomatosis — disease without renal involvement — may have a better prognosis. Biopsy of affected organs shows a necrotizing arteritis, often with formation of granulomas (Figure 23.3).

Kawasaki disease (mucocutaneous lymph node syndrome)
An acute vasculitis that primarily affects infants and young children. It presents with fever, rash, lymphadenopathy and palmpoplantar erythema. Coronary arteries become affected in up to one-quarter of untreated patients; this can lead to myocardial ischaemia and infarction.

Table 23.1 Classification of vasculitis

<table>
<thead>
<tr>
<th>Vessels predominantly affected</th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large arteries</td>
<td>Giant cell arteritis Takayasu’s arteritis</td>
<td>Aortitis associated with rheumatoid arthritis Infection (syphilis)</td>
</tr>
<tr>
<td>Medium arteries</td>
<td>Classic polyarteritis nodosa Kawasaki disease</td>
<td>Infection (hepatitis B)</td>
</tr>
<tr>
<td>Medium arteries and small vessels</td>
<td>Wegener’s granulomatosis Churg–Strauss syndrome Microscopic polyangiitis</td>
<td>Rheumatoid arthritis, systemic lupus erythematosus Sjögren’s syndrome Drugs Infection (HIV)</td>
</tr>
<tr>
<td>Small vessels (leucocytoclastic)</td>
<td>Henoch–Schönlein purpura Cryoglobulinaemia Leucocytoclastic vasculitis</td>
<td>Drugs Infection (hepatitis C)</td>
</tr>
</tbody>
</table>

Figure 23.1 Coeliac axis arteriogram showing typical aneurysm in polyarteritis nodosa

Medium-vessel vasculitis
Small-vessel vasculitis (leucocytoclastic or hypersensitivity) is usually confined to the skin, but it may be part of a systemic illness. The rash is purpuric, sometimes palpable, and occurs in dependent areas. The lesions may become bullous and ulcerate. Nailfold infarcts occur. Biopsy shows a cellular infiltrate of small vessels often with leucocytoclasis (fragmented polymorphonuclear cells and nuclear dust). Small-vessel vasculitis has a number of causes, of which drugs and infection are the most common.
Cryoglobulinaemia
Cryoglobulins are plasma proteins that precipitate in the cold. The condition presents with rash (including purpura digital ischaemia and ulcers) (Figure 23.5), arthralgia and neuropathy. A strong link exists between infection with hepatitis C virus and essential mixed cryoglobulinaemia: 80–90% of such patients are positive for anti-hepatitis C virus antibodies.

Behçet’s syndrome
Behçet’s syndrome is a systemic vasculitis of unknown aetiology, characterized by oro-genital ulceration. It is most common in Turkey and Japan. Ocular involvement occurs early in the disease course and affects 50% of patients. The pathergy phenomenon is characteristic and is a non-specific hyperreactivity in response to minor trauma.

Investigation
Investigation aims to establish and confirm the diagnosis, the extent and severity of organ involvement, and disease activity (Box 23.2).

Henoch–Schönlein purpura
This is a form of small-vessel vasculitis that occurs mainly in children and young adults. Patients present with rash, arthritis, abdominal pain and, sometimes, renal involvement (Figure 23.4). Deposits of immunoglobulin A can be detected histologically in the skin and renal mesangium.

Urine analysis
This is the most important investigation, because the severity of renal involvement is one of the key determinants of prognosis. Detection of proteinuria or haematuria in a patient with systemic illness needs immediate further investigation, and the patient is a medical emergency.
Vasculitis and Related Rashes

Blood tests
Leucocytosis suggests a primary vasculitis or infection. Leucopaenia is associated with vasculitis secondary to a connective tissue disease (typically systemic lupus erythematosus). Eosinophilia suggests Churg–Strauss syndrome or a drug reaction.

Liver function tests
Abnormal results suggest viral infection (hepatitis A, B or C) or may be non-specific.

Immunology
ANCA are associated with the primary systemic necrotizing vasculitides. ANCA in association with proteinase 3 antibodies are highly specific (>90%) for Wegener’s granulomatosis. Perinuclear ANCA (pANCA) associated with myeloperoxidase antibodies occur in microscopic polyangiitis and Churg–Strauss syndrome. Rheumatoid factors and antinuclear antibodies may indicate vasculitis associated with connective tissue disease. Complement levels are low in infection, lupus and cryoglobulinaemia.

Figure 23.4 Small-vessel vasculitis in Henoch–Schönlein purpura; (a) affecting the skin; (b) affecting the gut

Figure 23.5 Vasculitic rash in cryoglobulinaemia

Box 23.2 Investigation of vasculitis
Assessing inflammation
- Blood count and differential (total white cell count, eosinophils)
- Acute-phase response (erythrocyte sedimentation rate, C-reactive protein)
- Liver function

Assessment of organ involvement
- Urine analysis (proteinuria, haematuria, protein excretion)
- Renal function (creatinine clearance, 24-hour protein excretion, urine protein/creatinine ratio biopsy)
- Chest radiograph
- Liver function
- Nervous system (nerve-conduction studies, biopsy)
- Cardiac function (electrocardiography, echocardiography)
- Gut (angiography)

Immunological tests
- Antineutrophil cytoplasmic antibodies (including proteinase 3 and myeloperoxidase antibodies)
- Other autoantibodies (rheumatoid factor, antinuclear antibodies, anticardiolipin antibodies)
- Complement
- Cryoglobulins

Differential diagnosis
- Blood cultures
- Viral serology
- Echocardiography

Biopsy
Tissue biopsy is important to confirm the diagnosis before treatment with potentially toxic immunosuppressive drugs. The choice of tissue to biopsy is crucial.

Other investigations
Angiography can show aneurysms. Blood cultures, viral serology and echocardiography are important to exclude infection and other conditions that may present as systemic multi-system disease and mimic vasculitis (Boxes 23.3 and 23.4).
cold weather. It may lead to ulceration and is associated with vascular thrombosis (Sneddon’s syndrome) and the presence of antiphospholipid antibodies. It is also a feature of polyarteritis nodosa (Figure 23.6) and cryoglobulinaemia.

Bacterial infections
Direct bacterial infection of small arteries and arterioles causes a necrotizing vasculitis or thrombosis. Neisseria meningitidis (Figure 23.7), N. gonorrhoeae (Figure 23.8) and Streptobacillus moniliformis, for example, may infect the vascular endothelium directly and cause maculopapular or purpuric skin lesions. Biopsies of early lesions show small-vessel vasculitis. The organisms can be cultured from an aspirate of the lesions.

Infective endocarditis
Several organisms—streptococci, staphylococci, Gram-negative bacilli and Coxiella—can cause endocarditis. Polyarthritis may be accompanied by splinter haemorrhages, Janeway’s lesions (red macules over thenar and hypothenar eminences) (Figure 23.9), Osler’s nodes (tender papules over extremities of fingers and toes) and clubbing. Diagnosis is by blood culture and echocardiography.

Cholesterol embolism
Cholesterol embolism (Figure 23.10) may occur spontaneously or after trauma to the aortic wall during vascular surgery or angiographic procedures. Typical cutaneous manifestations are ischaemia of the digits, particularly the toes, from abdominal atheroma, emboli and livedo reticularis. Digital ischaemia usually presents as sudden onset of a small, cool, cyanotic and painful area of the foot (usually the toe). The lesions are tender to touch and may progress to ulceration, digital infarction and gangrene; this mimics systemic vasculitis. Presentation may be with a systemic illness caused by tissue inflammation; features include eosinophilia and a positive test for ANCA.

**Differential diagnosis**

**Livedo reticularis**
Livedo reticularis is characterized by persistent patchy reddish-blue mottling of the legs (and occasionally arms) that is exacerbated by

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**Box 23.3 Important mimics of vasculitis**
- Subacute bacterial endocarditis
- Atrial myxoma
- Cholesterol embolism
- Antiphospholipid antibody syndrome
- Calciphylaxis
- Cocaine abuse

**Box 23.4 Differential diagnosis of rash and arthritis**
- Infection
- Drug reaction
- Sarcoidosis
- Juvenile idiopathic arthritis
- Connective tissue disease
- Psoriasis
- Vasculitis

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**Figure 23.6** Livedo rash in cutaneous polyarteritis nodosa

**Figure 23.7** Haemorrhagic pustular rash in disseminated infection with Neisseria meningitidis

**Figure 23.8** Haemorrhagic pustular rash in disseminated infection with Neisseria meningitidis

**Figure 23.9** Haemorrhagic pustular rash in disseminated infection with Neisseria meningitidis
Cocaine abuse can cause destruction of the nasal mucosa and septum, mimicking systemic vasculitis.

Atrial myxoma
Cardiac myxomata are rare benign tumours found most often in the left atrium (90% of cases). Constitutional symptoms and systemic embolization may lead to a wrong diagnosis of vasculitis. Systemic manifestations seen in 90% of cases include fever, weight loss, Raynaud’s phenomenon, clubbing, elevated acute-phase proteins and hypergammaglobulinaemia. It is treated by surgical resection of the primary tumour and emboli.

Antiphospholipid antibody syndrome
Antiphospholipid antibody syndrome may present as catastrophic widespread thrombosis, and this can mimic systemic vasculitis. Livedo reticularis is the most typical cutaneous lesion, and it occurs in association with thrombosis and recurrent fetal loss.

Figure 23.8 Gonococcal pustules in disseminated infection with Neisseria gonorrhoeae

Figure 23.9 Janeway’s lesions in infective endocarditis

Figure 23.10 Cholesterol emboli
**Prognosis**

The natural history of untreated primary systemic vasculitis is of a rapidly progressive, usually fatal disease. Before corticosteroids were introduced in Wegener’s granulomatosis, the median survival was 5 months, with 82% of patients dying within 1 year and more than 90% within 2 years. The introduction of corticosteroids improved survival in polyarteritis nodosa to 50% at 5 years. The median survival in Wegener’s granulomatosis was only 12.5 months using corticosteroids alone, with most patients dying of sepsis or uncontrolled disease. The introduction of oral low-dose cyclophosphamide combined with prednisolone resulted in a significant improvement in the mortality of Wegener’s granulomatosis, with a survival rate at 5 years of 82%.

Small-vessel vasculitis confined to the skin without necrotizing features has an excellent prognosis. Takayasu’s arteritis has a good prognosis (3% mortality) but typically relapses.

**Treatment**

Treatment depends on the size of vessel involved (Box 23.5). Small vessel vasculitis can often be treated conservatively. Takayasu’s arteritis requires high-dose corticosteroids (oral prednisolone 40–60 mg/day), and additional immunosuppression with methotrexate or azathioprine. The dose of corticosteroid should be reduced rapidly according to clinical and laboratory parameters.

<table>
<thead>
<tr>
<th>Box 23.5 Aims of management of vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Induction of remission</td>
</tr>
<tr>
<td>• Maintenance of remission</td>
</tr>
<tr>
<td>• Recognition and early treatment of relapse</td>
</tr>
<tr>
<td>• Avoidance of drug toxicity</td>
</tr>
</tbody>
</table>

**Table 23.2 Treatment regimens for cyclophosphamide**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous low oral dose</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2 mg/kg/day</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1 mg/kg/day</td>
</tr>
<tr>
<td><strong>Intravenous pulse</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>10–15 mg/kg†</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>1 g</td>
</tr>
</tbody>
</table>

Cyclophosphamide dose should be adjusted according to white cell count, renal function and clinical response

*Pulse frequency: fortnightly (x3), then three-weekly; adjusted according to clinical response and toxicity

†White cell count should be checked 7, 10 and 14 days after the first two pulses and immediately before subsequent pulses. For oral cyclophosphamide the white cell count should be checked weekly for one month, fortnightly for two months and then every month.

The recently completed European randomized controlled trials in ANCA-associated vasculitis now guide the treatment approach. For patients with generalized disease, cyclophosphamide (Table 23.2) is used for remission induction and can be given either as continuous low-dose oral therapy or intermittent pulse therapy. Both routes are equally effective at inducing remission, but pulse therapy is probably associated with a slightly higher relapse rate. The major toxicities of cyclophosphamide are haemorrhagic cystitis, formation of bladder tumours, infertility and infection. Toxicity depends on the cumulative dose, so pulse therapy is less toxic. Mesna may reduce the frequency of bladder toxicity with intravenous cyclophosphamide. The risk of ovarian failure depends on age and cumulative dose of cyclophosphamide. Fertile males should be offered sperm storage before they are given cyclophosphamide. Prophylaxis with co-trimoxazole should be considered to prevent infection with *Pneumocystis jiroveci*. Immunosuppressed patients should receive vaccination with influenza and polyvalent pneumococcal vaccination.

Corticosteroids are started at a dose of 1 mg/kg, and the dose is reduced quite rapidly so that the drug can be discontinued at around 12 months. Alternate-day dosing may reduce the risk of infection. Intravenous methylprednisolone is often given with the first two pulses.

Once remission has been achieved with cyclophosphamide (usually after 3–6 months), azathioprine (or weekly oral methotrexate) is substituted for maintenance therapy. Cyclophosphamide should not be continued for more than 1 year because of the risks of toxicity. Survival has improved and remission can be obtained in most patients (85%) with cyclophosphamide, but many need prolonged immunosuppressive therapy (5–10 years), and the rate of relapse is still substantial (50% at 5 years).

Methotrexate may be considered in patients with localized disease, as an alternative to cyclophosphamide.

Patients with life-threatening disease (pulmonary haemorrhage) or a creatinine >500 µmol/l should receive plasma exchange in addition to intravenous methylprednisolone.

Regular assessment of disease activity is required, and treatment is tailored accordingly. Minor relapses may require an increase in maintenance therapy. Major relapses will require a further course of cyclophosphamide.

Intravenous immunoglobulin is effective in the treatment of Kawasaki disease, but its role in other vasculitides, where it induces temporary improvement, remains controversial at present. Etanercept does not improve relapse rate when used as adjunctive therapy to conventional therapy for remission maintenance. The role of tumour-necrosis-factor-α-blocking drugs in induction is uncertain. B-cell depletion with rituximab is a promising approach that is being investigated.

**Further reading**


This chapter describes investigations that may be performed in a patient with suspected and known rheumatologic disorders. Abnormal haematology tests, particularly anaemias and platelet abnormalities, are found commonly. Biochemical abnormalities include raised protein and globulin levels and reflect a non-specific inflammatory response. Haematological and biochemical investigations are useful for both diagnostic and monitoring purposes, while most immunological investigations are mainly used to facilitate diagnosis.

OVERVIEW
• Abnormal laboratory tests occur frequently in patients with rheumatologic disorders.
• Laboratory abnormalities suggesting non-specific inflammation are common and accompany many rheumatologic disorders.
• Routine blood tests (haematology and chemistry) are useful to monitor known rheumatologic diseases and may be helpful in diagnosis. Abnormalities may reflect adverse effects of medications or may indicate organ involvement from an underlying rheumatologic disease.
• Immunological testing is primarily for diagnostic purposes and may help subsetting patients (e.g. patients with systemic lupus erythematosus who are anti-Ro positive are more likely to be photosensitive); however, the antinuclear antibody test is not a diagnostic test.
• Genetic testing (such as HLA-B27) is expensive and not a diagnostic tool.

Haematology investigations
A full blood count and erythrocyte sedimentation rate (ESR) are used to monitor disease activity, to assess the effects of drug treatment, to exclude factors such as dietary deficiency or haemolysis that may be contributing to the morbidity of a rheumatological disease, and (rarely) to exclude a primary haematologic malignancy that can mimic various forms of arthritis (Table 24.1).

Platelet abnormalities
Platelet abnormalities are often seen in rheumatic disorders; the most common abnormality is a mild to moderate thrombocytosis, which correlates with disease activity. Thrombocytopenia may occur as a side effect of interventional treatments such as methotrexate, cyclophosphamide or mycophenolate mofetil. Thrombocytopenia may also be observed in patients receiving treatment with gold or penicillamine; however, these medications are now rarely used. An autoimmune thrombocytopenia (usually chronic but occasionally acute) occurs in up to 20% of patients with lupus and in patients with primary antiphospholipid antibody syndrome. In some of these patients it has been possible to demonstrate the presence of antiplatelet antibodies. Approximately 15% of patients with “idiopathic” thrombocytopenia later develop lupus. Thrombocytopenia may also be seen in the subset of rheumatoid arthritis with Felty’s syndrome (see below). Infections associated with arthralgia such as cytomegalovirus, hepatitis C and HIV can additionally be associated with thrombocytopenia.

White blood cell abnormalities
Felty’s syndrome, the association of rheumatoid arthritis with leucopenia (predominantly neutropenia) and splenomegaly (and often leg ulcers), is rare. Leucopenia, particularly lymphopenia, is common in lupus. Bone-marrow suppression is a well-recognized complication of immunosuppressive drugs such as azathioprine, methotrexate, leflunomide, sulfasalazine, cyclophosphamide and mycophenolate mofetil, which are used to treat rheumatoid arthritis, psoriatic arthritis and lupus. Patients taking these drugs require regular haematological assessments to allow early detection of bone-marrow suppression. Leucocytosis is occasionally found in flares of lupus, but is more often a reflection of corticosteroid-induced demargination of neutrophils. Infective causes of a leucocytosis (particularly neutrophilia) must be excluded. Less common abnormalities, such as monocytopenia and eosinophilia in rheumatoid arthritis and basopenia in lupus, are well described. A range of blood test abnormalities in rheumatological disease are shown in Table 24.2.
Coagulation abnormalities
Lupus anticoagulant is discussed in the section on antiphospholipid antibodies.

Acute-phase response
This response defines a coordinated set of systemic and local events associated with the inflammation that is the consequence of tissue damage. The term is misleading, as changes may occur in both acute and chronic inflammation. About 30 acute-phase proteins are known. Elevated serum concentrations of these proteins often last for several days after the initiating event, and their synthesis in the liver is triggered by cytokines—particularly interleukin-1 (IL-1), IL-6 and tumour necrosis factor-α (TNF-α). These cytokines derive from activated macrophages that have been demonstrated at the site of the injury. Other types of cells such as fibroblasts and endothelial cells are also sources of cytokines. There is some specificity in the cytokine–acute-phase reactant interactions: for example, the synthesis of C-reactive protein (CRP) is dependent on IL-6, while haptoglobin production is influenced by the three cytokines mentioned above.

Measurement of the acute-phase response is helpful to ascertain inflammatory disease, as well as for the assessment of disease activity, monitoring of therapy and the detection of intercurrent infection.

It is impractical and unnecessary to measure all aspects of the acute-phase response; the most widely used measurements are the ESR and CRP (Table 24.3). Less common measurements include plasma viscosity, serum amyloid A (SAA) protein, haptoglobin and fibrinogen.

Plasma levels of cytokines such as IL-6, IL-1 and TNF-α are not commercially available and are currently used solely as research tools. Other tests of potential use in the future are SAA protein and matrix metalloproteinase-3 (MMP-3); both may predict bone damage in early rheumatoid arthritis.

Biochemical investigations
The majority of biochemical tests are useful in monitoring organ-specific complications of disease or in assessment of side effects of therapy.

Hepatic function
Abnormalities in hepatic function may reflect disease activity in some rheumatic diseases (for example, elevated alkaline

<table>
<thead>
<tr>
<th>Table 24.1</th>
<th>Anaemia and rheumatologic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Indices</td>
</tr>
<tr>
<td>Iron-deficient</td>
<td>↓Serum Fe ↑Serum TIBC Microcytosis, hypochromasia</td>
</tr>
<tr>
<td>Megaloblastic</td>
<td>Macrocytosis ↓Folate ↓B₁₂ ↓TFTs</td>
</tr>
<tr>
<td>Haemolytic</td>
<td>Reticulocytes Haptoglobins Positive direct Coombs’ test</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>Normochromic, normocytic ↓serum iron, ↑TIBC, ↑ferritin</td>
</tr>
</tbody>
</table>

EPO = erythropoietin; IL-1 = interleukin-1; NSAIDs = non-steroidal anti-inflammatory drugs; TFT = thyroid function test; TIBC = total iron-binding capacity; TNF-α = tumour necrosis factor alpha

<table>
<thead>
<tr>
<th>Table 24.2</th>
<th>Blood test abnormalities in some rheumatological diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RA</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Chronic disease</td>
</tr>
<tr>
<td>Microcytic/hypochromic</td>
<td>++</td>
</tr>
<tr>
<td>Megaloblastic</td>
<td>++</td>
</tr>
<tr>
<td>Acute-phase response</td>
<td>ESR</td>
</tr>
<tr>
<td>CRP</td>
<td>+</td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>+</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>+</td>
</tr>
<tr>
<td>Uric acid</td>
<td>–</td>
</tr>
<tr>
<td>Bone biochemistry</td>
<td>Alk phos</td>
</tr>
<tr>
<td></td>
<td>Ca²⁺</td>
</tr>
<tr>
<td></td>
<td>PO₄⁻</td>
</tr>
</tbody>
</table>

Alk phos = alkaline phosphatase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PMR = polymyalgia rheumatica; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis
phosphatase activity has been reported in rheumatoid arthritis and polymyalgia rheumatica). Raised enzyme activities may be more frequent because of toxicity from drugs used to treat rheumatic diseases, notably methotrexate, azathioprine, cyclophosphamide, sulphasalazine and leflunomide. The recommended frequency of hepatic monitoring is dependent upon the particular pharmacologic intervention being used; however, a baseline assessment is generally recommended before initiating any of the drugs mentioned above.

Many of the “hepatic” enzymes and proteins originate in tissues other than the liver. Thus a common cause of an isolated rise in alkaline phosphatase activity is in Paget’s disease, in which the patient’s bone is the site of origin. Similarly, liver transaminases may be elevated in myositis due to muscle damage.

**Renal function**
Abnormal renal function may be a component of a rheumatic disease or a consequence of treatment. Non-steroidal anti-inflammatory drugs and methotrexate are often implicated in renal dysfunction and may necessitate a dose reduction or discontinuation of therapy. Measurement of plasma creatinine concentration is widely used as a test of renal function. However, it is not sensitive and requires a substantial loss of glomerular function before beginning to rise. The blood urea concentration is also an insensitive marker of renal function and is influenced by factors that include the rate of protein metabolism, adsorption of blood from the enteric tract and fluid balance. The chromium 51-labelled EDTA test, is an available and accurate measure of glomerular function. It is infrequently performed, as it is cumbersome to obtain and impractical for serial use.

Urinalysis is a simple method to detect renal involvement in patients with rheumatological disease. Patients with glomerulonephritis (accompanying vasculitis, lupus or other connective tissue diseases) will have an active urinary sediment with protein and/or blood on dipstick testing and red cells and granular or cellular casts on light microscopy.

Twenty-four-hour urine collection is the gold standard for quantification of proteinuria and to assess creatinine clearance. A spot urine protein:creatinine ratio is increasingly used, given its reliability and its ease of determination. Serial estimations of urinary protein excretion are helpful to monitor treatment in rheumatologic patients with renal involvement.

**Bone biochemistry**
The main diseases of bone presented to rheumatologists are osteoporosis, osteomalacia and Paget’s disease. The most commonly measured markers are serum alkaline phosphatase activity and serum calcium and phosphate concentrations. All three tend to be normal in osteoporosis, while a raised alkaline phosphatase activity of bone origin is the key biochemical feature of Paget’s disease. Severe cases of osteomalacia are associated with hypocalcaemia, hypophosphataemia and increased alkaline phosphatase activity. Parathyroid hormone levels may be high, while vitamin D levels are usually low with this condition.

Biochemical markers of bone and cartilage turnover, such as the cross-linked collagen derivatives, pyridinoline, deoxypyridinoline and N-telopeptides, may be used to assess bone turnover in osteopenia and osteoporosis. During periods of high bone turnover, such as after menopause, Paget’s disease and hyperparathyroidism, increased levels of these compounds are found in urine.

**Other biochemical tests**
Recent epidemiological studies suggest that patients with chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) are predisposed to atherosclerosis independently of other risk factors. These patients should be screened for modifiable conditions such as diabetes and hyperlipidemia, which may confer increased atherosclerotic risk. Assessment of fasting glucose, lipids and perhaps homocysteine should be made in all patients with chronic inflammatory diseases.

Plasma urate is discussed in Chapter 10.

Muscle disease is associated with a rise in creatine kinase (CK) activity. This enzyme occurs as three isoenzymes: CK MM originates from skeletal muscle, CK BB from brain and thyroid, and CK MB from myocardium and regenerating skeletal muscle. Serial measurements of CK activity often reflect disease activity in myositis, but interpretation of markedly elevated values should include consideration of the effects of vigorous exercise and intramuscular injections, which can dramatically but temporarily raise enzyme activity. Levels of cardiac troponin I are typically absent in non-

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**Table 24.3 Acute-phase reactants**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement</th>
<th>Pathophysiology</th>
<th>Affected by</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>Distance in mm that RBC column falls in 1 hour</td>
<td>Dependant upon rouleaux formation (aggregation of red cells) and PCV</td>
<td>Plasma proteins (i.e. fibrinogen, β2 microglobulin and immunoglobulins)</td>
</tr>
<tr>
<td>CRP</td>
<td>Immunoassay (mg/l)</td>
<td>Pentameric protein released from liver under influence of IL-6 within 4 hours of tissue injury</td>
<td>↑↑ in infection, often normal in SLE</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin-6; PCV = packed cell volume; RBC = red blood cell; SLE = systemic lupus erythematosus
cardiac muscle disease and a negative troponin I will help to exclude a potential cardiac origin for an elevated CK.

**Immunological investigations**

**Autoantibodies**

Autoantibodies are immunoglobulins that bind to self-antigens (molecules present in the patient’s own tissues). Low concentrations of autoantibodies are present in the plasma of normal individuals and have a higher prevalence in the normal elderly population. These antibodies are overexpressed in autoimmune conditions, owing to a variety of factors, including genetic predisposition and environmental triggers such as infection. Autoantibodies may be divided into those directed against organ-specific antigens (such as the acetylcholine receptor in myasthenia gravis or intrinsic factor in pernicious anaemia) and those that bind to more ubiquitous antigens such as DNA or the phospholipid component of cell membranes (such as cardiolipin). Relatives of patients with rheumatic diseases may make autoantibodies reflecting a genetic tendency to autoimmunity; these antibodies are usually not organ-specific.

Detection of autoantibodies in rheumatic disorders (Table 24.4) is generally more useful for diagnosis than for monitoring disease activity.

**Rheumatoid factors**

These antibodies are immunoglobulins (Ig) that bind the Fc (constant region) of IgG. Several assays are available, including the classic Rose-Waaler test, which relies on the ability of rheumatoid factors to agglutinate sheep erythrocytes coated with anti-sheep immunoglobulin, and the latex agglutination test, in which latex particles coated with human IgG aggregate in the presence of IgM rheumatoid factor. These tests identify only the IgM isotype. Detection of IgG and IgA rheumatoid factors by enzyme-linked immunosorbent assay (ELISA) is now widely available. Oligoarticular rheumatoid arthritis may be associated with a negative test for IgM rheumatoid factor but a positive test for IgG rheumatoid factor. The clinical specificity of IgA rheumatoid factor is not clear, but has been found early in the course of rheumatoid arthritis. Reference ranges vary between laboratories.

An elevated rheumatoid factor has a definite but limited value as a diagnostic test for rheumatoid arthritis. The test is positive in 70–80% of patients with rheumatoid arthritis and in some patients with other disorders, including other arthritic conditions (such as lupus and Sjögren’s syndrome). Rheumatoid factor positivity is additionally seen in infections such as tuberculosis, hepatitis B, hepatitis C and syphilis.

**Antinuclear antibodies**

Antinuclear antibodies (ANAs) are immunoglobulins that bind to antigens in the cell nucleus. ANAs are classically detected by immunofluorescence using murine liver or kidney cells, or a human epithelial cell line (HEp-2) (Figure 24.1). A titre of greater than 1:80 is usually considered positive, although autoimmune disease is generally associated with higher titres (≥1:320). Newer assays using ELISA or fluorescent microspheres (bead) technology are increasingly utilized by commercial laboratories. A positive test for ANA is not diagnostic of SLE, as an ANA may occur in several

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**Table 24.4 Autoantibodies associated with some rheumatological diseases**

<table>
<thead>
<tr>
<th>Condition</th>
<th>RF</th>
<th>ANA</th>
<th>dsDNA</th>
<th>Ro</th>
<th>La</th>
<th>Sm</th>
<th>RNP</th>
<th>ANCA</th>
<th>Jo-1</th>
<th>Topoisomerase</th>
<th>Cardiolipin</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>+++</td>
<td>+</td>
<td>–</td>
<td>+/</td>
<td>+/</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SLE</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Sjögrens</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Myositis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SSc</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Vasculitides</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; dsDNA = double-stranded DNA; RA = rheumatoid arthritis; RF = rheumatoid factor; RNP = ribonuclear protein; SLE = systemic lupus erythematosus; SSc = systemic sclerosis
conditions, including hepatic, pulmonary and haematological diseases and malignancy. In infectious diseases the test tends to be positive only transiently, but in the right clinical context a positive test is strongly suggestive of an autoimmune rheumatic disease.

The pattern of immunofluorescence varies according to which nuclear or cytoplasmic antigens are recognized (Table 24.5).

### Antibodies to DNA
Anti-DNA antibodies are typically detected by an ELISA or immunofluorescence test with the haemoflagellated organism *Crithidia luciliae* (Figure 24.2).

*Crithidia* contains pure double-stranded DNA (dsDNA) in a very large mitochondrion, and a positive assay is virtually specific to patients with lupus. Antibodies to dsDNA are often found in high titres in lupus and are especially likely to be found in patients with renal disease. These antibodies are monitored in lupus patients, as they may reflect disease activity, and a rising titre may be predictive of a flare. There are reports of the development of anti-dsDNA antibodies following treatment with TNF-α antagonists. These antibodies are predominantly of the IgM subtype and are rarely associated with a lupus-like syndrome.

### Antibodies to extractable nuclear antigens
Antibodies to extractable nuclear antigens (ENAs) are directed against antigens such as Ro, La, Sm, ribonuclear protein (RNP), centromere and topoisomerase. They were initially detected by counter-immunoelectrophoresis, a technique in which serum is tested against a saline extract of mammalian nuclei and compared with reference sera to determine a line of precipitation. More specific tests for each antigen (which consist of varying combinations of RNA and protein) are now available in many laboratories and are performed using immunoblot or ELISA.

The identification of antibodies to one or more antigens in a patient’s serum can be helpful in the diagnosis of an autoimmune disease (Table 24.4). For instance, antibodies to Sm are specific for lupus. Similarly, antibodies to Ro and La (also known as SS-A and SS-B) are often found in Sjögren’s syndrome. Some antibodies relate to specific subtypes of disease—anti-topoisomerase-1 is found in 25% of patients with systemic sclerosis with pulmonary and cardiac involvement, while anti-Jo-1 antibodies are specific to patients with myositis (polymyositis or dermatomyositis) and pulmonary fibrosis. However, as seen in Table 24.4, there is considerable overlap between expression of clinical disease and expression of particular antibodies.

Longitudinal measurement of antibodies to ENAs is usually unnecessary, as there is no consistent association between titres and disease activity. However, the presence of high titres of ENAs in an asymptomatic subject may pre-date the onset of clinical disease.

### Antibodies to cyclic citrullinated peptides
Antibodies to proteins involved in epithelial cell differentiation, known as filaggrins, are found in patients with rheumatoid arthritis. Antibodies to cyclic citrullinated peptides (CCPs), which cross-react with anti-filagrin antibodies are 90% specific for rheumatoid arthritis. These antibodies are measured by ELISA and are available in many immunology labs.

### Antiphospholipid antibodies
In the rheumatological context, antiphospholipid antibodies bind chiefly to negatively charged phospholipids such as cardiolipin. There are four tests available. The lupus anticoagulant test measures the ability of antiphospholipid antibodies to prolong clotting times (e.g. partial thromboplastin time, Russell’s viper venom time) (Figure 24.3). The simplest and cheapest antiphospholipid test is the ELISA for anticardiolipin antibodies. It allows detection and quantitation of IgG, IgM or IgA antibodies against the phospholipid cardiolipin. The Venereal Disease Research Laboratory test is used in the diagnosis of syphilis and utilizes a variety of phospholipids. Antibodies in test plasma may bind to these, creating a false-positive test for syphilis. This test is of limited diagnostic value for the detection of antiphospholipid antibodies. A fourth overlapping population of antiphospholipid antibodies comprises antibodies to a co-factor-binding protein, β2 glycoprotein-I. Similar to antibodies that directly bind phospholipid, anti-β2 glycoprotein-I antibodies are useful as markers of future thrombotic
or neurological events in patients with SLE and/or anti-phospholipid antibody syndrome (APLS).

Persistently raised concentrations of antiphospholipid antibodies (notably of the IgG isotype) associate with APLS. This syndrome consists of several clinical features including thrombosis (both arterial and venous), recurrent fetal loss, thrombocytopenia and various neurological disorders. APLS may occur in isolation or in the context of a connective tissue disease such as lupus.

**Antineutrophil cytoplasmic antibodies**

These are antibodies that bind to antigens in the cytoplasm of neutrophils and are often found in patients with vasculitides. The standard test is immunofluorescence demonstrated on normal neutrophils. Usually, one of two patterns is seen: a diffuse “cytoplasmic” staining (cANCA) or a “peripheral or perinuclear” staining pattern around the edge of the nucleus (pANCA). Different proteins are bound by cANCA and pANCA; cANCA binds almost exclusively to serine proteinase 3, while pANCA binds to myeloperoxidase (MPO) as well as other proteins. Antibodies to serine proteinase 3 and MPO may be directly measured by ELISA.

Antibodies to serine proteinase 3 are found in about 80% of patients with Wegener’s granulomatosis. Those against MPO are seen in patients with vasculitides such as microscopic polyangiitis and Churg–Strauss syndrome. Antibodies to other antigens, including lactoferrin, elastase, cathepsin G, catalase and lysozyme, stain as a pANCA and have been identified in patients with lupus, rheumatoid arthritis and inflammatory bowel diseases.

**Immunoglobulins**

A polyclonal rise in immunoglobulins is common in inflammation. In Sjögren’s syndrome total IgG concentrations may be substantially raised, often up to 30 g/l or more. Quantification of immunoglobulins and determination of their subtype by protein electrophoresis should be performed in patients with Sjögren’s syndrome, as these patients have approximately a 40 times increased risk of developing lymphoma.

**Complement**

Proteins of the complement cascade play a central role in cell lysis, opsonization of bacteria and clearance of immune complexes. C3 and C4 components are most commonly measured (and in some laboratories CH50, which is a measure of overall integrity of the complement pathway) and are useful in screening for complement deficiencies (Table 24.6).

Complement degradation products, particularly C3d and C4d, are currently available as research tools as markers of SLE disease activity.

**Genetic associations**

Most rheumatic disorders are polygenic, and analysis of genetic markers is of limited value. Close human leucocyte antigen (HLA) associations are found with diseases such as ankylosing spondylitis and rheumatoid arthritis. In the former, 95% of patients possess an HLA-B27 allele. The frequency of B27 in the general population is around 10%. However, HLA typing is expensive and usually unnecessary, as it is never diagnostic. A thorough clinical assessment with appropriate haematological, biochemical, immunological and radiological investigations should lead to a definitive diagnosis. HLA haplotype determinations are not tests for specific diseases, because HLA haplotypes do not associate with individual rheumatological diseases; furthermore, family members of patients with rheumatic diseases (e.g. ankylosing spondylitis) may have a rheumatic-disease-associated HLA and no clinical disease.

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**Table 24.6 Changes in C3, C4 and/or CH50 in diseases**

<table>
<thead>
<tr>
<th>Change in C3, C4 or CH50</th>
<th>Characteristic conditions</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>Bacterial infections</td>
<td>Part of acute-phase response</td>
</tr>
<tr>
<td>↑</td>
<td>Inflammatory diseases, including RA and seronegative arthritides</td>
<td></td>
</tr>
<tr>
<td>↓</td>
<td>SLE, especially lupus, nephritis, other vasculitides</td>
<td>Consumption by immune complexes</td>
</tr>
<tr>
<td>↓</td>
<td>Hereditary hypocomplementemic syndromes</td>
<td>Hereditary</td>
</tr>
</tbody>
</table>

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus
Microbiology

The differential diagnosis in any acute monoarthropathy must include septic arthritis. This is easily excluded by joint aspiration, with culture of synovial fluid and blood. It is necessary to inform the laboratory if tuberculosis or gonococcal infections are suspected, as specific culture media and techniques are required. Polyarthropathies may be associated with several viral and bacterial infections. Chronic hepatitis B or C or HIV infection may cause poliarthralgia. Acute rheumatic fever, which is still a major killer on a worldwide scale but rare in the Western world, is associated with streptococcal infection (i.e. positive anti-streptolysin O titre or *Streptococcus* species in blood or throat cultures). The seronegative spondyloarthropathies may be related temporally to a diarrhoeal illness or to urethritis. Organisms often implicated in these diseases include *Salmonella, Yersinia, Campylobacter* and *Chlamydia*. Parvovirus B19 has been associated with a self-limiting polyarthritis similar to rheumatoid arthritis. Other viruses such as rubella and human T-lymphotropic virus may present with an arthralgia. Lyme disease is associated with a rash and polyarthropathy and the diagnosis depends on demonstration of antibodies to the spirochete *Borrelia burgdorferi*.

Conclusions

Blood tests are useful in terms of assessment, diagnosis and monitoring in rheumatological diseases. There is a trend for laboratories (particularly in the USA) to use “rheumatology screens” with an array of markers often including rheumatoid factor, antinuclear antibody and ESR and CRP. This is not to be recommended, as it leads to many false-positive results. Blood tests should be used judiciously where there is an indication.

Further reading


CHAPTER 25

The Team Approach

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OVERVIEW

• Understand the meaning of a multidisciplinary team (MDT).
• Know which professionals make up the MDT.
• Understand the role of each professional and how this contributes to the holistic care of the patient.
• Understand how to refer to each professional and what conditions are managed by each.
• Understand the role of the general practitioner as gate-keeper to the service.

Background

Traditionally, the patient journey involved an initial consultation with a general practitioner (GP), sometimes followed by onward referral to a consultant rheumatologist in secondary care. The consultant, or one of their medical team, would assess the patient and formulate a treatment plan. Whether or not the patient saw anyone else in the team, such as a physiotherapist, depended very much on the local facilities. It would not have been unusual for a patient with a musculoskeletal problem only ever to see their GP and/or a consultant rheumatologist in the course of their treatment.

However, times have changed, and with this comes an increasing recognition of the potential benefits that patients may gain from a multidisciplinary approach to their management. Implicit within this is the changing role of patients themselves: the crucial function of the multidisciplinary team (MDT) is to use different approaches to empower patients to take an active role in their management. A multidisciplinary approach to management is subtly different to “shared care”, where therapists and doctors from primary and secondary care manage patients and share records. Shared care is not a new concept; it has been used for years in diabetic and antenatal care, but is often led by the needs of the doctors and therapists, rather than the needs of the patient.

The changing world of musculoskeletal service provision

Integrated-care pathways (ICPs) have been introduced as a core concept in the UK Department of Health document Musculoskeletal Services (MSK) Framework (Department of Health, 2006). The Framework proposes a redesign for musculoskeletal services, based on the patient’s entire journey. The development of multidisciplinary clinical assessment and treatment services (CATS) is the keystone of the service. CATS bring together skilled professionals from primary and secondary care, including allied health professionals (AHPS), extended-scope physiotherapists (ESPs), GPs with special interest (GPwSI), chiropractors, osteopaths and nurse practitioners, as well as hospital consultants and other specialists.

One of the main targets of the MSK framework is to reduce the waiting time for patients from first presentation to definitive treatment. However, the spin-off from this is an integrated team approach to the patient, according to which patients will be seen and assessed by the most appropriate specialist (doctor or AHP). Consequently there is enhanced opportunity for patient education and promotion of self-management by improving patients’ skills to cope with their pain.

This service redesign is in keeping with Standards of Care (see http://www.arma.uk.net/care.html) produced by the UK Arthritis and Musculoskeletal Alliance (ARMA), an umbrella organization that brings together a variety of national societies concerned with rheumatic and musculoskeletal diseases. These Standards highlight the importance of a multidisciplinary approach to the management of musculoskeletal conditions; for example, Standard 10 of this document states that “People with inflammatory arthritis should have ongoing access to the local multidisciplinary team, whether this is based in secondary care, or in the community”.

The multidisciplinary team

A few essential ingredients are needed to ensure the success of the MDT (Figure 25.1; Box 25.1). The first, and most important of these, is effective communication. It is vital that members of the team have the opportunity to talk to each other, that they have a shared agenda and that they speak the same language. Second, clinical-care pathways should be developed that, wherever possible, are underpinned by a robust evidence base. The evidence base
that GPs are able to recognize certain specific diagnoses, such as the early signs of inflammatory arthritis, to facilitate early referral to secondary care (Box 25.2). The British Society for Rheumatology (BSR) has recently published guidelines for the management of rheumatoid arthritis in the first 2 years (Luqmani et al., 2006), which stress the importance of early referral. The Primary Care Rheumatology Society (http://www.pcrsociety.org.uk) and the Arthritis Research Campaign (http://www.arc.org.uk) take an active role in supporting and educating GPs in these important functions.

General practitioners
The GP is, traditionally, the gate-keeper to musculoskeletal services, although this is changing with initiatives such as Physio-Direct. Most musculoskeletal conditions will be managed solely by the GP with first-line treatment such as advice and prescription of analgesics. However, the GP also fulfils the crucial role of screening for “red-flags”—signs and symptoms of potentially serious disease, which need urgent referral to secondary care. In addition, it is vital that GPs are able to recognize certain specific diagnoses, such as the early signs of inflammatory arthritis, to facilitate early referral to secondary care (Box 25.2). The British Society for Rheumatology (BSR) has recently published guidelines for the management of rheumatoid arthritis in the first 2 years (Luqmani et al., 2006), which stress the importance of early referral. The Primary Care Rheumatology Society (http://www.pcrsociety.org.uk) and the Arthritis Research Campaign (http://www.arc.org.uk) take an active role in supporting and educating GPs in these important functions.

Onward referral options for the GP will increasingly include a multidisciplinary clinic such as the CATS described above. However, the precise options available will depend upon the local service provision.
GPwSIs
GPwSIs are GPs who have developed an area of expertise above and beyond that demanded of normal general practice, and they may have obtained a diploma or further postgraduate qualification in a relevant area. Many GPwSIs will work in interface clinics (e.g. CATS) or in secondary care in the context of an integrated musculoskeletal service. A competency framework for musculoskeletal/ rheumatology GPwSIs has been published (Hay et al., 2007).

Physiotherapists
Physiotherapists are trained in the assessment and management of locomotor and muscular problems. A pivotal part of their role is educating patients about biomechanical dysfunction and actively promoting self-management through appropriate exercise regimes. Some physiotherapists may undertake more specialist roles within rheumatology, including management of flares of inflammatory arthritis, manual therapy or hydrotherapy.

Extended-scope physiotherapists
ESPs have extra expertise in diagnosing, as well as treating, patients with musculoskeletal problems and may assess new referrals in a similar way to GpwsIs. They will diagnose and formulate a treatment plan as part of the MDT and may have additional skills, such as joint and soft-tissue injections, or limited prescribing.

Occupational therapists
Occupational therapists (OTs) (Table 25.1) work with other members of the MDT to maintain the function of the patient in the context of a working or home environment. OTs are particularly skilled in assessing and treating hand problems, through advice, exercises, prescription of orthotics (appliances) and provision of labour- and pain-saving devices—for example specially adapted knives and forks with padded handles, which are easier to grip. Community-based OTs will perform domiciliary visits to assess the need for home aids such as stairlifts. As well as providing practical advice, OTs are skilled in helping patients deal with the psychological consequences of their disease using cognitive behavioural approaches and relaxation techniques.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Methods employed to improve patient care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess patient hand function;</td>
<td>Prescription of hand orthotics such as wrist splints</td>
</tr>
<tr>
<td>measure grip strength and assess dysfunction</td>
<td></td>
</tr>
<tr>
<td>Assess activities of daily living</td>
<td>Prescription of exercises such as trigger finger</td>
</tr>
<tr>
<td>Assess how the patient manages in their own home</td>
<td></td>
</tr>
<tr>
<td>Assess patient’s psychological well-being and coping strategies</td>
<td>Use cognitive-behaviour techniques and counselling to improve coping mechanisms</td>
</tr>
</tbody>
</table>

Table 25.1 Functions of an occupational therapist

Nurse specialists
In secondary care, nurse specialists play an important role in assessing and managing patients with a range of rheumatological complaints (Table 25.2). One particular area of expertise lies in counselling and follow-up of rheumatology patients receiving disease-modifying anti-rheumatic drugs and anti-tumour necrosis factor (anti-TNF) drugs. Nurses often take a lead role in monitoring patients with inflammatory arthritis for side effects and effectiveness, including blood and urine testing, performing disease activity scores and liaising with consultants and GPs as appropriate.

In accordance with agreed protocols, nurse specialists may administer drugs (e.g. intramuscular steroids or intra-articular injections) and teach patients to self-administer certain drugs, such as subcutaneous methotrexate or anti-TNF.

Nurse specialists often act as a crucial link between primary and secondary care, and between the patient and specialist services, through providing telephone helplines or drop-in clinics where patients can receive advice about acute problems such as flare-ups. Nurse specialists are key in the delivery of patient education.

Chiropodists and podiatrists
Chiropodists and podiatrists are specifically trained to assess, diagnose and manage foot- and gait-related pathology. This includes the direct treatment of painful lesions (i.e. corns and callouses) as well as more serious complications such as infection and ulceration. They will assess foot and lower limb function, footwear and gait to determine if this is contributing to soft-tissue and joint pathology. Treatment may involve patient education, prescription footwear, orthoses (custom shoe inserts) or injection therapy (i.e.

<table>
<thead>
<tr>
<th>Function of nurse specialist</th>
<th>Activities undertaken and benefits to patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seeing patients at diagnosis</td>
<td>Helping patients to come to terms with the diagnosis and understand the implications of the disease</td>
</tr>
<tr>
<td>Discussing drug therapies</td>
<td>Discussing possible side effects of drug therapies; discussing how to take medications</td>
</tr>
<tr>
<td>Drug monitoring</td>
<td>Coordinating blood and urine testing and interpreting results</td>
</tr>
<tr>
<td>Performing regular patient reviews</td>
<td>Assessing disease activity with disease activity scores</td>
</tr>
<tr>
<td>Administering drug treatments</td>
<td>Exploring patient’s perceptions and needs</td>
</tr>
<tr>
<td>Providing a patient telephone helpline</td>
<td>Administering subcutaneous and intramuscular injections</td>
</tr>
<tr>
<td>Liasing with other members of the team to act upon information received from telephone helpline or face-to-face interaction</td>
<td>Administering joint injections</td>
</tr>
</tbody>
</table>

Table 25.2 Functions of a rheumatology nurse specialist
Consultant rheumatologists
Consultant rheumatologists are trained to assess and manage patients with a range of musculoskeletal complaints, ranging from non-specific back and neck pain to complex multi-system conditions such as rheumatoid arthritis. Traditionally, they were the first point of contact for a GP referral into the musculoskeletal service, although, as we have seen, this pattern is changing with the developments in service provision outlined above. Consultants often take on the role of coordinating the MDT and have overall responsibility for ensuring holistic care for the patient. They may be responsible for ensuring clinical governance for the MDT through continuing professional development, appraisal and training of the staff.

Support agencies
Agencies such as the Arthritis Research Campaign (arc) and Arthritis Care (Table 25.3) offer educational resources and direct advice to patients with arthritis. They provide an invaluable service, both to patients and to professionals, who can use their resources as part of their treatment plan.

Wider aspects of team working
These professionals not only work together directly in the care of patients with rheumatoid arthritis, they also collaborate in the drawing up of guidelines for the management of the disease and the production of patient literature (Table 25.4).

Although the multidisciplinary team described in this chapter is based on the new UK model, the role and activities of the multidisciplinary team are generally the same worldwide. It has not been possible to focus on every single professional that may be involved in the complex care of patients with a rheumatological condition. Instead we have highlighted the philosophy of care that can be adapted to suit all conditions and embrace all members of the multidisciplinary team.

References
Musculoskeletal diseases account for around 10% of general practitioner (GP) consultations in the UK each year. The most common diseases are osteoarthritis (OA) and low back pain (LBP) (Figure 26.1). These diseases generally are more common in women than men and increase with age. It is estimated that the proportion of over 65s in the population will increase 3-fold in the next 30 years, increasing the burden on health-care systems from musculoskeletal disorders.

**Rheumatoid arthritis**

Rheumatoid arthritis (RA) is estimated to have a prevalence of around 0.8% of the adult population. It is three times more likely to occur in women than men (Figure 26.2). However, estimates are considerably higher in some populations and a prevalence of 6.8% has been recorded in some Native American populations. The disease most commonly presents in the sixth and seventh decades.

A number of genetic and environmental factors have been linked with the risk of developing RA (Box 26.1). Some factors increase the risk, whereas others are thought to offer a protective role in disease development. Data from national twin studies have shown that the heritability of RA is around 60%. This source of the genetic component has been extensively investigated, and links to genes encoding HLA-DRB1 alleles are well established. Other genes, albeit with weaker effects, have also been identified, and with the increasing use of whole genome screens it is likely that more candidate genes will be discovered in future.

Several studies have implicated hormonal factors in RA, although the results have been conflicting. The higher incidence in women may suggest a hormonal influence on disease onset. A consistent finding is that current or ever use of the oral contraceptive pill has a protective role. RA onset is also reduced by 70% during pregnancy, but there is a 5-fold increased risk in the post-partum period.

Socio-economic factors have not been consistently associated with RA, but several lifestyle factors have been associated with the disease. Cigarette smoking has been the subject of many studies, and one study reported that the risk of RA was increased 3-fold for males who smoke. Heavy smoking (increased risk of over 13-fold) and passive smoking have also been linked with RA, while the cessation of smoking has been shown to reduce the risk of RA. Dietary factors are an increasing area of interest for epidemiological studies. Low fruit and vitamin C intake and high red meat intake have both been linked with a 2-fold increased risk of RA. High intakes of antioxidants (β-cryptoxanthin and zeaxanthin) found in some fruits and vegetables may reduce the risk. The benefits of following a Mediterranean diet (high proportion of oily fish and vegetables) may confer a protective role. The role of caffeine intake on RA is not yet clear, and studies so far have produced mixed results. Infectious agents have been implicated as a risk factor for RA. Both pet ownership and prior blood transfusion have been shown to
year it is estimated that over 2 million people in the UK visit their GP with OA symptoms. The site most frequently affected is the knee, although the hip and hand are also commonly affected. Hip OA is less common but is more disabling than knee OA.

A number of risk factors are associated with OA, of which the strongest is age (Box 26.2). Genetic factors are important, and OA in some families displays classical Mendelian inheritance. The heritability of cartilage volume, as a marker of degeneration, has been estimated at over 70%. Congenital joint deformities may increase the stress on the cartilage and contribute to OA development. The increase of obesity in the population is one of the major factors associated with both the development of knee OA and with the progression of the disease. Having a high body mass index has been associated with an up to 9-fold increased risk of knee OA. Joint injury can also increase the risk of OA. This may be due to direct cartilage damage or a result of increased stress on the cartilage due to the injury. Certain occupations are at an increased risk, e.g., jobs that have excessive knee-bending and farming. Factors that affect the progression of OA are also increasingly being studied. Recent studies have shown that a low vitamin D intake can increase the risk of OA, and a high vitamin C intake may reduce the risk.

Musculoskeletal pain

Most patients presenting with musculoskeletal pain do not have a definite arthritis such as RA or OA. The most commonly reported causes of musculoskeletal pain are LBP, shoulder pain, and fibromyalgia/chronic widespread pain (CWP). Estimates of the occurrence of musculoskeletal pain vary widely. It is difficult to gain robust estimates due to the episodic nature of most musculoskeletal pain syndromes; the onset of pain is not always clearly defined and is subject to recall bias.

Low back pain

LBP is common, and at least 50% of the general population will report an episode of LBP in their lifetime. A recent study estimated that the prevalence of LBP has tripled in men and doubled in women over the past 40 years. LBP is generally more common in women and the prevalence increases with age (Figure 26.4). A number of risk factors are implicated with LBP, including poor posture, occupation, poor job satisfaction, smoking, obesity, previous LBP episode and low social class (Box 26.3). In both men and women as the number of children increases so does their risk of LBP.
Fibromyalgia/chronic widespread pain
CWP, defined as both axial and limb pain affecting both upper and lower limbs on both sides of the body, is more common in women and is more likely to develop with increasing age (Figure 26.6). The prevalence estimates for CWP are consistent, between 11 and 14%. CWP has been reported more frequently in South Asian women. There is some evidence that patients with depressive symptoms are at an increased risk of developing CWP. Subjects with an increased tendency to visit their GP were found to be nine times more likely to develop CWP. The fibromyalgia syndrome (CWP plus widespread tender points) has a prevalence of between 1 and 11%, the variation being due to the method of ascertainment.

Other rheumatic diseases
The incidence of some of the other rheumatic diseases seen in rheumatological practice is summarized in Table 26.1.

Ankylosing spondylitis—Ankylosing spondylitis (AS) is three times more common in males than females, and peak onset is between 20 and 40 years of age. Prevalence is around 0.5–2.0/1000 in European populations. It is relatively rare in some African and Japanese populations but more frequent in Native Americans, with a prevalence of 6% reported in Haida and Bella Indians. The causes of the disease are still unknown, although a strong link with HLA-B27 has been established, with the frequency of the gene in white AS patients at around 90%. There is an increased risk of the disease in relatives of probands, and results of twin studies show concordance rates of 50–75% in monozygotic twins. Infection may play a part in the disease, but the data are conflicting despite several decades of study.

Psoriatic arthritis—Psoriatic arthritis (PsA) has a prevalence of around 0.1–0.2%, and there is little difference in the rate between genders or age bands. Risk factors for the disease include family history, and there is some evidence that the disease is linked to HLA alleles. There are also a number of environmental triggers associated with PsA. The disease is known to start after HIV

Shoulder pain
Up to one-third of the population will report an episode of shoulder pain at some time. Reported rates are dependent on how shoulder pain is classified (i.e. what is the shoulder?) and how the data are collected. Population studies based on self-reported symptoms estimate shoulder pain prevalence is between 20 and 40%. A recent study estimated that the prevalence of shoulder pain has doubled in men and quadrupled in women over the past 40 years. The number of patients who consult their GPs with shoulder pain increases with age (Figure 26.5) and is generally higher in women than men.

Risk factors for shoulder pain include social class and mechanical and psychosocial factors. Workplace risk factors for men developing shoulder pain include carrying weights, damp and cold working environment, working with hands above shoulder level or stretching below knee level and using arms or wrists in a repetitive manner. Performing monotonous work has been associated with a 3-fold increased risk of shoulder pain in both sexes.
infection, and prior trauma has also been associated with disease onset.

**Systemic lupus erythematosus**—Systemic lupus erythematosus (SLE) has a prevalence of between 10 and 250/100,000. It is more common in women than men, with an onset between 35 and 50 years of age. It is noticeably higher in African American, Asian and Afro-Caribbean populations than in white populations. There is strong evidence for a genetic cause for the disease, and first-degree relatives of patients are at an up to 9-fold increased risk of disease development. Twin studies also show a high concordance rate, supporting a genetic contribution for the disease. Associations with HLA have been reported, but these vary between populations. Despite the high female excess, so far no hormonal link to the disease has been found, and there is limited support for environmental risk factors, although infectious agents and chemical exposure have all been studied.

**Scleroderma**—Scleroderma is a rare disease; it usually presents between the ages of 35 and 55, with an up to 8-fold female excess. Population prevalence studies estimate the prevalence of scleroderma to be between 30 and 1130/million—the wide variation is due to the lack of population studies, as the disease is rare. There is some evidence suggesting that the disease has a higher incidence in black African populations. So far only a weak association between HLA and scleroderma has been found, although stronger links have been found with specific autoantibodies (anti-topoisomerase and anti-centromere antibodies). A number of environmental triggers are thought to be risk factors for the disease. Exposure to silica dust (stone masons and gold miners) has been linked with the disease but there is no evidence that silicone implants increase the disease risk. Exposure to organic solvents has been linked to an increased risk of scleroderma, and there is some evidence from case reports that specific drugs may be linked with the disease.

**Gout**—Gout is more common in men (around 1–2%) than women (around 0.2–0.5%). The prevalence varies in different populations. Extremely high rates are found in Polynesians (up to 10% in New Zealand Maori males), whereas gout is rarely found in African populations. Two recent studies in the USA and New Zealand suggest that the incidence of gout has increased 2-fold over the past 30 years. The main susceptibility factor for gout is hyperuricaemia. Risk factors for hyperuricaemia include obesity, hypertension, alcohol consumption, diet and some genetic factors.

**Polymyalgia rheumatica and giant cell arteritis**—Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related disorders that usually present in the over 50s. Prevalence over the age of 50 is between 0.2 and 2.2/1000 for GCA and 5.5 and 10.9/1000 for PMR. Both diseases are more common (2- to 3-fold higher) in women than men. Both diseases increase with age, peaking around 70 years with a decline after that. There is some evidence that there is a genetic link for HLA alleles and PMR/GCA, but results have not been consistent in different populations. Reports suggest that both diseases may be seasonal in incidence, but again the results have been inconsistent. There are a number of reports that suggest infectious agents as a risk factor for these diseases, and peak incidences have followed outbreaks of *Mycoplasma pneumoniae*, human parvovirus B19 and *Chlamydia pneumoniae*.

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