Rheumatology: a clinical handbook is an essential resource for medical students and junior doctors which provides all the information needed during a rheumatology placement. Written by two medical students and an experienced consultant rheumatologist, the book combines a reader-friendly writing style with the clinical experience of a professional in the field.

The book covers the core elements of diagnosis and treatment based on the latest national guidelines to swiftly bring the reader up-to-date. A definition and brief pathophysiology for each condition is provided, which is linked to the respective clinical features. Self-assessment questions and an OSCE chapter provide a way of checking that users have understood and grasped the core material, as well as enabling students to be well-equipped for their written and OSCE examinations. Further material, in the form of 30 SBAs and 50 EMQs is available online to purchasers of the book, together with detailed answers.

Printed in full colour throughout, with an attractive design, the book benefits from a range of pedagogical features including mnemonics, clinical photos, diagrams, top tips and highlighted red flags. Rheumatology: a clinical handbook is exactly the sort of book medical students and newly qualified doctors should read.

Pre-publication reviews from medical students:

"I found the book extremely easy to read and follow. The key bullet points, excellent illustrations and OSCE tips will certainly make this a hit amongst medical students. The best part about this book is that I could follow it even though I have not done my rheumatology placement yet. This shows how clearly the information has been presented." (4th year student, Nottingham)

"The layout is excellent, and the use of colour makes the book more appealing and eye-catching. The use of colour to denote different key points stands out, and the OSCE boxes are something which will be extremely useful." (3rd year student, Durham)

"...both detailed and succinctly written." (3rd year student, Edinburgh)

"I think it’s at a great level. It gives enough physiology to refresh subjects learnt in the earlier years of medicine, but not too much to be irrelevant. I like the way it is set out. It is simple and has a very set format, lots of diagrams and tables also. This makes it much easier to retain, especially for visual workers." (4th year student, Newcastle)
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2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder which primarily affects joints that are lined with synovium. It is typically characterized by a symmetrical, occasionally deforming, peripheral polyarthritis. Because it is a systemic disease, it can also affect the whole body, including the heart, lungs and eyes.

**Pathophysiology**

- The actual cause of RA is not entirely understood.
- It is likely that genetically susceptible individuals are exposed to an unknown antigen resulting in self-stimulation of the immune system (autoimmunity).
- The immune response cross-reacts with the host tissue (synovial membrane) resulting in inflammation of the synovial membrane (synovitis) that lines joints and tendon sheaths. This gives rise to synovial hypertrophy.
- This process can eventually lead to cartilage damage and bone destruction.
- T-cells seem to be the most important mediators of the disease. They stimulate the immune system via the release of a variety of inflammatory cytokines, most importantly TNF-α, IL-1 and IL-6, resulting in a pro-inflammatory state (Fig. 2.1.1).

![Fig. 2.1.1: (a) Normal healthy joint with thin synovial membrane and (b) an RA joint. Various inflammatory cells, such as T-cells, macrophages and plasma cells infiltrate the synovial membrane to make it hyperplastic. Ultimately it develops into a ‘pannus’ which migrates onto and into articular cartilage and underlying bone.

**Epidemiology and risk factors**

- **Prevalence:** there are approximately 400 000 people with RA in the UK.
- **Incidence:** approximately 20 000 people are diagnosed with new RA each year in the UK.
- Certain risk factors have been linked to RA (Table 2.1.1).
2.1 Rheumatoid arthritis

### Table 2.1.1: Risk factors for RA

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Before menopause, RA is 3 times more common in women than men; after menopause the distribution is similar.</td>
</tr>
<tr>
<td>Age</td>
<td>Rheumatoid arthritis can affect any age group but the age of onset is often 20–40 years.</td>
</tr>
<tr>
<td>Familial</td>
<td>Estimated to account for 60% of disease susceptibility.</td>
</tr>
<tr>
<td>Genetic</td>
<td>There are strong associations between HLA-DR4 and HLA-DR1 and RA, which may be familial or non-familial (sporadic).</td>
</tr>
<tr>
<td>Environmental factors</td>
<td>Smoking, infection, diet and hormonal.</td>
</tr>
</tbody>
</table>

### Clinical features

The S factor:

1. **Stiffness** in the morning >1 hour
2. **Symmetrical** joint pain
3. **Swollen joints** (polyarthritis)
4. **Small joints** of the hand, feet and wrist (mainly affected)
5. **Sex**: female:male ratio is 3:1
6. **Speed**: quick onset over weeks to months
7. **Specific signs for the hand**:
   a. **Early**: swollen metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrist or metatarso-phalangeal (MTP) joints.
   b. **Later** (Fig. 2.1.2a): **Boutonnière deformity** (flexion of the PIP and hyperextension of the distal interphalangeal (DIP) joints), **swan neck deformity** (hyperextension of PIP and flexion of DIP joints), Z-thumb (hyperextension of the interphalangeal joint, and fixed flexion and subluxation of the MCP joint) and **ulnar deviation** (subluxation of proximal phalanges towards the ulnar side).
8. **Several extra-articular manifestations** (Fig. 2.1.3).

**Fig. 2.1.2**: (a) Late specific signs of RA; (b) Late X-ray features of RA.
**Chapter 2  Specific conditions**

**OSCE tips:** RA vs OA clinical features!
- RA usually presents symmetrically, osteoarthritis (OA) usually presents with asymmetrical joint pain
- RA morning stiffness > 1 hour, OA < 30 minutes
- OA is worse on movement, RA is not
- Common age of onset for RA is 20–40 years and >50 years for OA
- RA onset is relatively rapid (weeks to months), OA typically years
- RA presents with systemic symptoms, OA doesn’t
- RA tends to be worse in the morning, OA is worse after activities, especially towards the end of the day

**Fig. 2.1.3:** The extra-articular manifestations of the disease can occur at any age after onset and occur more commonly in males despite RA being more common in females. Extra-articular organs may involve the skin, eyes, heart, lungs and kidneys.

**Diagnosis and investigations (see Table 2.1.2)**

All people suspected of having RA should be referred for specialist assessment.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prognostic indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hx</strong></td>
<td>Pain duration (usually ≥6 weeks), morning stiffness &gt;1 hour</td>
</tr>
<tr>
<td><strong>Ex</strong></td>
<td>≥3 swollen tender joints, symmetrical joint involvement, subcutaneous nodules</td>
</tr>
</tbody>
</table>
| **Ix**    | ↑ Serum rheumatoid factor (RF)  
↑ Anti-cyclic citrullinated peptide antibodies (anti-CCP)  
↑ Erythrocyte sedimentation rate (ESR) / C-reactive protein (CRP)  
*Note: RF has ↑ sensitivity and ↓ specificity; anti-CCP has ↑ specificity and ↓ sensitivity* | Full blood count: ↑ platelet count, ↑ serum ferritin, anaemia of chronic disease  
Renal and liver function tests  
X-ray: chest, hands (Fig. 2.1.2b) and feet  
MRI: identify synovitis early  
Ultrasound: joint effusion and Baker’s cysts |
| **DDx**   | Psoriatic arthritis  
Connective tissue disease, e.g. systemic lupus erythematosus (SLE) | Reactive arthritis  
Polymyalgia rheumatica |
### Table 2.1.2: The 2010 American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) criteria

<table>
<thead>
<tr>
<th>Score</th>
<th>A. Joint involvement:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 large joint</td>
</tr>
<tr>
<td>1</td>
<td>2–10 large joints</td>
</tr>
<tr>
<td>2</td>
<td>1–3 small joints (with or without involvement of large joints)</td>
</tr>
<tr>
<td>3</td>
<td>4–10 small joints (with or without involvement of large joints)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Serology:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Acute phase reactants:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Duration of symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

Note: The 2010 EULAR and ACR criteria replaced the 1987 ACR criteria as they focus on features at an earlier stage of the disease that are associated with persistent and/or erosive disease, rather than defining the disease by its late-stage features. As a result, this refocuses attention on the important need for earlier diagnosis and therefore earlier treatment.

### Management

The aim of management in RA is to reduce/slow the joint inflammation and disease progression to maintain the patient’s lifestyle. Early use of disease-modifying antirheumatic drugs (DMARDs) and biological agents improves the long-term outcome of the disease. Treatment should be started within 3 months of symptom onset, based on NICE CG79 (2009).

- Refer urgently to a rheumatologist, in order to prevent irreversible destruction of joint(s) if:
  - the small joints of the hand and feet are affected
  - more than one joint is affected
  - there has been a delay of 3 months or longer between the onset of symptoms and seeking medical advice.

- Specialists usually start with a DMARD and short-term corticosteroids (if appropriate). Emphasis should be placed on reaching a clinical effective dose rather than on the choice of DMARD.

- The disease activity of RA should be monitored by measuring CRP and the DAS28 score (Box 2.1.1). The aim is to reduce the DAS28 score below 3.

### Non-pharmacological management

- Encourage regular exercise: aerobic activities, flexibility and muscle strength exercises, core stability exercise, balance rehabilitation, promotion of lifestyle physical activity, smoking cessation.
- People with RA should have access to a multidisciplinary team such as specialist nurses, physiotherapists, occupational therapists and podiatrists.
### Table 2.1.3: Pharmacological management of rheumatoid arthritis

| DMARDs | • Are first-line  
• Early DMARD treatment is associated with better long-term prognosis. Ideally within 3 months of the onset of persistent symptoms  
• **Methotrexate**, sulfasalazine and hydroxychloroquine are the most commonly used  
• NICE recommends a combination of DMARDs, including methotrexate and at least one other DMARD, plus short-term glucocorticoids (if not contraindicated) |
| --- | --- |
| Corticosteroids | • Rapid reduction in symptom onset and inflammation  
• Can be given via intra-muscular, intra-articular and oral routes  
• NICE recommends a combination of corticosteroids and DMARDs |
| NSAIDs | For symptomatic relief and also to reduce inflammation, e.g. ibuprofen, diclofenac, etodolac |
| Biological agents | (TNF-α inhibitors, B-cell blockers, and anti-IL-1 & IL-6 agents). Indications: after the failure of 2 conventional non-biological DMARDs. Failure is measured objectively using DAS28 (indicated by a score >5.1) |
| TNF-α inhibitors | • Block the pivotal action of TNF-α, a key cytokine in the pathogenesis of RA  
• Include **infliximab**, adalimumab and etanercept  
• Very expensive and used in severe cases (high DAS28 score)  
• Should normally be used in combination with methotrexate |
| B-cell blockers | • **Rituximab** is a B-cell blocker  
• It works by targeting the B-cell surface marker, CD-20  
• A combination of rituximab and methotrexate is recommended as an option for the treatment of adults with RA who are intolerant of other DMARDs or whose response to them is inadequate. |
| Anti IL-1 & IL-6 agents | • Like TNF-α, IL-1 and IL-6 are pro-inflammatory cytokines which are heavily involved in the disease process.  
• **Anakinra** is an IL-1 receptor antagonist  
• **Tocilizumab** is an anti-IL-6 receptor monoclonal antibody  
• On the balance of its clinical benefits and cost-effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis |
**Pharmacological:** see *Table 2.1.3*

**Surgery:**
- Consider the following for surgical opinion if they do not respond to non-surgical management:
  - **Persistent pain** due to joint damage or other identifiable soft tissue cause
  - **Worsening joint function**
  - **Progressive deformity**
  - **Persistent localized synovitis**.
- Surgical procedures may include:
  - **Joint prosthesis:** *hip* and *knee*
  - **Arthroscopy:** remove abnormal synovium, cartilage and eroded bone
  - **Tendon reconstruction:** restore function when tendon ruptured.

**Box 2.1.1: The Disease Activity Score (DAS28)**
- It assesses **tenderness and swelling at 28 joints** (see Fig. 2.1.4), ESR, and patients’ **self-reported symptom** severity, to calculate a disease activity score.
- **DAS28 score of:**
  - >5.1 = high disease activity
  - 3.2–5.1 = moderate disease activity
  - <3.2 = low disease activity
  - <2.6 = remission
- **A decrease in DAS28 score by:**
  - 0.6 points or less = poor response
  - >1.2 points = moderate or good response
  (depending on whether an individual’s DAS28 score at the end point is above or below 3.2, respectively)

---

**Self-assessment**

A 45 year old woman complains of symmetrical pain and swelling of her MCP joints.

**You think that a diagnosis of RA is likely.**

1. What clinical features would suggest a diagnosis of RA in this lady?
2. What specific questions would you like to ask her?
3. What blood tests would you initially perform, and what might they show?
4. The blood tests confirm a diagnosis of RA. Which group of pharmacological agents would you use to start specific treatment? Name the most commonly used drugs in this group and their main side-effects.
5. Name two ways of monitoring response to treatment.

Answers to self-assessment questions are to be found in *Appendix A*. 
2.2 Osteoarthritis

Osteoarthritis (OA) is the **most common form of arthritis** and is a major cause of **impaired mobility**. It is a condition characterized by cartilage damage and joint space narrowing resulting in pain, functional limitation and impaired quality of life. It can affect any joint but the **hip, knee, lumbar** or **cervical spine**, and **wrist joints** are most commonly affected.

**Pathophysiology**

- OA is viewed as a **metabolically dynamic process** where there is an imbalance between joint breakdown and sufficient repair process.
- Normal joint articulating cartilage, **hyaline cartilage**, undergoes turnover in which ‘worn out’ collagen and other matrix components are degraded and replaced by **chondrocyte cells**.
- Both **genetic and environmental** factors can stimulate **apoptosis** of chondrocytes, disrupting the normal repair mechanism and thereby causing cartilage damage.
- Certain **cytokines** (e.g. IL-1 and TNF-α) and **protease enzymes** (e.g. metalloproteinase) increase in the cartilage; this triggers osteoarthritic changes through direct cartilage damage.
- Eventually, cartilage destruction exposes underlying bone, resulting in abnormal **subchondral bone growth** (subchondral sclerosis), **osteoophytes** and **bone cysts** *(Fig. 2.2.1)*.

**Epidemiology and risk factors**

- Worldwide estimates indicate that 9.6% of men and 18% of women ≥60 years have symptomatic OA.
- At least 4.4 million, 550 000 and 210 000 people in the UK have X-ray evidence of moderate to severe OA of the hands, knees and hips, respectively.
2.2 Osteoarthritis

### Table 2.2.1: Risk factors for OA

<table>
<thead>
<tr>
<th>Systemic risk factors</th>
<th>Mechanical risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>• Risk increases with age; partly due to age-related changes such as ligament laxity.</td>
<td><strong>Obesity</strong></td>
</tr>
<tr>
<td></td>
<td>• Places mechanical stress on joint cartilage.</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>• Polyarticular OA is more common in women.</td>
<td><strong>Injury</strong></td>
</tr>
<tr>
<td>• A high prevalence in post-menopausal women suggests a role for sex hormones.</td>
<td>• Ligament damage or fractures can lead to abnormal stress on joint cartilage.</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td><strong>Joint damage</strong></td>
</tr>
<tr>
<td>• 40–60% of ‘common OA’ is thought to have a hereditary component.</td>
<td>• Joint damage due to underlying disease e.g. RA, Paget’s disease, varus and valgus deformity or trauma (secondary OA).</td>
</tr>
<tr>
<td><strong>Bone density</strong></td>
<td><strong>Occupation</strong></td>
</tr>
<tr>
<td>• ↑ bone density e.g. Paget’s disease ↑ risk of OA.</td>
<td>• Cleaners have ↑ risk of hip, knee and shoulder OA.</td>
</tr>
<tr>
<td>• ↓ bone density e.g. osteoporosis ↓ risk of OA.</td>
<td>• Hairdressers have ↑ risk of hand OA.</td>
</tr>
<tr>
<td></td>
<td>• Farmers have ↑ risk of hip OA.</td>
</tr>
</tbody>
</table>

### Clinical features

- Clinical features depend on the joint sites affected (*Table 2.2.2*).

**Symptoms**: Joint pain – worse on movement, load bearing and at the end of the day, joint stiffness – in the morning or after rest for <30 minutes, reduced joint function and joint instability.

**Signs**: Periarticular tenderness, crepitus, ↓ range of movement, muscle wasting, joint deformity and instability, squaring of the thumb, swelling of the hands (*Bouchard’s nodes* and *Heberden’s nodes*; *Fig. 2.2.2*), mild synovitis and effusion.

### Table 2.2.2: American College of Rheumatology (ACR) criteria for hand, hip and knee OA

<table>
<thead>
<tr>
<th>Nodal OA</th>
<th>Hip OA</th>
<th>Knee OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal OA or primary generalized OA commonly affects post-menopausal women. There is hand pain, aching, or stiffness for most days of the prior month. Heberden’s and Bouchard’s nodes in ≥2 joints are characteristic of nodal OA.</td>
<td>Hip pain for most days of the prior month. Categorized largely radiographically: femoral and / or acetabular osteophytes and radiograph hip joint-space narrowing.</td>
<td>Commonly presents in obese women ≥38 years of age. There is knee pain for most days of the prior month, crepitus on movement, morning stiffness ≤30 minutes and bony enlargement of the knee on examination.</td>
</tr>
</tbody>
</table>
Diagnosis and investigations

**Hx**
- **Joint pain** (worsened by exercise & relieved by rest) and **stiffness** (morning / after rest).
- **Reduced joint function** and **joint instability**.
- Ask about **risk factors** e.g. family history and trauma.

**Ex**
- **Look** → pain on movement, muscle wasting and limp/antalgic gait.
- **Feel** → periarticular tenderness, swelling of joints, mild synovitis and effusion, and absence of systemic features, e.g. fever.
- **Move** → pain on movement, ↓ range of movement, joint deformity, joint instability and crepitus.

**Ix**
- **Blood tests**: ESR and CRP are usually normal, RF and anti-CCP negative.
- **X-ray (‘LOSS’)**: Loss of joint space, **Osteophytes**, Subchondral sclerosis, **Subchondral cysts** (Figs. 2.2.3 and 2.2.4).
- **MRI**: can demonstrate early thinning of cartilage.
- **Arthroscopy**: cartilage loss and erosion.
- **Joint aspiration**: sterile, viscous fluid; white cell count (WCC) may be slightly elevated.

**DDx**
- Large joint involvement:
  - Monoarticular inflammatory arthropathy
  - Chronic infection e.g. tuberculosis
  - Calcium pyrophosphate disease (CPPD) (if knee is involved)
- Small polyarticular joint involvement:
  - RA

---

**Fig. 2.2.3**: X-ray of an individual with a normal right hip and a left hip with OA demonstrating reduced joint space, subchondral cysts and subchondral sclerosis.

**Fig. 2.2.4**: X-ray of (a) a normal joint and (b) X-ray of an osteoarthritic knee which shows reduced joint space and bony spurs (osteophytes).
OSCE tips: Specific questions to ask someone with suspected OA

- **Presenting complaint** → Joint pain worse on exercise or after rest? Morning stiffness? Slow timing of onset? Reduced joint function and stability? Weight-bearing joint(s)? Particular joint(s) that is ‘overused’?
- **Predisposing factors** → e.g. trauma?
- **Past medical history** → Secondary causes e.g. RA and Paget’s disease?
- **Family history** → Family history of OA?
- **Social history** → Occupation?

Management (NICE guidelines, 2014)

- Management of OA includes non-pharmacological management (Table 2.2.3), pharmacological pain relief (Fig. 2.2.5) and surgical intervention.

### Table 2.2.3: Non-pharmacological management of OA

<table>
<thead>
<tr>
<th>Education and advice</th>
<th>Education, advice and access to information are core treatments which should be offered to everyone with OA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>Exercise should be a core treatment for people with OA and should consist of local muscle strengthening and general aerobic fitness.</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Should be a core treatment for OA individuals who are obese or overweight.</td>
</tr>
<tr>
<td>Transcutaneous nerve stimulation</td>
<td>A method of electrical stimulation to provide a degree of pain relief. Can be used as an adjunct to core treatment for pain relief.</td>
</tr>
<tr>
<td>Aids and devices</td>
<td>Advice on appropriate footwear should be given as part of core treatment for people with lower limb osteoarthritis. People with biomechanical joint pain or instability should be considered for bracing / joint supports / insoles as an adjunct to their core treatment.</td>
</tr>
<tr>
<td>Physiotherapy</td>
<td>Can be useful for some individuals with OA.</td>
</tr>
</tbody>
</table>

**Fig. 2.2.5:** Pharmacological management of OA.

- **Paracetamol and/or topical NSAIDs/capsaicin** ↓ pain + inflammation (NSAID)
- **Addition of weak opioid (codeine)** ↓↓ pain
- **Oral NSAID + proton pump inhibitor (PPI)** ↓↓ pain + inflammation
- **Intra-articular corticosteroid injections** ↓↓↓ pain + inflammation

Paracetamol and/or topical NSAIDs/capsaicin ↓ pain + inflammation (NSAID)
Surgical intervention is indicated when joint symptoms have a substantial impact on the patient's quality of life and medical management has failed:

- **Replacement of joint** – the most common operations are to replace hip, knee, and base of thumb joints. The ankle joint can be fused or replaced.
- **Arthroscopy lavage and debridement** – patients should only be referred if they have OA of the knee with a clear history of mechanical locking.

## Self-assessment

A 68 year old female has been complaining of bilateral hip pain for the last 6 weeks. An X-ray is then performed (Fig. 2.2.6).

1. Describe any abnormalities you see in the X-ray.
2. What pharmacological agents would you begin with? If these don’t work, what is your next plan of action?
3. She returns to your clinic some months later complaining that the medications are not working. What are the indications for surgical intervention and what procedure should be performed?

Answers to self-assessment questions are to be found in Appendix A.

Fig. 2.2.6: X-ray of pelvis.
2.3 Septic arthritis

Septic arthritis is the acute infection (usually bacterial) of a native or prosthetic joint. Since septic arthritis can lead to rapid joint destruction, immediate accurate diagnosis and treatment are essential. Any joint can be affected, particularly the lower limb joints, most commonly the hip and knee.

**Pathophysiology**

- Septic arthritis usually occurs due to the spread of bacteria from another site to the joint:
  - The commonest route of spread is haematogenous (respiratory or urinary tract infection (UTI)).
  - Other routes include local tissue infection (cellulitis and osteomyelitis), penetrating trauma and inoculation (skin opportunistic pathogens may spread when there is a break in the skin).
- Release of cytokines leads to hydrolysis of proteoglycans and collagen, cartilage destruction, and eventually bone loss (if left untreated).
- Bacteria are the most common causative pathogens (Fig. 2.3.1). Viruses and fungi rarely cause septic arthritis.

![Fig. 2.3.1: Causative bacteria of septic arthritis.](image)

**Epidemiology and risk factors**

- The estimated incidence of septic arthritis in the UK is 2–10 cases per 100,000 of the population.

<table>
<thead>
<tr>
<th>Table 2.3.1: Risk factors for septic arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prosthetic joint</strong></td>
</tr>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
</tr>
<tr>
<td><strong>Low socioeconomic status</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Intravenous drug use</strong></td>
</tr>
<tr>
<td><strong>Osteomyelitis</strong></td>
</tr>
<tr>
<td><strong>Intra-articular injection/aspiration</strong></td>
</tr>
</tbody>
</table>
Clinical features

- Usually one joint is affected. However, less commonly two or more joints may be affected at the same time due to the spread of bacteria.
- The knee is the most common site of infection (>50%), followed by the hip (more common in children), then the shoulder, wrist, elbow and ankle. Other joints are rarely affected.
- Symptoms/signs include:
  - Extremely painful, red (erythema), swollen joint (acute).
  - Muscle spasm resulting in joint immobility.
  - Systemic features – tachycardia, fever, rash, malaise and anorexia.
  - Loosening of the implant (chronic infection in prosthetic joint).
- The clinical picture may be partially masked in the elderly, immunocompromised, those with RA and IV drug users.

Rapid diagnosis: Septic arthritis in children (Kocher criteria for a child with a painful hip)
- Non-weight-bearing on affected side
- Raised ESR
- Fever
- Raised WCC
- Probability that child has septic arthritis: 4/4 = 99%, 3/4 = 93%, 2/4 = 40%, 1/4 = 3%

Diagnosis and investigations

Hx
- Presenting complaint: extreme pain, overlying skin is red, swollen joint and fever (60%). In most cases of septic arthritis there is a rapid onset of symptoms (<2 weeks) and only one joint is affected.
- Past medical history e.g. diabetes, RA and other risk factors (Table 2.3.1).
- Social history: low socioeconomic status and IV drug use.
- Sexual history: gonorrhoeal infection.

Ex
- Look → signs of erythema, swelling and obvious effusion.
- Feel → tenderness, warmth and effusion.
- Move → marked limitation of movements and inability to bear weight.
- Presence of systemic features (fever, malaise, rash and tachycardia).

Ix
- Aspiration of the joint: to obtain a sample of synovial fluid. Synovial fluid is sent for immediate Gram stain, WCC, culture and polarized light microscopy (to rule out gout/CPPD). May show presence of microorganisms; WCC is often raised. Subsequent culture reveals organism type and sensitivities to antibiotic therapy.
- Blood culture: presence of microorganisms; reveals organism type and sensitivities to antibiotic therapy.
- Blood test: ↑ESR, WCC and CRP. Electrolyte and liver function tests can be performed to indicate whether there is systemic sepsis.
- X-ray: usually normal but may reveal any underlying joint disease at presentation, e.g. RA.
- Ultrasound: may show presence of effusion to guide aspiration.
2.3 Septic arthritis

<table>
<thead>
<tr>
<th>DDx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gout</td>
<td>• Flare-up of RA</td>
</tr>
<tr>
<td>• Pseudogout</td>
<td>• Transient non-specific synovitis (hip)</td>
</tr>
<tr>
<td>• Acute exacerbation of OA</td>
<td>• Reactive arthritis</td>
</tr>
<tr>
<td>• Bursitis</td>
<td>• Haemarthrosis</td>
</tr>
</tbody>
</table>

Management

**Antibiotics**

- **Empirical antibiotics** (initially IV) whilst waiting for synovial fluid joint analysis (refer to local guidelines and consult microbiologist).
- The choice of empirical therapy depends on the most likely causative organism:
  - **Flucloxacillin** (0.5–1 g/6 hours IV for 4–6 weeks) for *Staphylococcus aureus* and **vancomycin** for MRSA.
  - If **penicillin-allergic** then **IV clindamycin** should be given (0.6–2.7 g daily in 2–4 divided doses for 4–6 weeks).
  - **Cefotaxime** (1 g every 12 hours IV for 4–6 weeks) for *gonococcal* or **Gram-negative bacteria**.
- Other antibiotics may be indicated and added, depending on the results of culture and sensitivity testing.
- Antibiotic therapy should be continued for at least **6 weeks**.

**Non-pharmacological management**

- **Orthopaedic review** for the consideration of arthrocentesis, lavage and debridement, particularly if **prosthetic joint** is affected.
- **Joint immobilization** followed by **physiotherapy**.
- **Regular review** and examination of the affected joint as well as follow-up blood tests for inflammatory markers.

**Self-assessment**

A 9 year old boy presents with an acute red, swollen hip and is unable to walk. You suspect that he has septic arthritis.

1. What findings would you expect on examination?
2. An aspiration of the joint is performed to obtain a sample of synovial fluid. What tests should be performed on the sample?
3. What is the most likely causative organism for sepsis in this case?
4. What empirical antibiotic would you prescribe?
5. List some risk factors of septic arthritis.

Answers to self-assessment questions are to be found in Appendix A.
Introduction to spondyloarthropathies

- Spondyloarthropathies are a group of inflammatory arthropathies which include the following conditions (‘PEAR’):
  - Psoriatic arthritis (Sec. 2.4)
  - Enteropathic spondyloarthropathies – associated with inflammatory bowel disease and GI bypass surgery (this condition is not discussed any further in this book)
  - Ankylosing spondylitis (Sec. 2.5)
  - Reactive arthritis (Sec. 2.6)
- The spondyloarthropathies frequently overlap and have several clinical features in common:
  - Rheumatoid factor negative (seronegative)
  - HLA-B27 association – HLA-B27-positive individuals have a 20-fold increased risk of developing a spondyloarthropathy
  - Axial arthritis – arthritis of the spine and sacroiliac joints
  - Asymmetrical large joint oligoarthritis (<5 joints) or monoarthritis
  - Enthesitis – inflammation of the site of tendon or ligament insertion e.g. plantar fasciitis and Achilles tendinitis
  - Dactylitis (‘sausage digit’) – inflammation of the entire digit as a result of soft tissue oedema, and tenosynovial and joint inflammation
  - Extra-articular manifestations – these differ from RA, e.g. inflammatory bowel disease (IBD) and iritis

The European Spondyloarthropathy Study Group criteria for spondyloarthropathy

**Inflammatory spinal pain, or synovitis** (asymmetric, predominantly in the lower extremities) and one or more of the following:
- Family history: first-degree or second-degree relative with ankylosing spondylitis, psoriasis, acute iritis, reactive arthritis or IBD
- Past or present psoriasis
- Past or present IBD
- Past or present pain alternating between the two buttocks
- Past or present spontaneous enthesitis on examination
- Episode of diarrhoea occurring within one month before onset of arthritis
- Non-gonococcal urethritis or cervicitis occurring within one month before onset of arthritis
- Sacroiliitis (meeting the criteria shown in Fig. 2.5.2)
Psoriatic arthritis (PsA) is a chronic inflammatory arthritis and the most common type of seronegative oligoarthritis. PsA is unique compared to other seronegative spondyloarthritides in that the small joints of the hand are commonly affected. A variety of joint patterns are recognized in PsA, although these may overlap.

**Pathophysiology**

- The pathogenesis of PsA remains poorly understood.
- Like other autoimmune joint diseases, genetically susceptible individuals are exposed to an environmental trigger (bacteria, stress, or enthesal-related peptide) which may then activate the immune system.
- This results in T-cell infiltration and chemokine / cytokine release.
- The process is amplified by angiogenesis and cellular infiltration of involved tissues.
- Human leucocyte antigen (HLA) and other genes may determine the exact pattern of tissue involvement.

**Epidemiology and risk factors**

- The prevalence of PsA in the UK is approximately 2%.
- Men and women are equally affected.

<table>
<thead>
<tr>
<th>Table 2.4.1: Risk factors for PsA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psoriasis</strong></td>
</tr>
<tr>
<td><strong>Hereditary</strong></td>
</tr>
<tr>
<td><strong>Joint or tendon trauma</strong></td>
</tr>
<tr>
<td><strong>HIV</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
</tr>
</tbody>
</table>
Clinical features

- A variety of PsA patterns of joint involvement are recognized (Table 2.4.2).

<table>
<thead>
<tr>
<th>Table 2.4.2: Patterns of PsA – ‘DR SAM’</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIP joint disease</strong> &lt;br&gt;(5–10%)</td>
</tr>
<tr>
<td><strong>Rheumatoid pattern</strong> &lt;br&gt;(25%)</td>
</tr>
<tr>
<td><strong>Spondyloarthritis</strong> &lt;br&gt;(20%)</td>
</tr>
<tr>
<td><strong>Asymmetrical oligoarthritis</strong> &lt;br&gt;(50%)</td>
</tr>
<tr>
<td><strong>Mutilans arthritis</strong> &lt;br&gt;(1–5%)</td>
</tr>
</tbody>
</table>

- General symptoms and signs:
  - **Joint pain** and stiffness – inflammatory joint pain is characterized by prolonged morning stiffness (>30 mins), improvement with use, and recurrence with prolonged rest.
  - **Dactylitis** or ‘sausage digits’ (Fig. 2.4.3).
  - **Enthesitis** – pain, stiffness and tenderness of insertions into bone e.g. the Achilles tendon (Fig. 2.4.4).
  - Extra-articular features – psoriatic skin rash (Fig. 2.4.5), nail changes (pitting, onycholysis and hyperkeratosis) and uveitis.

**Rapid diagnosis: CASPAR criteria for PsA**

Established inflammatory articular disease and \( \geq 3 \) points is diagnostic of PsA:

A. **Current psoriasis** = 2 points
B. **History of psoriasis** (in the absence of A) = 1
C. **Family history of psoriasis** (in the absence of A or B) = 1
D. **Dactylitis** = 1
E. **Juxta-articular new bone formation** = 1
F. **RF negative** = 1
G. **Nail dystrophy** = 1
### Diagnosis and investigations

**Hx**
- **Clinical presentation** *(see above).*
- **Family history** – psoriasis or psoriatic arthritis.
- **Past medical history** – psoriasis, history of scalp or nail problems, joint or tendon trauma and HIV.

**Ex**
- Recognition of the pattern of joint involvement is essential to the diagnosis of PsA *(Table 2.4.2).*
- **Swelling and tenderness** of individual joints (synovitis) during inspection and palpation.
- ‘**Sausage digits**’.
- **Skin, scalp and nail** involvement – patients may not know they have psoriasis!
- **Pain at site of tendon attachment** – commonly affected sites include **Achilles tendon, plantar fascia, and epicondyles**.
- **Spinal stiffness** with low back pain due to **sacroilitis** (uncommon).

**Ix**
1. **X-rays:**
   - Soft tissue swelling may be the only radiographical finding seen in early disease.
   - Erosion in the DIP joint and periarticular new-bone formation; osteolysis and ‘pencil-in-cup’ deformity in advanced disease *(Fig. 2.4.6).*
2. **Blood tests:**
   - Normal or raised ESR and CRP (in active disease).
   - Immunology – RF, anti-CCP and antinuclear antibodies (ANA) negative.

**DDx**
- RA (symmetrical pattern)
- Erosive OA
- Gout (monoarthritic, large joint, especially knee)
- Reactive arthritis
- Sarcoid dactylitis

---

Fig. 2.4.4: Achilles tendon bursitis.

Fig. 2.4.5: Psoriatic skin rash.

Fig. 2.4.6: Arrows show ‘pencil-in-cup’ deformity caused by underlying osteolysis.
### Table 2.4.3: Management of PsA

<table>
<thead>
<tr>
<th><strong>NSAIDs</strong></th>
<th>First-line for <strong>pain relief</strong> and <strong>soft tissue inflammation</strong>.</th>
</tr>
</thead>
</table>
| **DMARDs** | • First-line for those with **progressive peripheral joint disease** who require more aggressive treatment.  
  • **Methotrexate** is usually the first-line DMARD.  
  • Alternative DMARDs include **ciclosporin**, **sulfasalazine** and **leflunomide**.  
  • The combination of methotrexate and ciclosporin is particularly effective.  
  • An initial trial of a DMARD for PsA is **3 months**. |
| **Intra-articular corticosteroid injections** | • May be indicated if non-steroidal anti-inflammatory drugs (NSAIDs) alone are not sufficient for symptomatic relief.  
  • Corticosteroid injection is given once and then reassessed. |
| **Anti-TNF-α therapy** | • Highly effective for **severe skin** and **joint disease**.  
  • There is no preferred TNF-α inhibitor – **etanercept**, **adalimumab**, **infliximab** or **golimumab** can be used. |
| **Physiotherapy** | Helps improve range of motion and pain, as well as muscle strengthening of joints with associated periarticular muscle atrophy. |

### Self-assessment

A 52 year old male with a past medical history of psoriasis complains of symmetrical pain and swelling in both of his hands. You suspect psoriatic arthritis.

1. Apart than psoriatic skin rash, what are some of the other extra-articular features of psoriatic arthritis?
2. What clinical features and blood tests help to distinguish between rheumatoid arthritis and psoriatic arthritis?
3. An X-ray is later performed. What abnormalities might you see?
4. Name two pharmacological agents for pain relief in psoriatic arthritis.
5. Name the first-line pharmacological agent to prevent disease progression and its side-effects.

Answers to self-assessment questions are to be found in *Appendix A*. 
Ankylosing spondylitis (AS) is the most common of the seronegative spondyloarthopathies (SpA). It is a chronic inflammatory disorder of the sacroiliac joints and spine. Other clinical features include peripheral arthritis, enthesitis, and extra-articular organ involvement.

**Pathophysiology**

- Both genetic and environmental factors interplay in the pathogenesis of AS.
- HLA-B27 is the most common predisposing gene in AS.
- The disease is first characterized by inflammation of the sacroiliac (SI) joints.
- SI joint involvement is followed by involvement of several structures including the intervertebral discs, zygapophysial, costovertebral, and the costotransverse joints, as well as the paravertebral ligaments.
- Early lesions include subchondral granulation tissue which erodes the joint and is replaced gradually by fibrocartilage and then ossification. This occurs in ligamentous and capsular attachment sites to bone (enthesitis).
- In the later stage, the outer layer of the annulus fibrosis starts to calcify, creating a bony bridge between the vertebral bodies (syndesmophytes).
- These may then fuse with the vertebral body above, causing ankylosis (Fig. 2.5.1).

**Epidemiology and risk factors**

- AS is the most common seronegative SpA with a prevalence of 150 per 100 000 in the UK.
- A significant number of patients with mild symptoms remain undiagnosed.

**Clinical features**

- Dull back pain (radiating from the SI joints to the hips / buttocks) and stiffness >6 months. These symptoms are worse at night and in the early morning and are relieved by exercise and worsened by rest.
- Reduced motion in the lumbar spine, and cervical spine movements can be globally reduced.

**Box 2.5.1: Extra-articular features of AS (‘The A factor’)**

- Atlanto-axial subluxation
- Anterior uveitis
- Apical lung fibrosis
- Aortic incompetence
- AV (atrioventricular) node block
- Achilles tendinitis
- Amyloidosis (a rare and late complication)
• Loss of lumbar lordosis.
• Reduced chest expansion due to progressive loss of spinal movements.
• Thoracic kyphosis and neck hyperextension (‘question mark posture’) – uncommon and occurs with progressive disease.
• Peripheral synovitis (approx. 30%). Typically asymmetrical oligoarthritis, most commonly affecting the hip and knee.
• Extra-articular features (Box 2.5.1).

**OSCE tips: Schober’s test**

- The modified Schober’s test examines flexion of the spine.
- An inferior mark at the level of posterior superior iliac spines is drawn and a 10 cm segment above this point is marked on the patient’s back.
- The increase in distance on maximal forward spinal flexion with locked knees is measured.
- The measured distance should increase from 10 cm to at least 13.5–15 cm in healthy adults.

**Diagnosis and investigations**

- Based on the modified New York (NY) criteria, a definite diagnosis of AS requires the presence of radiological criteria and at least one clinical criterion (history and examination).

**Hx**

History of back pain and stiffness for longer than 3 months which improves with exercise but is not relieved by rest.

**Ex**

- Limitation of motion of the lumbar spine in both sagittal and frontal planes (see OSCE tips).
- Limitation of chest expansion to 1 inch or less.

**Ix**

- **X-ray** (modified NY radiological criterion): Sacroiliitis grade ≥2 bilaterally or grade 3 or 4 unilaterally (See Fig. 2.5.2 for sacroiliitis grading).
  - Other radiographic features include:
    - **Early**: Bone erosions, widening of the SI joints and vertebral bodies appear square with shiny corners (Romanus lesions).
    - **Later**: Ossification of longitudinal ligaments of the spine (syndesmophytes) giving it a ‘bamboo spine’ appearance (Fig. 2.5.3).
  - **MRI scanning**: Although not included in the modified NY criteria, it is very useful for identifying early sacroiliitis and early inflammatory changes affecting the spine and therefore it can pick up AS at the early stages of the disease.
  - **Blood tests**: FBC normal, ↑CRP and ESR (active disease), RF and ANA negative, HLA-B27 (this has little role in diagnosis, but may indicate a predisposition to AS in the appropriate clinical context).
  - **Ultrasound scanning**: can help in diagnosing enthesitis.
2.5 Ankylosing spondylitis

**DDx**
- Mechanical back pain
- Other seronegative SpAs
- Degenerative lumbar or cervical spondylosis
- Trauma
- Infection
- Neoplasm

**Fig. 2.5.3:** X-ray of ‘bamboo spine’ in AS.

**Management**
- Early diagnosis and patient education are essential for effective AS management (Table 2.5.2).

**Table 2.5.2:** Management of AS based on Assessments in Ankylosing Spondylitis International Society (ASAS) / European League against Rheumatism (EULAR) recommendations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise and physiotherapy</td>
<td>Intense exercises or activities such as badminton and swimming to strengthen muscle and provide better stability.</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>First-line therapy for AS patients with pain and stiffness. Relieves symptoms and may slow radiographic progression. Examples – ibuprofen and naproxen.</td>
</tr>
<tr>
<td>Other analgesics</td>
<td>Offered when NSAIDs are insufficient or contraindicated. Examples – codeine and paracetamol.</td>
</tr>
<tr>
<td>Local corticosteroids</td>
<td>Temporarily relieve pain that does not respond well to NSAIDs.</td>
</tr>
<tr>
<td>Anti-TNF-α therapy</td>
<td>Given to patients with persistently high disease activity or if NSAIDs fail. Examples – adalimumab, etanercept and golimumab.</td>
</tr>
<tr>
<td>Surgery</td>
<td>Hip replacements are offered to patients with advanced hip involvement who suffer from refractory pain and disability.</td>
</tr>
</tbody>
</table>
• An instrument called the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has been formulated for measuring the disease activity of AS by asking 6 questions related to 5 major symptoms of AS: fatigue, spinal pain, arthralgia, enthesitis and morning stiffness.

**Self-assessment**

A 22 year old male presents with low back pain and stiffness that has persisted for more than 3 months. His back symptoms are worse when he awakes in the morning, and the stiffness lasts more than 1 hour. There is no history of obvious injury.

1. What condition do you think this man has and why?
2. What special test would you perform on clinical examination? Describe how this is performed.
3. Which gene is strongly linked to the likely cause of his presentation?
4. What abnormalities might you see if an X-ray is performed on this man’s lower back?
5. Outline a management plan for this patient.

Answers to self-assessment questions are to be found in *Appendix A*. 
2.6 Reactive arthritis

Reactive arthritis is an acute aseptic arthritis that develops in response to an extra-articular infection, typically originating from the gastrointestinal (GI) or genitourinary (GU) tract. It is a seronegative spondyloarthropathy classically presenting with asymmetrical oligoarthritis, usually in the lower limbs.

**Pathophysiology**

- Reactive arthritis is thought to be caused by an infectious trigger, usually a bacterial GI or GU infection (Fig. 2.6.1) in genetically susceptible individuals.
- This leads to immune activation and cross-reactivity with self-antigens causing acute inflammation in the affected joint and other tissues approximately 2–6 weeks after the initial infection.
- As well as inflammation of joints, inflammation of the entheses, axial skeleton, skin, mucous membranes, GI tract and eyes may also occur.
- HLA-B27 is positive in most patients and it is not only a strong risk factor of reactive arthritis, but it may also predict the severity and chronicity of the disease.

**Epidemiology and risk factors**

- The estimated incidence of reactive arthritis in the UK is approximately 30–40 cases per 100 000 of the population.

<table>
<thead>
<tr>
<th>Table 2.6.1: Risk factors for reactive arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI/GU infection</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>HLA-B27</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
</tr>
</tbody>
</table>

**Clinical features**

- **Arthritis** – acute, asymmetrical large joint arthritis (often lower limbs), occurring 2–6 weeks after the initial infection (most often acute, and may be accompanied by malaise, fatigue and fever).
- Other features:
  - **Enthesitis** – plantar fasciitis and Achilles tendinitis.
  - **Conjunctivitis** (usually bilateral and painful) and anterior uveitis (usually unilateral).
Chapter 2  Specific conditions

- **Dactylitis** – may occur at one or more toes.
- **Urethritis** and **circinate balanitis** (ulcers and vesicles surrounding the glans penis).
- **Lower back pain** due to sacroiliitis and spondylitis.
- **Mouth ulcers**.
- **Nail dystrophy** and **keratoderma blennorrhagica** (Fig. 2.6.2).
- **Reiter’s syndrome** – triad of **reactive arthritis**, **conjunctivitis** and **urethritis**. Although rare, it follows a GU or GI infection. It can be easily remembered using the mnemonic ‘can’t see, can’t wee and can’t bend your knee’!

### Diagnosis and investigations

**Hx**
- **Presenting complaints**: peripheral arthritis, axial arthritis (sacroiliitis), systemic features (fever, fatigue and weight loss) and enthesitis are all common.
- **History of GI or GU infection** prior to infection.
- **Family history** of reactive arthritis.
- Consider a **sexual health review**.

**Ex**
- Examine the affected joint(s).
- **Eyes** – conjunctivitis and uveitis.
- **Mouth** – oral ulcers.
- **Lower back** – pain due to sacroiliitis.
- **Genitals** – urethritis and circinate balanitis.
- **Foot** – plantar fasciitis, Achilles tendinitis, keratoderma blennorrhagica, ‘sausage toes’ and nail dystrophy.
- **Systemic features** – malaise, fatigue and fever.

**Ix**
- **Blood tests**: raised CRP, ESR, leucocytosis and thrombocytosis (acute phase), ANA, RF and anti-CCP are negative, HLA-B27 positive in 75%.
- **X-ray**: normal in early stages. Marginal erosions, plantar spurs, sacroiliitis and asymmetrical syndesmophytes may occur in chronic cases.
- **Joint aspiration**: to rule out crystal or septic arthritis. Synovial fluid is usually sterile and cloudy with high WCC.
- **Stool, throat or urine culture**: identify causative organism.
- **Serology** for Chlamydia.
- **MRI**: asymmetrical sacroiliitis and enthesitis (chronic stage).
2.6 Reactive arthritis

**DDx**
- Other seronegative spondyloarthropathies
- Gonococcal arthritis
- Gout
- Inflammatory bowel disease
- RA
- Septic arthritis

**OSCE tips:** Specific questions to ask someone with suspected reactive arthritis

- **Presenting complaint is usually asymmetrical joint pain:** Is it warm? Red? Sudden onset? Occurred after a bowel or urine infection? If so, how many days / weeks after?
- **Past medical history:** Recent stomach bug or urine infection?
- **Family history:** Has anyone in your family suffered from anything similar?
- **Sexual history:** Unprotected sex? New partner?

**Management**

<table>
<thead>
<tr>
<th>Table 2.6.2: Management of reactive arthritis</th>
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</thead>
<tbody>
<tr>
<td><strong>Non-pharmacological</strong></td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
</tr>
<tr>
<td><strong>DMARDs</strong></td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
</tr>
<tr>
<td><strong>Anti-TNF-α therapy</strong></td>
</tr>
</tbody>
</table>
A 21 year old male presents with a 2 week history of an acute painful, hot, and swollen left knee, and low back pain with bilateral buttock pain. Further review of symptoms indicates the patient was treated for a Chlamydia infection after he developed dysuria approximately 2 months ago. You suspect reactive arthritis.

1. What risk factors predispose this patient to reactive arthritis?
2. On examination, why would you look at the soles of the feet?
3. What is the name of the reactive arthritis manifestation shown in Fig. 2.6.3?
4. What blood tests would you perform and what do you expect to find?
5. How would you manage this patient acutely?

Answers to self-assessment questions are to be found in Appendix A.
2.7 Gout

Gout is an inflammatory arthritis which progresses from asymptomatic hyperuricaemia (elevated circulating uric acid levels). It is caused by deposition of urate crystals in the synovial fluid of joints, bone and other tissues.

Pathophysiology

- There is an association between gouty arthropathy and hyperuricaemia which is often asymptomatic for up to 20 years before the initial attack (Fig. 2.7.1).

![Fig. 2.7.1: Time scale of gout development.](image)

- The build-up of urate crystal (a purine product) can be caused by impaired renal excretion, overproduction of uric acid and/or by overconsumption of purine-rich foods that are metabolized to urate.

Epidemiology and risk factors

- The prevalence of gout in the UK is approximately 1.4% and is increasing (more common in countries such as the USA) because of obesity and dietary factors.
- The annual incidence of acute attacks of gout in the UK is around 12 cases per 10,000.

<table>
<thead>
<tr>
<th>Table 2.7.1: Risk factors for gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperuricaemia</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Diet</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Other risk factors</td>
</tr>
</tbody>
</table>
Clinical features
Most commonly affects the first metatarso-phalangeal joint (MTP) – gout here is also known as podagra (Fig. 2.7.2a). Other common sites include small joints of the foot (mid-tarsal) and hand, the ankle, knee and elbow.

- A single peripheral joint which becomes excruciatingly painful (often nocturnal), red, hot and swollen suggests acute gout.
- Polyarthritis, tophi (nodular subcutaneous deposition of uric acid crystals, see Fig. 2.7.2b and c), fever and malaise (uncommon) suggest chronic gout (uric acid kidney stones may also develop).

OSCE tips: Key questions to ask patients with suspected gout
- First time? Timing of onset and duration? Is it painful when socks are worn? Night attacks – painful with bed covers?
- Family history of gout / other arthritic conditions?
- Do you suffer from diabetes, hypertension or kidney problems? Do you take ‘water pills’?
- Have you had any recent tests that included the injection of dye?
- Have you ever been told your serum urate levels are high?
- Diet habits and alcohol intake?

Diagnosis and investigations

Hx
- Typically, abrupt development of severe joint pain that reaches its maximum within 6–12 hours and may undergo remission within 2 weeks (acute gout).
- Risk factors including age, family history, use of medication, diet and alcohol.

Ex
- 90% of gout attacks are monoarthritic, and the majority occur in the first MTP.
- Swelling, erythema, shiny surface and tenderness of the affected joint.
- Tophi → hallmark of chronic gout.

Ix
- Joint aspiration and synovial fluid analysis → definitive diagnosis demonstrated by the presence of negatively birefringent crystals under polarized light microscopy.
- Serum urate measurement → often elevated. Useful for monitoring the response to treatment.
- Radiographs – soft tissue swelling (early), possibly punched-out erosions (later).
2.7 Gout

**DDx**
- Septic arthritis
- Pseudogout
- Acute flare of osteoarthritis (most common condition that affects the 1st MTP)
- Cellulitis

**Management**
- Confirm the diagnosis of gout and exclude other conditions, especially septic arthritis.
- The management of gout can be principally divided into prevention and treatment of acute attacks of gout (*Table 2.7.2*).

**Table 2.7.2: Management and prevention of gout in accordance with NICE (2012)**

<table>
<thead>
<tr>
<th>Management of acute gout</th>
<th>Prevention of gout</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
<td><strong>Lifestyle changes</strong></td>
</tr>
<tr>
<td>Prescribe as soon as possible and continue until 48 hours after the gout has resolved. Use ‘strong’ NSAIDs, e.g. indomethacin (50 mg/8 hours), or naproxen (0.5–1 g daily). Co-prescribe a PPI in high-risk individuals.</td>
<td>↓ Body weight, ↓ excessive consumption of food rich in purines (meat and seafood), ↓ alcohol, take regular exercise and stop smoking.</td>
</tr>
<tr>
<td><strong>Colchicine</strong></td>
<td><strong>Allopurinol</strong></td>
</tr>
<tr>
<td>If NSAIDs are contraindicated, not tolerated, or have been ineffective in previous attacks, prescribe oral colchicine (0.5 mg/6 hours).</td>
<td>Start allopurinol 1–2 weeks after inflammation has settled and titrate the dose until serum uric acid (SUA) level &lt;300 µmol/L. Co-prescribe a low-dose NSAID, or low-dose colchicine, for at least 1 month to prevent acute attacks of gout. Avoid stopping allopurinol in subsequent acute attacks once established on treatment.</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td><strong>Febuxostat</strong></td>
</tr>
<tr>
<td>If NSAIDs and colchicine are contraindicated, e.g. in renal impairment, consider a short course of oral systemic corticosteroids. Intra-articular corticosteroids are an option if no more than 2 joints are affected.</td>
<td>Consider as second-line therapy if allopurinol is contraindicated / not tolerated.</td>
</tr>
<tr>
<td><strong>Paracetamol</strong></td>
<td></td>
</tr>
<tr>
<td>With / without codeine, in addition to above drugs or alone, solely for pain relief.</td>
<td></td>
</tr>
</tbody>
</table>
A 55 year old obese male complains of a sudden onset painful, red and swollen big toe. A diagnosis of crystal arthritis is strongly suspected.

1. Which conditions would you consider in your differential diagnosis? Name the most important one and state why.
2. What are the typical clinical features of an attack of acute gout?
3. What risk factors predispose the patient to gout?
4. A joint aspiration is performed. How would you examine the aspirate and what results would you expect?
5. An X-ray (Fig. 2.7.3) is taken. What abnormalities does it show?
6. What are the main treatments for acute gout? What are the side-effects of these medications?
7. How can recurrent attacks of gout be prevented?

Answers to self-assessment questions are to be found in Appendix A.
Calcium pyrophosphate disease

Calcium pyrophosphate disease (CPPD), often referred to as pseudogout, is caused by the deposition of calcium pyrophosphate crystals into the joint space. CPPD commonly coexists with osteoarthritis and is the most common cause of chondrocalcinosis (calcification of cartilage seen on X-ray).

Pathophysiology

- Calcium pyrophosphate (CPP) crystals form extracellularly when inorganic pyrophosphate reacts with calcium.
- The crystals first deposit in the joint cartilage (fibrocartilage and hyaline cartilage) which can result in inflammation and later damage to the cartilage and surrounding tissue.
- This deposition can result in chondrocalcinosis.

Epidemiology and risk factors

- The prevalence of CPPD is ~7% in the UK.
- Men and women are equally affected.

Clinical features

- May be asymptomatic but picked up on routine X-ray.
- Acute tender, red, hot, swollen joint suggests acute CPPD (also known as pseudogout).
- Pain and stiffness with long-term damage to joints (usually knees, wrists, hips, and shoulders) suggests chronic CPPD.

<table>
<thead>
<tr>
<th>Table 2.8.1: Risk factors for CPPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
</tr>
<tr>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
</tr>
<tr>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

OSCE tips: Gout vs CPPD

<table>
<thead>
<tr>
<th>Gout</th>
<th>CPPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negatively birefringent crystals under polarized light microscopy</td>
<td>Positively birefringent crystals under polarized light microscopy</td>
</tr>
<tr>
<td>Deposition of monosodium urate crystals</td>
<td>Deposition of CPP crystals</td>
</tr>
<tr>
<td>Typically affects 1st MTP; ankle and mid-tarsal joints are also commonly affected</td>
<td>Typically affects larger joints, e.g. knee, wrist and ankle</td>
</tr>
<tr>
<td>More common in men</td>
<td>Equal sex distribution</td>
</tr>
<tr>
<td>Presentation is similar for both acute gout and acute CPPD, but there is usually a difference in joint distribution</td>
<td></td>
</tr>
<tr>
<td>Acute management for both conditions is very similar (NSAIDs and colchicine); allopurinol has no role in the prevention of CPPD</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2.8.1: (a) Plain X-ray showing CPP deposition in the fibrocartilage of the knee (chondrocalcinosis). (b) Ultrasound of the knee showing similar deposition.
Diagnosis and investigations

**Hx**
- **Severe joint pain** and **swelling** that reaches its maximum within 6–24 weeks is likely to be acute crystal inflammation, though this is not specific for acute CPP crystal arthritis.
- **Risk factors** *(Table 2.8.1).*

**Ex**
- **Large joints** affected, e.g. knee.
- **Tenderness** and **erythema**.
- **Signs** of the **underlying cause**, e.g. **osteoarthritis**.

**Ix**
- **Blood tests**: ↑ WCC, ↑ ESR, ↑ CRP (acute attack).
- **Joint X-rays**: chondrocalcinosis *(Fig. 2.8.1a)* and changes of OA.
- **Ultrasound**: *(Fig. 2.8.1b).*
- **Aspiration of the joint and synovial fluid analysis**: ↑ WCC. Positive birefringent rhomboid-shaped crystals (i.e. CPP crystals) under polarized light microscopy. The joint fluid may appear purulent in nature.

**DDx**
- Septic arthritis
- Gout
- Osteoarthritis (chronic CPPD)
- Cellulitis

**Management**
- Any underlying causes need to be managed appropriately.
- Optimal treatment requires both non-pharmacological and pharmacological treatments.
  - **Non-pharmacological management** – initial rest followed by gradual mobilization of the joint. Ice packs may have a role in the short term for symptom relief.
  - **Pharmacological management** – **NSAIDs**, **colchicine**, intra-articular injection of long-acting **corticosteroids**.
2.9 Vasculitis

Vasculitides (singular, vasculitis) are a heterogeneous group of diseases that are categorized by inflammation of blood vessels, leading to compromise of the vascular lumen and ischaemia. The commonest form of vasculitis is giant cell arteritis (GCA; see Sec. 2.10). Other less common vasculitides include Takayasu's arteritis, polyarteritis nodosa (PAN), Wegener's granulomatosis (WG), Churg–Strauss syndrome (CSS) and Henoch–Schönlein purpura (HSP).

Pathophysiology

Vasculitides can affect small, medium or large vessels (mainly arterial vessels). Disease aetiology can be classified into either:

- **Primary** (idiopathic, which are autoimmune disorders and account for 45–55% of vasculitides) (Fig. 2.9.1).
- **Secondary**, mainly due to:
  - **infection** (15–20%) such as hepatitis B and C, tuberculosis (TB) and syphilis
  - **connective tissue disease** (15–20%) such as SLE, mixed connective tissue disease (MCTD) and RA
  - **drugs** (10–15%) e.g. hydralazine, propylthiouracil, sulphonamides, beta-lactams and quinolones

**Fig. 2.9.1:** Vasculitis classification. International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC 2012).
Table 2.9.1: Classification of vasculitis

<table>
<thead>
<tr>
<th>Category</th>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large arteries</td>
<td>Giant cell arteritis (GCA)</td>
<td>Discussed in Section 2.10.</td>
</tr>
<tr>
<td></td>
<td>Takayasu’s arteritis</td>
<td>Granulomatous inflammation of the large arteries supplying the arm, head, neck and heart, leading to aortic arch syndrome. Occurs mainly in young women.</td>
</tr>
<tr>
<td>Medium arteries</td>
<td>Polyarteritis nodosa (PAN)</td>
<td><strong>PAN</strong> is necrotizing arteritis without glomerulonephritis and is not associated with ANCA. This can lead to aneurysm, thrombosis and infarction.</td>
</tr>
<tr>
<td>Small arteries (c-ANCA and/or p-ANCA +ve)</td>
<td>Granulomatosis with polyangiitis (Wegener’s)</td>
<td>A necrotizing vasculitis which is usually associated with granulomatous inflammation of the respiratory tract and glomerulonephritis.</td>
</tr>
<tr>
<td>Small arteries (p-ANCA +ve)</td>
<td>Churg–Strauss syndrome (CSS)</td>
<td>Eosinophil-rich and necrotizing granulomatous inflammation associated with asthma and eosinophilia.</td>
</tr>
<tr>
<td>Small arteries (ANCA –ve)</td>
<td>Anti-glomerular basement membrane (GBM) disease</td>
<td>Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with deposition of anti-basement membrane autoantibodies.</td>
</tr>
<tr>
<td>Immune complex small vessel vasculitis</td>
<td>Henoch–Schönlein purpura (HSP)</td>
<td>IgA dominant immune deposition. Usually affects the skin and GI tract and frequently causes arthritis.</td>
</tr>
<tr>
<td>Variable vessel vasculitis</td>
<td>Behçet’s syndrome</td>
<td>Vasculitis that can affect arteries or veins, although mainly venules. Almost any organ can be affected. Common in those of Turkish descent, and very rare in the UK.</td>
</tr>
</tbody>
</table>

Epidemiology and risk factors

- Vasculitis is a rare condition.
- Epidemiology varies, depending on the gender, the subtype of vasculitis and the geographical location.
Table 2.9.2: Risk factors for vasculitis

<table>
<thead>
<tr>
<th>Other disorders</th>
<th>RA and SLE can cause secondary vasculitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A history of <strong>asthma and/or nasal allergies</strong> is associated with CSS.</td>
</tr>
<tr>
<td>Age</td>
<td>WG and CSS occur mainly in those aged &gt;40.</td>
</tr>
<tr>
<td></td>
<td>HSP occurs mainly in children and young adults.</td>
</tr>
<tr>
<td>Gender</td>
<td>Large vessel vasculitis is more common in women.</td>
</tr>
<tr>
<td></td>
<td>PAN affects men more than women.</td>
</tr>
<tr>
<td>Infection</td>
<td>Syphilis, TB and hepatitis B and C are associated with secondary vasculitis.</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Many forms of vasculitis are more common in Caucasian patients compared to other ethnicities.</td>
</tr>
<tr>
<td></td>
<td>Behçet’s disease common in those of Turkish descent.</td>
</tr>
<tr>
<td>Geographical and environmental factors</td>
<td>WG is more common amongst northern Europeans and commonly presents in winter following respiratory infection.</td>
</tr>
<tr>
<td></td>
<td>Microscopic polyangiitis is more common in southern Europe.</td>
</tr>
</tbody>
</table>

**Clinical features**

**Takayasu’s arteritis**
- Usually presents with claudication of the arm.
- Loss of arm pulses, variation in blood pressure >10 mmHg between arms.

**Polyarteritis nodosa (PAN)**
- Presents with ischaemia or infarction within affected organs:
  - **GI tract** – abdominal pain, bleeding or perforation
  - **Heart** – angina or MI
  - **Kidneys** – hypertension and renal failure
  - **Peripheral nerves** – mononeuritis multiplex (due to inflammation of vessels supplying the nerve)
- Other presentations include weight loss, fever, raised diastolic blood pressure (>90 mmHg) and livedo reticularis (Fig. 2.9.2).
- PAN is common secondary to hepatitis B virus (HBV) infection.

**Granulomatosis with polyangiitis, also known as Wegener’s granulomatosis (WG)**
A typical presentation involves the upper respiratory tract, lungs and kidneys:
- **Upper airway**
  - Nasal obstruction and crusting, with rhinorrhea
  - Epistaxis, hyposmia (due to mucosal swelling) and epiphora (watering eye) due to involvement of the nasolacrimal duct and lacrimal sac

*Fig. 2.9.2: Livedo reticularis on the anterior surface of the thigh.*

*Fig. 2.9.3: Saddle nose deformity.*
Chapter 2 Specific conditions

- Scleritis / episcleritis
- Sinusitis, nasal septal perforation and saddle nose deformity (*Fig. 2.9.3*)
- Recurrent otitis media (diminished hearing)
- Subglottic stenosis is classical feature in WG present with hoarseness of voice.

**Pulmonary airway**
- A common radiological feature is the presence of single or multiple *cavitary nodules* (*Fig. 2.9.4*) at cortical and sub-pleural sites
- This can manifest as a persistent cough (usually unproductive), pyrexia, haemoptysis, dyspnoea and post-obstructive infection.

**Kidneys**
- Nephritic syndrome (haematuria, proteinuria, hypertension and uraemia).

Other clinical features include skin rash (palpable purpura), conjunctival haemorrhages and scleritis.

The pathological hallmarks of WG are chronic granulomatous inflammation and vasculitis.

**Churg–Strauss syndrome**
- Classically presents with skin lesions (purpura or nodules) and mononeuritis multiplex with asthma.
- 50% have abdominal pain due to mesenteric arteritis.

**Microscopic polyangiitis (MPA)**
- Shares many similarities with WG. Classically presents with rapidly progressive glomerulonephritis and sometimes alveolar haemorrhage.
- Common symptoms include tiredness, loss of appetite, myalgia and arthralgia.

**Anti-glomerular basement membrane (GBM) disease**
- Usually presents as part of the classic Goodpasture’s syndrome.
- Goodpasture’s syndrome is defined by the triad of anti-GBM antibodies, glomerulonephritis and pulmonary haemorrhage.

**Henoch–Schönlein purpura (HSP)**
- Typically presents with palpable purpuric rash (small raised reddish / purple bumps; *Fig. 2.9.5*) over buttocks and lower leg.
- Abdominal pain and asymmetrical arthritis following upper respiratory tract infection.
- Glomerulonephritis occurs in 40% of patients.

*Fig. 2.9.4: Cavitary WG nodule in the right lung.*

*Fig. 2.9.5: Purpuric rash.*
Behçet’s disease

Behçet’s disease is a systemic vasculitis of unknown cause. Typical presentation includes:

- Oral ulceration (*Fig. 2.9.6*)
- Genital ulceration
- Ocular involvement (anterior and posterior uveitis or retinal vascular lesions)
- Cutaneous lesions (including erythema nodosum or papulopustular rash)
- Arthritis (mono- or oligo-)
- GI features, including diarrhoea and anorexia
- Neurological features, including encephalitis, confusion or cranial nerve palsy.

**Diagnosis and investigations**

**Hx**
- Secondary vasculitis → any connective tissue disorders, recent infection and drug history.
- Ask about asthma and recent blood transfusions (HBV).

**Ex**

**General examination**
- **Skin:**
  - Palpable purpura – HSP, WG, CSS
  - Nodules, papules, ulcers, digital ischaemia – PAN
  - Vesiculobullous (blisters) lesion – CSS, HSP
  - Pallor – seen in any vasculitis
- **Blood pressure:**
  - Hypertension – PAN
- **Oral cavity:**
  - Strawberry tongue, lip cracking, congestion of oropharyngeal mucosa – Kawasaki syndrome
  - Strawberry gums, gum ulceration – WG
  - Oral ulcers – hallmark of Behçet’s disease
- **Other:**
  - *Nose*: septal perforation, saddle nose deformity, mucosal ulceration – WG
  - *Pulse*: unequal pulse between left and right sides – Takayasu’s arteritis

**Systematic examination**
- *Respiratory system*: asthma – CSS
- *CVS*: congestive heart failure – CSS
- *GI*: abdominal tenderness (mesenteric ischaemia) – PAN
- *MSK*: migratory polyarthritis – WG, CSS, MPA
## Chapter 2 Specific conditions

### Blood tests:
- **FBC**: normocytic anaemia; leucocytosis (e.g. eosonophilia), thrombocytosis (primary vasculitis); leucopenia or thrombocytopenia (secondary vasculitis)
- **Electrolytes**: hyperkalaemia in renal failure
- **Raised creatinine** in renal failure
- **LFT abnormal** in hepatitis B or C (may need to test for serology to confirm / rule out)

### Immunology:
- Presence of c-ANCA and anti-proteinase 3 (anti-PR3) is very specific (>90%) for WG
- Presence of p-ANCA and anti-MPO is seen in MPA and CSS

### Urine dipstick (glomerulonephritis)

### Imaging:
- **CXR** (lung involvement) and echocardiogram (cardiac abnormalities)
- **Angiograph**: look for aneurysms, stenosis and post-stenotic dilatations in Takayasu’s and PAN

### Biopsy of the suspected vessel:
- Commonly taken from the site where vasculitis is suspected; e.g. temporal artery, nasal mucosa, sinuses and skin

### Skin pathergy test:
- **Performed when Behçet’s syndrome suspected** (very specific)
- Needleprick leads to papule formation within 48 hrs

### DDx
- Primary vasculitis
- Secondary vasculitis
- Peripheral vascular disease, e.g. venous thromboembolism
- Antiphospholipid syndrome

### Management

#### General principles:
- **Induce remission**: this can be achieved by high-dose steroids or cyclophosphamide (both orally and intravenously).
- Once remission is induced, the dose of steroid is **gradually reduced** and a steroid-sparing agent such as methotrexate or azathioprine is started.
- **The patient is maintained** on low-dose steroids and a steroid-sparing agent whilst being actively monitored.
- Additional therapies include angioplasty, plasma exchange and biological agents such as an IL-6 inhibitor.
- Supportive therapy such as analgesia and anti-inflammatory drugs are given when needed.
2.9 Vasculitis

Self-assessment

A 35 year old woman presents with recurrent otitis media. She has a history of numerous episodes of epistaxis. On examination you notice that she has a prominent saddle nose, dark crusts in her nose and diminished hearing. Nasal mucosal biopsy shows granulomata and large areas of necrosis. Blood tests show positive c-ANCA.

1. What is the most likely diagnosis?
2. What other signs and symptoms may she have?
3. What is the pharmacological agent of choice for this condition?

Answers to self-assessment questions are to be found in Appendix A.
Giant cell arteritis

Giant cell arteritis (GCA) is the commonest form of vasculitis, typically affecting the temporal artery.

**Pathophysiology**

- GCA is an autoimmune disorder, where exposure to an unknown environmental trigger causes breakdown of immune tolerance, resulting in an autoimmune reaction against the arterial wall.
- GCA mainly affects the extra-cranial branches of the carotid artery, specifically the temporal artery. However, it can affect any branch of the aorta.
- The histopathological hallmark of GCA is the predominance of mononuclear infiltrates or granulomas, usually with multinucleated giant cells.
- Inflammatory cells stimulate the release of metalloproteases (MMPs) and reactive oxygen species (ROS) which damage the extracellular matrix of the blood vessel wall.

**Epidemiology and risk factors**

- GCA is the most common vasculitis in the UK, with approximately 13,000 new cases each year.

<table>
<thead>
<tr>
<th>Table 2.10.1: Risk factors for primary vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymyalgia rheumatica</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
</tr>
</tbody>
</table>

**Clinical features**

- Abrupt-onset **headache**, usually unilateral in the temporal area.
- **Scalp pain**.
- Temporal artery **tenderness** and **swelling** (Fig. 2.10.1) with loss of pulsation.
- **Visual symptoms**, due to ophthalmic artery involvement, are a very serious complication of GCA. Specific symptoms of visual involvement should always be asked. These should not be missed and include:
  - **Amaurosis fugax** (transient loss of vision in one eye)
  - Blurring and diplopia
  - Partial or complete loss of vision
- **Jaw** and **tongue claudication**
- Systemic features of PMR commonly include: fever, fatigue, weight loss and muscle aching.

*Fig. 2.10.1: Swollen temporal artery in GCA patient.*
Diagnosis and investigations

Hx
- Ask about whether they have polymyalgia rheumatica (PMR) or PMR symptoms.
- Ask about visual symptoms (amaurosis fugax, diplopia, and partial or complete loss of vision).
- Patient might complain of jaw claudication (‘Painful jaw when chewing?’).
- Sudden onset of severe headache, often in the temporal or occipital region; worse at night.

Ex
Vascular:
- Scalp tenderness
- Tenderness of temporal artery and / or decreased temporal artery pulse
- Carotid bruits might be heard on auscultation
- Abdominal bruits or abnormal pulsatile aneurysmal swelling

Examination of the eye and vision:
- Ophthalmoscopic examination may reveal pale optic disc associated with severe loss of vision acuity
- Referral to ophthalmologist to perform slit-lamp examination may be required.

Ix
Blood tests:
- ↑ ESR ≥50 mm/hour.
- FBC → normocytic, normochromic anaemia, thrombocytosis.

Biopsy of the suspected vessel:
- Biopsy of the involved vessel may show a typical appearance of intermittent inflammation (‘skip lesions’), or it may even be negative (20–30%).

Imaging:
- Ultrasound may reveal thickening of the affected blood vessel wall (‘halo sign’).

DDx
- Migraine
- Tension headache
- Trigeminal neuralgia

Rapid diagnosis box: The ACR classification criteria for GCA
1. Age at disease onset ≥50 years.
2. New headache (localized pain in the head).
3. Temporal artery abnormality (tenderness to palpation or decreased pulsation).
4. Elevated ESR (≥50 mm/hour).
5. Abnormal artery biopsy – mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells).

For purposes of classification, a patient shall be said to have giant cell (temporal) arteritis if at least 3/5 criteria are present.
Management

- Immediate initiation of high-dose glucocorticoid treatment after clinical suspicion of GCA is raised.
- Visual loss occurs early in the course of disease and is irreversible.
- Early treatment with high-dose glucocorticoid is essential to prevent any further visual deterioration.

Fig. 2.10.2: Overview of GCA management (Adapted from the British Society of Rheumatology).

- Bone protection, such as a bisphosphonate and calcium/vitamin D supplementation, should be strongly considered.
- Tapering regimen: 40–60 mg prednisolone continued for 4 weeks. Then reduce dose by 10 mg every 2 weeks to 20 mg. Then by 2.5 mg every 2–4 weeks to 10 mg. Then by 1 mg every 1–2 months (provided there is no relapse).
Self-assessment

A 60 year old female presents with partial vision loss in her left eye. She complains of bitemporal headache for several weeks, along with pain and stiffness in the neck and shoulders. There are also signs of low grade fever, fatigue and weight loss. On physical examination, there is tenderness of the scalp over the temporal areas as well as thickening of the temporal arteries.

1. What is the most likely diagnosis?
2. What medication should be immediately administered?
3. Why does this patient have stiffness in the neck and shoulders?
4. What specific blood test would you request?
5. You request a temporal artery biopsy to confirm diagnosis and it comes back normal. Does this exclude your initial diagnosis?

Answers to self-assessment questions are to be found in Appendix A.
Polymyalgia rheumatica (PMR) is an inflammatory condition that results in muscle pain and stiffness in the shoulder and pelvic girdle. Giant cell arteritis (GCA) is a more serious condition which usually coexists with PMR.

**Pathophysiology**
- Cause is unknown; genetic polymorphisms and environmental factors contribute to disease susceptibility.
- Association of HLA-DR4 has been reported in various population studies.
- Inflammation is central to the pathogenesis of PMR.

**Epidemiology and risk factors**
- The incidence of the disease in patients over 50 is around 100 per 100,000 in the UK.
- PMR is mainly seen in people of north European ancestry.

**Table 2.11.1: Risk factors for PMR**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Almost exclusively present in patients over the age of 50, with peak incidence at age 65.</td>
</tr>
<tr>
<td>Gender</td>
<td>Female:Male, 3:1</td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>Approximately 40–60% of those with GCA have PMR.</td>
</tr>
<tr>
<td>Genetics</td>
<td>Having siblings with PMR increases the risk.</td>
</tr>
</tbody>
</table>

**Clinical features**
- Bilateral shoulder (90%) or thigh muscle aching pain persisting for ≥1 month
- Morning stiffness lasting for >1 hour.
- Systemic features:
  - Loss of appetite
  - Weight loss
  - Low grade malaise
  - Signs and symptoms of GCA
  - Depression
- It’s important to exclude other conditions such as active infection, malignancy and GCA!
- Main characteristic of PMR is the prompt response to corticosteroids.

**Diagnosis and investigations**

**Hx**
- Presence of risk factors e.g. age (>50 years).
- Acute onset shoulder / hip girdle pain and stiffness.
- Systemic features: low grade malaise, weight loss, depression.
2.11 Polymyalgia rheumatica

Ex
- Normal muscle strength at initial presentation.
- There may be muscle tenderness proximally.
- Temporal artery tenderness suggests coexisting GCA.

Ix
Blood tests:
- Inflammatory markers:
  - Raised ESR → >40 mm/hour
  - Raised CRP
  - Urea and electrolytes → kidney function
- Serum protein electrophoresis → measures paraprotein level to exclude multiple myeloma.
- Thyroid function test → exclusion of thyroid diseases.
- Radiography → exclusion of non-erosive joint disease.
- Temporal artery biopsy → if GCA is clinically suspected.

DDx
- Polymyositis
- Metabolic bone e.g. osteomalacia
- Hypothyroidism
- Elderly onset of RA
- Fibromyalgia
- Possible underlying malignancy, e.g. multiple myeloma

Management
- Start with standardized daily dose of 15–20 mg prednisolone. **Clinical response of >70% in one week** is expected in PMR. Inflammatory markers should be normalized in 4 weeks.
- The dose of prednisolone is reduced slowly for 3–6 months to a low maintenance level which is sustained for a further 6–12 months then gradually reduced over the next 6 months, with the aim of stopping altogether.
- Due to long-term use of steroids, bone protective agent (e.g. **bisphosphonate**) and gastroprotective agent (e.g. **proton pump inhibitor (PPI)**) should be used.
- Most treatment can be discontinued after 18–24 months.
- Steroid-sparing agents, such as methotrexate and azathioprine, may also be used. Patients should be **monitored for the emergence of GCA**.
- If GCA occurs, then a higher initial prednisolone dose should be used (40–60 mg / day).
Self-assessment

A 56 year old female presents with a 4 week history of fatigue, weight loss, fevers, and bilateral pain and stiffness in the shoulder and hip girdles. She experiences difficulty getting out of bed in the morning due to stiffness, but these symptoms improve as the day progresses.

1. What is the most likely diagnosis? Give reasons for this.
2. What further questions would you like to ask to exclude other important differentials?
3. What investigations would you perform and why?
4. How should this patient be managed?

Answers to self-assessment questions are to be found in Appendix A.
Systemic lupus erythematosus (SLE) is a chronic multi-systemic autoimmune disease of unknown cause that most commonly affects women during their reproductive years. Since it can affect any organ system, its presentation and course are highly variable. The disease is characterized by the presence of antinuclear antibodies (ANA). There are other types of lupus (other than systemic), for instance discoid lupus, drug-induced lupus and overlap syndromes.

**Pathophysiology**

- Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic and environmental factors such as oxidative stress, infections, UV light exposure and drugs (drug-induced lupus).
- Many innate and acquired immune disturbances occur in SLE, which eventually results in the development of autoantibodies and autoreactive T-cells (Fig. 2.12.1).
- Defective clearance of apoptotic cells and immune complexes also contributes to the pathogenesis, and activation of the complement system plays a major role in tissue damage.
- Antiphospholipid antibodies are a specific family of autoantibodies directed against anionic phospholipids located in cell membranes (antiphospholipid syndrome, see Box 2.12.2).

**Genetic susceptibility:**
- HLA-DR2, HLA-DR3, complement levels and hormone levels

**Environmental susceptibility:**
- UV exposure, microbial response and drugs

**Autoimmune proliferation:**
- Hyperactive B-cell/T-cell activation, defective immune complex clearance & impaired tolerance

**Autoantibody production:**
- Apoptosis and self-exposure, self-recognition and cross-reactivity

Fig. 2.12.1: Summary of pathogenesis of SLE.

**Epidemiology and risk factors**

- The prevalence of SLE is approximately 28 cases per 100,000 in the UK.
- The incidence of SLE is approximately 4 cases per 100,000 in the UK.
Table 2.12.1: Risk factors for SLE

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>The female to male ratio is approximately 10:1.</td>
</tr>
<tr>
<td>Age</td>
<td>The incidence increases in women of childbearing age (15–45).</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>More common in Afro-Caribbeans and Asians.</td>
</tr>
<tr>
<td>Drugs</td>
<td>Minocycline, isoniazid, terbinafine, phenytoin, carbamezepine, and sulphasalazine can cause drug-induced lupus.</td>
</tr>
<tr>
<td>Sun exposure</td>
<td>May be an important environmental trigger of SLE.</td>
</tr>
<tr>
<td>Family history</td>
<td>Genetic factors include HLA, complement, FC gamma receptor, cytotoxic T-lymphocyte antigen-4, and cytokine genes.</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>Smoking is linked not only to the development of SLE but also to the prognosis of the disease.</td>
</tr>
</tbody>
</table>

Clinical features

- SLE is a remitting and relapsing illness, typically presenting with non-specific constitutional symptoms of malaise, fatigue, myalgia and fever.
- See Box 2.12.1 for specific features.
- Other features include lymphadenopathy, weight loss, alopecia, nail-fold infarcts, non-infective endocarditis, Raynaud’s, migraine, stroke, and retinal exudates.

Box 2.12.1: The American College of Rheumatology revised criteria

Any four or more of the eleven criteria are required to classify a patient as having SLE. It can easily be memorized using the mnemonic ‘SOAP BRAIN MD’:

1. **Serositis** (one of the following):
   - Pleuritis: convincing history of pleuritic pain, pleural rubs on auscultation, or evidence of pleural effusion.
   - Pericarditis: documented by ECG, pericardial rub, or evidence of pericardial effusion.

2. **Oral ulcers**: oral or nasopharyngeal ulceration, usually painless, observed by physician.

3. **Arthritis**: non-erosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling, or effusion.

4. **Photosensitivity**: skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.

5. **Blood disorders** (one of the following):
   - Haemolytic anaemia: with reticulocytes
   - Leucopenia: <4 × 10⁹/L on ≥2 occasions
   - Lymphopenia: <1.5 × 10⁹/L on ≥2 occasions
   - Thrombocytopenia: <100 000 × 10⁹/L in the absence of offending drugs

6. **Renal disorder**: persistent proteinuria >0.5 g/day or >3+ if quantification not performed. Cellular casts: may be red cell, haemoglobin, granular, tubular or mixed.

7. **ANA positive**: an abnormal titre of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome. Positive in >95%.
Box 2.12.1: The American College of Rheumatology revised criteria (continued)

8. **Immunological disorder** (one of the following):
   - Anti-dsDNA: presence of antibody to native DNA in abnormal titre
   - Anti-Smith: presence of antibody to Smith nuclear antigen
   - Positive findings of antiphospholipid antibodies (anti-cardiolipin or lupus anticoagulant)

9. **Neurological disorder** (one of the following):
   - Seizures: in the absence of offending drugs or known metabolic derangements; for example, uraemia, ketoacidosis, or electrolyte imbalance
   - Psychosis: in the absence of offending drugs or known metabolic derangements; for example, uraemia, ketoacidosis, or electrolyte imbalance

10. **Malar rash** (Fig. 2.12.3): Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds.

11. **Discoid rash** (Fig. 2.12.4): Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.

**Diagnosis and investigations**

**Hx**
- **Clinical presentation** *(see above)*
- **Family history**
- **Drug history**
- Other risk factors – sun exposure and tobacco smoking.

**Ex**
Since any organ system can be affected in SLE, multiple organ systems need to be assessed *(Fig. 2.12.2)*:

1. **Mucocutaneous**: painful / painless oral ulcers, malar rash, diffuse or patchy alopecia *(Fig. 2.12.5)* and photosensitivity (common), nasal and vaginal ulcers, and Raynaud’s phenomenon (less common).

2. **Musculoskeletal system** (MSK): generalized arthralgia with morning stiffness is very common. Myalgia is common. Frank arthritis may involve the small joints of the hands and wrists (usually symmetrical, polyarticular and non-erosive). Deformities are very rare but include Jaccoud’s arthropathy *(Fig. 2.12.6)* which occurs due to ligament laxity.

3. **Renal system**: hypertension and haematuria may be present. Oedema, weight gain and hyperlipidaemia are common physical findings related to nephrotic syndrome or volume overload with renal failure.

4. **Nervous system**: the central and peripheral nervous system should be assessed. Headache, seizures and aseptic meningitis are common.

5. **Cardiopulmonary**: pleuritis or pericarditis *(see above)*.

6. **GI system**: abdominal pain, nausea, vomiting and diarrhoea can occur in up to 50% of patients with SLE.
Chapter 2 Specific conditions

**Generalized systems**
- weight loss, fever, fatigue, aching, weakness

**Central nervous system**
- seizures, paralysis, psychiatric disorders, neuropathies

**Eye**
- retinal exudates, blindness, conjunctivitis

**Skin covering**
- baldness, discoid LE, butterfly rash, Raynaud's syndrome, photosensitivity, mucosal ulcers of nose, mouth and vagina

**Lymphadenopathy**
- spleen enlargement

**Reproductive**
- menorrhagia, amenorrhea, prematurity, stillbirths

**Blood**
- decreased platelets, abnormal autoantibodies

**Lining membranes**
- pericarditis, pleurisy, endocarditis

**Kidney**
- renal failure, proteinuria, oedema, hypertension

**Gastrointestinal tract**
- poor appetite, vomiting, diarrhoea

**Musculoskeletal**
- arthralgias, arthritis and myalgias

**Fig. 2.12.2:** SLE manifestations.

**Fig. 2.12.3:** Malar rash.

**Fig. 2.12.4:** Discoid rash.

**Blood tests:**
- FBC – anaemia, leucopenia, thrombocytopenia and rarely pancytopenia.
- Activated prothrombin time – may be prolonged in patients with antiphospholipid antibodies.
- ESR and CRP – elevated (non-specific).
- Immunology – ANA antibodies, dsDNA (highly specific), Smith antigen (highly specific) positive.
- Urea and electrolytes – elevated in renal disease.

**Urinalysis:** haematuria, casts (red cell, granular, tubular or mixed) or proteinuria.

**Chest X-ray:** all patients presenting with cardiopulmonary symptoms should have a chest X-ray performed for pleural effusion, infiltrates and cardiomegaly.

**X-ray of affected joints:** periarticular osteopenia.

**MRI:** in suspected CNS lupus.

**ECG:** all patients presenting with cardiopulmonary symptoms should have an electrocardiogram (ECG). It may exclude other causes of chest pain.

**Echocardiogram:** to investigate pericardial involvement.

**Clinical facts:** Complications of SLE

SLE patients are at increased risk of other serious conditions: **atherosclerosis, hypertension, dyslipidaemia, diabetes mellitus, osteoporosis, avascular necrosis, permanent neurological damage** and **lymphoma**.

**DDx**
- RA
- Antiphospholipid syndrome
- Systemic sclerosis
- Mixed connective tissue disease
Box 2.12.2: Antiphospholipid syndrome

Antiphospholipid syndrome may be associated with SLE but mostly exists as a primary disease. It is an important cause of recurrent arterial and venous thrombosis and miscarriages. It is associated with the presence of antiphospholipid antibodies.

**Clinical features** (‘CLOT’):
- Coagulation defects, Livedo reticularis, Obstetric (recurrent miscarriage), Thrombocytopenia.

**Diagnosis** (one clinical and one laboratory finding):
- Clinical – one episode of arterial and / or venous thrombosis, or morbidity in pregnancy
- Laboratory – anti-cardiolipin antibodies or lupus anticoagulant in plasma.

**Management**: low-dose aspirin, or warfarin if recurrent thromboses. Seek expert advice for pregnancy.

Management

**Patient education**
- Advice about sun exposure – patients with sun-induced rashes should use sunscreen regularly for about 6 months over the summer. Other patients with SLE should be aware that sun exposure may precipitate a flare.
- Smoking cessation.
- Pregnancy and contraception – pregnancy should be planned. Risk of problems with pregnancy is greatly reduced if disease is well controlled prior to conception. Drug therapy should be reviewed before pregnancy. 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.
- Infections should be avoided and treated promptly if appropriate.

**Monitoring disease activity**
- Anti-dsDNA antibody titres.
- Complement system: C3↓ C4↓, and C3d and C4d↑ suggests increased activity.
Chapter 2  Specific conditions

- ESR
- Others → BP, urinalysis for casts and protein, FBC, U & Es, LFTs, CRP (usually normal).

Pharmacological management
- Analgesic / NSAIDs for arthritis.
- Cardiovascular risk reduction.
- Intra-articular steroids for joint problems.
- Hydroxychloroquine for skin and joint disease.
- High-dose steroids and cyclophosphamide for patients with severe renal, cardiac or neurological involvement or associated systemic vasculitis.
- Azathioprine, methotrexate and mycophenolate are used as steroid-sparing agents.

Self-assessment

An 18 year old female presents to her GP with symptoms of fatigue, muscle pain and a facial rash. On examination she is noted to be thin with malar skin changes. No other abnormality is found. You suspect SLE.

1. What are the possible characteristic facial rashes that occur in SLE?
2. What haematological disorders may occur in SLE?
3. What autoantibodies are present in almost all patients with SLE? Which autoantibodies are most specific to SLE?
4. How can the disease activity of SLE be monitored?
5. What general advice would you give to this patient?

Answers to self-assessment questions are to be found in Appendix A.
Polymyositis (PM) is a rare autoimmune connective tissue disease characterized by inflammation and weakness of skeletal muscle. Although PM primarily affects the muscles, it may also affect other parts of the body such as joints, the oesophagus, lungs and heart. When PM pathology extends to the skin, the condition is termed dermatomyositis (DM). DM may coexist with other connective tissue disorders such as SLE.

**Pathophysiology**

- The pathophysiology of PM and DM remains largely uncertain but both environmental and genetic factors are likely to play a part in the disease process (Fig. 2.13.1).

**Molecular pathways**

- **Genetic factors**
  - HLA markers e.g. HLA-DQA1
  - Genes regulating cytokines and their receptors e.g. PTPN22, IL-1 and TNF-α

- **Environmental factors**
  - UV light
  - Infection

- **Inflammation of muscle and skin**
  - Autoantibodies
  - Complement activation
  - Infiltration of B-cells and T-cells
  - Pro-inflammatory cytokines (IL-1 and TNF-α) in muscle tissue

- **Muscle damage**
  - PM: muscle damage appears to be predominantly via cytotoxic T-cell damage
  - DM: muscle damage is mainly thought to be from complement-mediated damage of intra-muscular microvasculature
  - Creatine kinase (a muscle enzyme) is usually released into the blood during muscle damage

*Fig. 2.13.1: Overview of the pathophysiology of PM and DM.*

**Epidemiology and risk factors**

- PM and DM are rare – the combined incidence is approximately 2–10 cases per million each year in the general population.

**Table 2.13.1: Risk factors for polymyositis and dermatomyositis**

<table>
<thead>
<tr>
<th>Genetic predisposition</th>
<th>There is an association between particular HLA subtypes and increased risk of developing PM and DM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>DM has a <strong>bimodal age distribution</strong> with peaks at 5–15 and 40–60 yrs. PM is rare in childhood and occurs mainly in adults (peak 40–60 yrs).</td>
</tr>
<tr>
<td>Female sex</td>
<td>The overall female: male ratio is <strong>2.5:1</strong>.</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>PM and DM 3 × more common in <strong>black people</strong> than in Caucasians.</td>
</tr>
<tr>
<td>Malignancy</td>
<td>DM may occur 2° to malignancy.</td>
</tr>
<tr>
<td>Environmental factors</td>
<td><strong>UV light:</strong> the rash in DM often develops in sun-exposed areas and some patients report photosensitivity.</td>
</tr>
<tr>
<td></td>
<td><strong>Infections:</strong> viruses, bacteria and protozoa have been associated with DM.</td>
</tr>
</tbody>
</table>
## Clinical features

<table>
<thead>
<tr>
<th>PM</th>
<th>DM (presents with PM features and dermatological features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly present with insidious, progressive and <strong>symmetrical proximal muscle weakness</strong> (weeks–months). The patient particularly experiences difficulties in walking up stairs or rising from a chair.</td>
<td><strong>Gottron’s papules</strong>: scaly, erythematous eruptions particularly over the extensor surfaces of the MCP, PIP and DIP joints (<a href="#">Fig. 2.13.2</a>). Macular erythema (without scaly eruption) can occur in other extensor surfaces e.g. of the elbows and knees, known as <strong>Gottron’s sign</strong> (<a href="#">Fig. 2.13.3</a>).</td>
</tr>
<tr>
<td><strong>Muscle pain</strong> (approximately 1/3).</td>
<td><strong>Heliotrope rash</strong>: violet discoloration of the eyelids, occasionally accompanied by periorbital oedema (<a href="#">Fig. 2.13.4</a>).</td>
</tr>
<tr>
<td><strong>Systemic features</strong>: fever, fatigue, and weight loss (due to oesophageal dysmotility).</td>
<td><strong>Photosensitivity</strong></td>
</tr>
<tr>
<td><strong>Aspiration pneumonia, dysphagia, dysphonia and respiratory failure</strong> (if there is involvement of the respiratory and pharyngeal muscles).</td>
<td><strong>Nail-fold erythema</strong></td>
</tr>
<tr>
<td><strong>Pulmonary fibrosis</strong> (30%)</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 2.13.2**: Gottron’s papules.  
**Fig. 2.13.3**: Gottron’s sign.  
**Fig. 2.13.4**: Heliotrope rash.

## Diagnosis and investigations

**Hx**
- See above for clinical presentation
- Risk factors e.g. family history and recent infection
- Drug history – to exclude drug-induced myopathy

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2.13 Polymyositis and dermatomyositis

**Ex**

**Polymyositis:**
- **Proximal muscle weakness** and **atrophy** occur with comparative sparing of distal muscles.
- Difficulties in arising from sitting position due to involvement of pelvic girdle muscle.
- Forced flexion of the neck is weak.
- As muscular atrophy occurs, flexor plantar response and normal sensation are maintained.
- Muscles are **tender** on palpation.

**Dermatomyositis** (in addition to PM clinical features):
- **Gottron’s sign and papules** – present in 60–80% of DM patients.
- **Heliotrope rash** – present in ≤50%.

**Ix**

**Blood tests:**
- **Creatine kinase** (CK) – can be up to 50 x higher than normal. It is rarely normal in active disease and the level is usually a good indicator of disease activity.
- Other enzymes are ↑ – aldolase, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH).
- **ESR, plasma viscosity** and **CRP** may be raised.
- **Autoantibodies:**
  - A positive **ANA** finding is found in approximately 60% of patients.
  - **Anti-Mi-2 antibodies** are specific for DM, but found in only 25% of patients.
  - **Anti-Jo-1 antibodies** are more common in patients with PM than in patients with DM. They are associated with interstitial lung disease, Raynaud’s phenomenon and arthritis.

**MRI:** may show areas of inflammation in the muscle.

**Electromyography (EMG):** abnormal but can be normal in up to 15% of patients with DM.

**Muscle biopsy:** confirms diagnosis. Shows evidence of myositis.

**DDx**

- Drug-induced myopathy (e.g. statins)
- Mixed connective tissue disease
- Hereditary neuromuscular diseases
- SLE

**OSCE tips: Malignancy in DM**

DM may occur 2° to a malignancy:
- Ask about **non-specific features of malignancy** e.g. weight loss and malaise
- Perform **systems review**
- Consider performing **whole body CT**, **GI tract imaging** and **mammography**
Management

Non-pharmacological

- Sun-blocking agents should be used for DM.
- Encourage physical activity in order to maintain muscular strength. Involvement of a physiotherapist and occupational therapist may be beneficial.
- Evaluation of swallowing may be required. Speech and language therapist may help with difficulties of swallowing.
- Monitor CK levels.
- Screen thoroughly for malignancy in DM.

Pharmacological

- Start high-dose prednisolone: 60–80 mg/24 hours. The dose should be gradually reduced according to the clinical response of CK levels.
- DMARDs and steroid-sparing drugs can be used in early resistant cases e.g. azathioprine, methotrexate and ciclosporin.
- Intravenous immunoglobulins may help in some patients.
- Hydroxychloroquine and tacrolimus may help with skin disease.

Self-assessment

A 47 year old woman presents with a 5 week history of progressive weakness in her thighs and upper arms. She has difficulty getting out of a chair unaided and complains of fatigue and breathlessness. On examination, proximal muscle strength is symmetrically reduced but distal muscle strength is normal. Chest examination reveals fine bilateral basal crepitations. You suspect polymyositis.

1. What skin features help to distinguish dermatomyositis from polymyositis?
2. What blood tests would you perform on this patient and why?
3. What further definitive tests can be performed?
4. How would you measure the clinical response to treatment?

Answers to self-assessment questions are to be found in Appendix A.
Sjögren’s syndrome (SS) is an autoimmune disorder of unknown cause characterized by inflammation of the salivary, lacrimal and other exocrine glands. The disease is referred to as primary if it develops in isolation, and secondary if it occurs with other autoimmune diseases, usually RA, SLE or scleroderma.

Pathophysiology

- Environmental or endogenous antigens trigger an immune induced inflammatory response in susceptible individuals.
- The close relationship between primary SS and SLE has led to the suggestion that primary SS is likely to share similar features to the pathogenesis of SLE.
- There is particular lymphocytic infiltration and fibrosis of the lacrimal and salivary glands producing the main symptoms of xerophthalmia (dry eyes), xerostomia (decreased saliva production) and enlargement of the parotid glands.
- Other organs may also be involved but this occurs less commonly.

Epidemiology and risk factors

- The prevalence of Sjögren’s syndrome in the UK is approximately 3–4%.

<table>
<thead>
<tr>
<th>Table 2.14.1: Risk factors for Sjögren’s syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
</tr>
<tr>
<td><strong>SLE</strong></td>
</tr>
<tr>
<td><strong>RA</strong></td>
</tr>
<tr>
<td><strong>Scleroderma</strong></td>
</tr>
<tr>
<td><strong>HLA markers</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Family history</strong></td>
</tr>
</tbody>
</table>

Clinical features (‘D factor’)

- Keratoconjunctivitis sicca (dry eyes).
- Xerostomia leading to dry mouth.
- Parotid swelling (Fig. 2.14.1).
- Vaginal dryness and dyspareunia, dry cough and dysphagia (other glands).
- Systemic features: polyarthritis, arthralgia, Raynaud’s, lymphadenopathy, vasculitis, lung, kidney and liver involvement, peripheral neuropathy, myositis and fatigue.
- It is associated with other autoimmune diseases, e.g. SLE, and there is an increased risk of non-Hodgkin’s B-cell lymphoma.
Diagnosis and investigations

**Hx**
- **Clinical presentation**: fatigue, dry eyes and dry mouth are all common.
- **Key risk factors**: female gender, SLE, systemic sclerosis, RA, HLA type II, age (30s–50s) and post-menopause.

**Ex**
- **Eyes**: dilatation of the conjunctival vessels may be present. Look for corneal lesions and gently pull down the lower eyelid to assess the tear pool. Blepharitis may be present.
- **Mouth**: may look dry and a wooden tongue depressor may stick to the tongue. There may be evidence of oral candidiasis and dental caries. Submandibular glands may be enlarged but bilateral enlargement of the parotid glands is more obvious.
- **Features of other autoimmune disorders**: most commonly RA, SLE and scleroderma.

**Ix**
- **Schirmer’s test** *(Fig. 2.14.2)*: quantitatively measures tears. A filter paper is placed in the lower conjunctival sac. The test is positive if less than 5 mm of paper is wetted after 5 minutes.
- **Blood tests**:
  - Antibodies to the ribonucleoproteins 60 kD Ro (SS-A) and La (SS-B) are found in up to 90% of patients with SS.
  - Raised ESR and hypergammaglobulinaemia.
  - Positive ANA and RF.
- **Salivary gland or lip biopsy**: shows lymphocyte infiltration.
- **Lissamine green test and rose Bengal staining**: may show keratitis.
- **Salivary gland scintigraphy**: decreased salivary gland function.
- **Parotid sialography**: gross distortion of the normal pattern of parotid ductules together with significant retention of contrast material.

**Rapid diagnosis**: American–European Consensus Group classification criteria

Requires 3 of 4 objective criteria:
1. Objective ocular signs: Schirmer’s test, rose Bengal testing or lissamine green and fluorescein.
2. Involvement of salivary gland by functional testing: salivary scintigraphy, parotid sialography.
3. Anti-Ro ± anti-La autoantibodies.

Or 4 of 6 criteria, of which at least one of anti-Ro, anti-La, and/or histopathology must be present:
1. Objective ocular signs (i.e. Schirmer’s test).
2. Involvement of salivary gland by functional testing (sialometry).
3. Autoantibodies anti-Ro or anti-La.
5. Oral symptoms.
6. Ocular symptoms.
2.14 Sjögren's syndrome

DDx
- SLE
- RA
- Scleroderma
- Salivary gland tumours
- Sarcoidosis

Management
- There is no specific treatment for SS but symptoms can be contained.

Dry eyes
- Artificial tears are first-line therapy.
- Ophthalmic ciclosporin drops can also be given.
- Spectacle eye shields – a recommended adjunct to help maintain a humid environment. Also, patients should take regular breaks while reading.
- Humidifiers – to alleviate loss of secretions by evaporation.

Dry mouth
- Patients should be encouraged to drink plenty to keep the mouth moist.
- Salivary substitutes for improving lubrication and hydration of oral tissues are used alone as first-line therapy.
- Cholinergic drugs to stimulate secretion of exocrine glands e.g. pilocarpine and cevimeline.

Other features
- Vaginal lubricants may be required and infections such as vaginal candidiasis are more likely.
- Emollients – may benefit dry skin.
- Hydroxychloroquine – may be useful in suppressing arthralgia and skin symptoms.

- The Systemic Clinical Activity Index (SCAI) has been developed to assess systemic involvement in primary SS. Factors analysed to develop the index included fatigue, musculoskeletal involvement and Raynaud's syndrome.

Self-assessment
A 35 year old woman presents with fatigue and a history of positive ANAs. She has had a recurrent sensation of sand in her eyes and dry mouth for over 3 months. You suspect Sjögren's syndrome.
1. What questions would you like to ask this patient?
2. What other conditions are positive for ANA?
3. What autoantibodies are specific to SS?
4. What investigation would you perform specifically for dry eyes?
5. Outline an appropriate management plan for this patient's symptoms.

Answers to self-assessment questions are to be found in Appendix A.
Scleroderma, which is Greek for ‘hard skin’, is an autoimmune connective tissue disorder that affects the skin and other organs. There are two main types: localized and systemic sclerosis (SSc). Localized scleroderma is more common in children and is confined to the skin and subcutaneous tissue. Systemic scleroderma may be limited (also known as CREST syndrome), which accounts for 70% of cases. The remaining 30% of cases are diffuse.

Pathophysiology

- The exact pathophysiology is not fully known. However, three processes are agreed to be important in disease progression:
  1. Immune system activation and development of autoimmunity. ANA is positive in 90% of patients with SSc.
  2. Up-regulation of certain cytokines (e.g. IL-1, -4, -6) contributes to overproduction and accumulation of collagen, which leads to hardening of the tissue.
  3. Systemic sclerosis pathology and inflammation extends to small blood vessels, which can result in serious comorbidities and mortality. Clinical manifestations of vasculopathy include Raynaud’s phenomenon (see OSCE tips), digital ulcers, renal crisis (accompanied by hypertension), pulmonary hypertension, and abnormalities in nail fold capillaries.

Epidemiology and risk factors

- The UK prevalence is 1:10 000.
- Although systemic sclerosis is rare, it has a high mortality rate.

<table>
<thead>
<tr>
<th>Table 2.15.1: Risk factors for scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive ANA</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Environmental factors</td>
</tr>
</tbody>
</table>
2.15 Scleroderma

Clinical features

**Systemic**

**Limited / CREST syndrome**

- **Slow onset**
  - Affects skin of head and extremities (Fig. 2.15.1a)
  - Calcinosis, typically underneath fingertips
  - Raynaud’s phenomenon; usually the first sign to show up (Fig. 2.15.1e)
  - Esophageal dysmotility, which might present as dysphagia or GORD
  - Sclerodactyly (stiff fingers)
  - Telangiectasia (dilated small blood vessels)

**Diffuse**

- **Sudden and aggressive onset**
  - Diffuse skin oedema, usually itchy
  - Raynaud’s phenomenon may not present initially
  - Telangiectasia (Fig. 2.15.1b)

**Morphoea**

- **Oval itchy skin patches** (Fig. 2.15.1c);
  - waxy and red in appearance
  - Does not involve the fingers
  - Raynaud’s phenomenon is uncommon

**Linear**

- **Thickened line of skin; a ‘knife-like scar’**
  - Occurs on arm, leg or forehead
  - Develops in childhood
  - Raynaud’s phenomenon is uncommon

**Fig. 2.15.1:** (a) Skin involvement distribution in SSc; (b) Telangiectasia (red spots); (c) Oval morphoea skin patch; (d) Prayer sign (unable to contact palmar surfaces together); (e) Raynaud’s phenomenon (white/ischaemic colour stage).

- Raynaud’s phenomenon is the first symptom in nearly all patients with SSc (especially limited SSc); the next symptoms usually appear within two years.

- **Skin thickness** is reliable diagnostic clinical sign; usually starts as swelling and puffiness of the skin (typically in the hands).

- SSc can affect internal organs:
  - **Lung → pulmonary hypertension**, due to blood vessel damage, is a leading cause of mortality in patients with **limited SSc**. Overproduction of collagen can lead to **interstitial lung disease** (diffuse SSc).
• Heart → right heart failure and pericardial effusions.
• Kidney → renal impairment.

OSCE tips: Raynaud’s phenomenon
WHITE → BLUE → RED!
• Transient vasospasm of the peripheral blood vessels (typically in the digits) leading to hypoxia. In extreme conditions it can cause ischaemic gangrene and digital ulcers.
• It is a common condition which affects 1–3% of population.
• Stress and cold are classic triggers of the phenomenon.
• Two types:
  • Primary (Raynaud’s disease) which accounts for 90% of cases.
  • Secondary (10%) – usually due to connective tissue disorders such as SSc.
• Clinically diagnosed → digits change colour from white to blue to red.

Diagnosis and investigations

Hx
• Nature of onset and duration of signs and symptoms are key.
• CREST syndrome → may present as gastro-oesophageal reflux disease (GORD, heartburn), dysphagia (liquids and solids), and weight loss.
• Risk factors including family history and environmental factors.

Ex
• Raynaud’s phenomenon → initial sign for SSc.
• Hand swelling and stiffness due to thickened or hardened skin (worse in morning) → reduced range of movement (prayer sign; Fig. 2.15.1d).
• Note the extent of skin involvement.
• Subcutaneous calcinosis and telangiectasia.
• Foot swelling → prompt CVS examination (heart failure) and kidney function tests (renal impairment).
• Respiratory system examination → interstitial lung disease signs.
Blood tests:
- Haematology – usually normal.
  - ESR and WCC may be raised.
  - Anaemia of chronic disease.
- Immunology:
  - ANA – found in up to 90% of patients but lacks specificity.
  - **Anti-topoisomerase-1 (Scl 70)** antibody – associated with lung fibrosis and renal disease in both subsets of systemic sclerosis.
  - **Anti-centromere antibody (ACA)** – only in patients with CREST syndrome.
  - **Anti-RNA polymerase I and III antibody** – associated with diffuse scleroderma, especially with kidney involvement.
- Biochemistry:
  - Blood urea and creatinine – elevated in renal impairment.

Respiratory (lung involvement is major cause of mortality in SSc):
- Complete pulmonary function test – interstitial lung disease and pulmonary hypertension.
- Chest X-ray – interstitial lung disease, enlarged pulmonary arteries or enlarged right ventricle.
- High resolution CT – interstitial lung disease.

Cardiovascular system: echoangiogram shows raised pulmonary artery pressure and right ventricle dysfunction.

Gastrointestinal: barium swallow test (oesophageal dysmotility).

DDx
- Primary Raynaud’s
- Other secondary causes of Raynaud’s
- Other connective tissue disorders or mixed connective tissue disorders
- Scleromyxoedema
- Paraneoplastic syndromes
## Specific management

Specific management is formulated dependent on the organ involved:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
<td>Skin hygiene and use of emollients for dry skin. Low-dose <strong>prednisolone</strong> or <strong>methotrexate</strong> (if synovitis is associated).</td>
</tr>
</tbody>
</table>
| **Vascular**           | Avoiding triggering factors for Raynaud’s phenomenon. For Raynaud’s use one of the following vasodilators:  
|                        | • Phosphodiesterase type 5 (PDE5) inhibitors  
|                        | • Endothelin-1 receptor antagonists (ERA)  
|                        | • Prostacyclin agonists  
|                        | • Calcium channel blockers                                                               |
| **Gastrointestinal**   | Avoid eating 2–3 hours before bedtime and avoid caffeine.  
|                        | **PPI inhibitors** or **H2-receptor agonists** for exacerbated conditions.               |
| **Renal disease**      | An angiotension-converting enzyme (**ACE inhibitor**) for patients at risk of renal crisis. |
| **Cardiac**            | Oral prednisolone + close monitoring of blood pressure (cardiac tamponade) for patients with pericardial effusion.  
|                        | Patients with cardiac tamponade require urgent medical care.                             |
| **Pulmonary hypertension** | **ERA, PDE5 inhibitor or prostacyclin agonists.**                                      |
| **Respiratory**        | **Cyclophosphamide** for patients with interstitial lung disease. The main disadvantage is that it increases patient’s risk of infection. |

### Self-assessment

**A 39 year old woman complains of distal finger pain and tightening. She also has a history of Raynaud’s for the past 4 years.**

1. What clinical feature is illustrated in the patient’s finger (Fig. 2.15.2)?
2. What is the most likely diagnosis?
3. What other signs would you look for during examination?
4. Which serum autoantibodies is she mostly likely to be positive for?

The patient revisits you after 6 months complaining of difficulty breathing.

5. What is the most likely underlying cause of her symptoms and what further investigations will you perform?

Answers to self-assessment questions are to be found in **Appendix A**.
2.16 Fibromyalgia

Fibromyalgia is a syndrome of chronic pain and the presence of hyperalgesic points at specific anatomical sites, as well as a range of other physical and psychological symptoms with no identifiable organic cause.

Pathophysiology

The cause of fibromyalgia is poorly understood but abnormal central and peripheral pain processing is thought to be responsible for reduced pain threshold, hyperalgesia (amplification of pain) and allodynia (pain produced by a non-noxious stimulus).

Epidemiology and risk factors

- The prevalence of fibromyalgia in the general population is approximately 2–4%, but it is a condition that is underdiagnosed.
- The incidence of fibromyalgia in primary care in the UK is approximately 14 700 new cases per year.
- There are recognized risk factors for fibromyalgia but they only contribute approximately 5–10% to disease development (Table 2.16.1).

Table 2.16.1: Risk factors for fibromyalgia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>10 x more common in women than men.</td>
</tr>
<tr>
<td>Age</td>
<td>More common in individuals aged 20–50.</td>
</tr>
<tr>
<td>Physical trauma</td>
<td>For example whiplash type injuries to the neck and trunk.</td>
</tr>
<tr>
<td>Psychological trauma</td>
<td>Stress, anxiety and depression.</td>
</tr>
<tr>
<td>Viral infections</td>
<td>May occur as a post-viral syndrome.</td>
</tr>
</tbody>
</table>

Clinical features

’Fibro’:

- **F**atigue (chronic)
- **I**nsomnia, **I**rritability, **I**rritable bowel and **I**rritable bladder
- **B**‘Blues’ – anxiety and depression
- **R**igidity – muscle and morning joint stiffness
- **O**’Ow’ – pain (widespread and chronic) and others – tender points (Fig. 2.16.1), paraesthesia, temperature changes, migraine, feeling of swollen joints, panic attacks, memory lapses and concentration deficit

Fig. 2.16.1: Distribution of hyperalgesic tender points.
**Diagnosis and investigations**

**Hx**
- See above for symptoms and risk factors.
- A full social, personal, family and psychological history should be taken to reveal any past physical trauma or psychological disturbance.

**Ex**
- Widespread pain, above and below the waist as well as the axial skeletal system, for at least 3 months.
- The presence of 11/18 tender points shown in Fig. 2.16.1.
- Digital palpation using the thumb to assess tender points. The pressure applied should be just enough to blanch the examiner's thumbnail. In the absence of fibromyalgia, the palpation would not be enough to cause pain.

**Ix**
- Blood tests → normal
  - Haematology
  - Biochemistry
  - Immunology
- Imaging → normal

**DDx**
- Chronic fatigue syndrome (myalgic encephalomyelitis)
- Hypothyroidism
- Polymyalgia rheumatica
- Polymyositis

**Yellow flags:** Psychosocial risk factors for developing persisting chronic pain and long-term disability
- Belief that pain and activity are harmful
- Demonstration of sickness behaviour e.g. prolonged rest
- Withdrawal from society
- Emotional problems – low mood, anxiety and stress
- Problems or dissatisfaction at work
- Problems with claims for compensation or time off work
- Overprotective family or lack of social support
- Inappropriate expectations of treatment

**Rapid diagnosis:** A typical fibromyalgia patient
- A 30–50 year old female patient with a long-standing history of diffuse pain.
- She may have a history of physical or psychological trauma.
- The symptoms are constant but are exacerbated by certain stressors.
- She may not have received treatment from previous doctors based on normal investigation findings.
- This may have exacerbated her symptoms by causing further anxiety and possibly even depression.
- On examination hyperalgesic points that are tender to palpate may be demonstrated.
Management (based on EULAR recommendations, 2008)

General points

- Pain and function should be assessed in a psychosocial context.
- Access to a multidisciplinary team with treatments taking into account the patient’s needs including pain intensity, function, depression, fatigue and sleep disturbance.

Non-pharmacological

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heated pool treatment</td>
<td>Can improve pain and function with or without exercise.</td>
</tr>
<tr>
<td>Exercise programmes</td>
<td>Individually tailored exercise programmes which include aerobic training and muscle strengthening.</td>
</tr>
<tr>
<td>Cognitive behavioural therapy</td>
<td>A form of psychotherapy that is based on scientific principles that help people change the way they think, feel and behave.</td>
</tr>
<tr>
<td>Others</td>
<td>Relaxation, rehabilitation, physiotherapy and psychological support.</td>
</tr>
</tbody>
</table>

Pharmacological

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>A moderate opioid which is recommended for pain management.</td>
</tr>
<tr>
<td>Mild pain relief</td>
<td>Paracetamol and weak opioids such as codeine can also be considered.</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Reduce pain and improve function e.g. fluoxetine and amitriptyline.</td>
</tr>
<tr>
<td>Pramipexole and pregabalin</td>
<td>Relatively new treatments which reduce pain.</td>
</tr>
</tbody>
</table>

Self-assessment

A 40 year old woman complains of muscle pain all over the body and lack of sleep. On examination, tender symmetrical spots are identified on multiple sites.

1. What is the most likely diagnosis?
2. What would you expect to see if routine blood tests are performed?
3. Name two non-pharmacological approaches which can be offered.
4. Name suitable mild and moderate forms of pain relief for this patient.

Answers to self-assessment questions are to be found in Appendix A.
2.17 Osteoporosis

Osteoporosis is a **progressive, systemic skeletal disorder** characterized by **low bone mass** and **micro-architectural deterioration** of bone tissue, with a resultant increase in bone **fragility** and susceptibility to **fracture**. Osteoporosis exists when bone mineral density (BMD) values are reduced by more than 2.5 **standard deviations** below that observed in young healthy adults.

**Pathophysiology**

- The underlying cause of osteoporosis is excessive **bone resorption** by osteoclast cells at a rate that exceeds **bone formation** by osteoblast cells.
- This results in **decreased bone mass** and **incomplete bone remodelling**.
- **Oestrogen deficiency** as a result of menopause is the commonest cause of osteoporosis.
- **Oestrogen deficiency** → ↑ production of **RANK ligand (RANK-L)** by osteoblasts → ↑ osteoclast formation, function and survival → ↑ osteoclastic activity → ↑ bone resorption → ↓ BMD.
- Individuals with **inherited low peak bone mass**, impaired absorption of calcium and other coexisting **metabolic bone diseases** such as hyperparathyroidism → ↑ risk of osteoporosis.
- Long-term use of **glucocorticoid therapy** ↓ osteoblastic activity → ↑ risk of osteoporosis.
- Based on the **pattern of bone loss** and **fracture**, osteoporosis can be classified (Fig. 2.17.1) as:

**Fig. 2.17.1:** Classification of osteoporosis.

**Epidemiology and risk factors**

- It is estimated that over **200 million people** have **osteoporosis worldwide**.
- There are approximately **2.8 million people** with osteoporosis in the **UK**.
- Risk factors include **female sex**, **family history** and ‘SHATTERED’:
2.17 Osteoporosis

<table>
<thead>
<tr>
<th>S</th>
<th>Steroid use, Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypo/Hyperthyroidism, Hyperparathyroidism, Hypercalcinuria</td>
</tr>
<tr>
<td>A</td>
<td>Age (&gt;50), Alcohol</td>
</tr>
<tr>
<td>T</td>
<td>Thin (BMI &lt;22)</td>
</tr>
<tr>
<td>T</td>
<td>Testosterone deficiency</td>
</tr>
<tr>
<td>E</td>
<td>Early menopause</td>
</tr>
<tr>
<td>R</td>
<td>Renal, liver failure</td>
</tr>
<tr>
<td>E</td>
<td>Erosive bone disease, e.g. RA or myeloma</td>
</tr>
<tr>
<td>D</td>
<td>Deficiency of calcium and/or vitamin D, Diabetes</td>
</tr>
</tbody>
</table>

**Clinical features**

- Usually asymptomatic.
- Clinical signs arise with fractures which commonly occur in the spine (Fig. 2.17.2), hip (Fig. 2.17.3) and wrist (Fig. 2.17.4):
  - Back pain, reduced height, kyphosis and respiratory difficulty (vertebral fracture).
  - Painful, shortened and externally rotated hip (hip fracture).
  - Pain and deformity (wrist/other fractures).

![Fig. 2.17.2: Old osteoporotic compression fracture.](image)

![Fig. 2.17.3: Intra-capsular neck of femur fracture.](image)

![Fig. 2.17.4: Colles’ wrist fracture.](image)

**Diagnosis and investigations**

<table>
<thead>
<tr>
<th>Hx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually asymptomatic unless a fracture is present.</td>
</tr>
<tr>
<td>Ask about risk factors, e.g. steroid use, family history and menopause.</td>
</tr>
</tbody>
</table>
Ex
• Height loss and kyphosis (vertebral fracture).
• Painful, shortened and externally rotated hip (hip fracture).
• Pain and deformity (other fractures).

Ix
Blood tests:
• ↑ Parathyroid hormone (PTH) levels → hyperparathyroidism
• Thyroid function tests (TFT) → ↓ T3, T4 (hypothyroidism) ↑ T3, T4 (hyperthyroidism)
• ↑ Serum FSH, ↓ sex hormones, ↓ androgens → sex hormone deficiency / menopause.
• ↓ Vitamin D → vitamin D deficiency
• ↑ ESR → inflammatory disease e.g. RA or myeloma
• Bone biomarkers, e.g. calcium and alkaline phosphate are usually normal

X-ray: to confirm fracture (if suspected); cannot determine if patient has osteoporosis but can predict if bones are osteopenic.

Dual-energy X-ray absorptiometry (DEXA) scan: works out the BMD of the patient in the spine and hip; two scores are calculated:
• T-score → diagnostic of osteoporosis; gives the number of standard deviations the BMD is from a young healthy adult (Table 2.17.1)
• Z-score → compares an individual’s results to others of the same age and gender; a Z-score of <−1.5 raises concern of factors other than ageing contributing to osteoporosis.

DDx
• Osteomalacia
• Paget’s disease
• Hyperparathyroidism
• Multiple myeloma

Table 2.17.1: WHO osteoporosis criteria

<table>
<thead>
<tr>
<th>T-score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0</td>
<td>BMD better than reference population</td>
</tr>
<tr>
<td>0 to −1</td>
<td>No evidence of osteoporosis</td>
</tr>
<tr>
<td>−1 to −2.5</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>−2.5 or below</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>−2.5 or below plus fracture</td>
<td>Established osteoporosis</td>
</tr>
</tbody>
</table>

Clinical facts: Osteoporosis
• Osteoporotic fractures cause significant morbidity and ↑ the likelihood of mortality.
• Hip fractures have the highest morbidity and mortality, with 20–30% of patients dying within the first year of fracture.
• The Fracture Risk Assessment Tool (FRAX) can be used to predict fractures based on clinical risk factors, with or without the use of femoral neck bone mineral density.
Management

Non-pharmacological management

Smoking cessation and reduction in alcohol consumption, weight-bearing muscle exercises, dietary (adequate source of calcium and vitamin D), physiotherapy, assessment of home safety and reducing the risk of falls (especially in the elderly).

Pharmacological management

See Table 2.17.2.

| Table 2.17.2: Pharmacological management of osteoporosis based on National Institute for Health and Care Excellence (NICE) recommendations (2012) |
|------------------|----------------------------------|
| **Bisphosphonates** | First-line. Inhibit bone resorption by inhibiting osteoclasts. Examples include alendronate (first-line), risedronate and zoledronate. Can be taken orally once a week (alendronate) or as once-yearly IV injections (zoledronate). GI side-effects are common with oral medication and patients are asked to sit or stand for at least 30 minutes to reduce side-effects of oesophagitis. |
| **Denosumab** | Monoclonal antibodies directed against RANK-L. Used as an alternative treatment to bisphosphonates. Given as 6-monthly injections. |
| **Strontium ranelate** | Mechanism of action unknown but thought to stimulate osteoblasts and inhibit osteoclasts (dual action). Taken once daily in water (preferably at bedtime). Used as an alternative to bisphosphonates. Side-effects: nausea, diarrhoea, headache, dizziness. Limited use because of risk of DVT and thromboembolism. |
| **Teriparatide** | A parathyroid hormone analogue. Intermittent exposure to parathyroid hormone activates osteoblasts more than osteoclasts and thus stimulates new bone formation. Taken as a once-daily injection into the thigh or abdomen. Very expensive. Used in very severe cases. |
| **Other** | Raloxifene, calcitonin, hormone replacement therapy (HRT) – these are less commonly used. |

Self-assessment

A 32 year old man being treated for sarcoidosis develops back pain 6 months after steroid treatment was commenced. The radiologist reports a vertebral crush fracture and suggests that the ‘bones look osteopenic in nature’. A diagnosis of osteoporosis is later confirmed.

1. What is the mechanism by which osteoporosis has been caused?
2. How could this have been prevented?
3. What first-line treatment would you prescribe? Name the most common side-effects.
A 43 year old woman has been complaining of amenorrhoea and hot flushes. The patient is later diagnosed with premature ovarian failure. A routine DEXA scan is performed and T-scores of −2.2 and −1.3 are reported in the vertebrae and hip, respectively.

4. What do the T-scores reveal in this patient?
5. What blood tests would you like to perform and why?
6. What lifestyle advice would you recommend to this lady?

Answers to self-assessment questions are to be found in Appendix A.
Page 2.18 **Paget’s disease**

Paget’s disease is a common bone disease characterized by focal increases in bone remodelling, resulting in the abnormal production of bone which is mechanically weak. The most commonly affected bones include the pelvis, spine, skull, femur and tibia.

**Pathophysiology**

**Genetic factors**
- Family history confers susceptibility
- Autosomal dominant inheritance has been described in families
- 4 gene mutations have been found – sequestosome 1 (SQSTM1) is the most important

**Environmental factors**
- Infections – from viruses such as paramyxoviruses
- Mechanical stress

**Three phases of Paget’s disease**

**Lytic phase**
Transient ↑ osteoclast activity causing ↑ bone resorption and marked ↑ in alkaline phosphatase (ALP)

**Mixed phase**
Both osteoclastic and osteoblastic activity, with ↑ levels of bone turnover leading to deposition of structurally abnormal bone

**Sclerotic phase**
A chronic sclerotic phase, during which bone formation outstrips bone resorption

**Fig. 2.18.1:** Outline of the pathophysiology of Paget’s disease.

**Epidemiology and risk factors**
- The UK has the highest prevalence of Paget’s disease in the world – approximately 2% in Caucasians over the age of 55.
- The condition is very rare in Asians.
Table 2.18.1: Risk factors for Paget’s disease

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>The mean age of onset is approximately <strong>55 years</strong>.</td>
</tr>
<tr>
<td>Gender</td>
<td>The male:female ratio is <strong>2:1</strong>.</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Common in the UK but very rare in Asian countries.</td>
</tr>
<tr>
<td>Family history</td>
<td>The relative risk can be <strong>up to 7-fold</strong> in <strong>first-degree relatives</strong> of patients with Paget’s disease.</td>
</tr>
</tbody>
</table>

**Clinical features**

- Paget’s disease is usually **asymptomatic** (70–90%) and therefore diagnosed on incidental abnormal X-ray or biochemical findings (↑ **ALP**).
- Complications depend on the site affected as well as the activity of the disease (*Table 2.18.2*).

**Table 2.18.2: Typical complications of Paget’s disease**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>Most common</td>
</tr>
<tr>
<td>Bone deformity &amp; enlargement</td>
<td>Typically the pelvis, lumbar spine, skull, femur and tibia (<em>Fig. 2.18.2</em>)</td>
</tr>
<tr>
<td>↑ Temperature over affected bone</td>
<td>Due to hypervascularity</td>
</tr>
<tr>
<td>Pathological fractures</td>
<td>Due to mechanically weak bone</td>
</tr>
<tr>
<td>2° OA</td>
<td>Due to Paget’s disease surrounding the joint</td>
</tr>
<tr>
<td>Hearing loss and tinnitus</td>
<td>If Paget’s disease affects the skull bones and compresses the vestibulocochlear nerve</td>
</tr>
</tbody>
</table>

- **Less common complications**: spinal stenosis, nerve compression syndromes and cauda equina syndrome.
- **Rare complications**: hypercalcaemia, high output cardiac failure, paraplegia and osteosarcoma.

**Diagnosis and investigations**

- **Hx**: Usually **asymptomatic** but **bone pain, pathological fractures, deformities, ↑ local temperature** and **hearing loss** are all common.
- **Family history**.
2.18 Paget’s disease

**Ex**
- Look for head signs – ↑ skull size, frontal bossing, deep-set eyes, large maxilla with prominent arches.
- Look for other deformities such as bowing of long bones and kyphosis.
- Feel for temperature over affected bone.
- Weber’s and Rinne’s test – to elicit possible sensorineural hearing loss.
- Signs of other complications such as OA and spinal cord compression.

**Ix**
- Blood tests: ↑ ALP, bone-specific ALP (if known liver disease), phosphate and calcium are normal.
- X-ray: (Figs 2.18.3 and 2.18.4): localized enlargement, patchy cortical thickening with sclerosis, osteolysis and deformity, advancing lytic lesion in the long bones.
- MRI: for suspected spinal stenosis and cord compression.

**DDx**
- Osteomalacia
- Osteoporosis
- Fibrous dysplasia
- Myeloma

**Management**

### Conservative management
- Observation, regular follow-up, patient education and preventive measures.
- Orthotic devices, sticks and walkers may be useful for Paget’s disease of the legs.
- Adequate intake of calcium and vitamin D.

### Pharmacological management
- Main indication is bone pain.
- Bisphosphonates to reduce bone turnover e.g. oral risedronate or IV zoledronate.
- NSAIDs and paracetamol for pain relief.

### Surgical management
- Bone deformity, osteoarthritis, pathological fractures and nerve compression may necessitate surgery.
- Surgical procedures include fracture fixation (pathological fracture), joint replacement (secondary OA), and osteotomy (deformity).
A 50 year old man complains of constantly aching legs. Blood tests reveal an elevated level of serum ALP. Subsequent X-ray of the tibia shows a degree of tibial bowing. You suspect Paget’s disease.

1. List some risk factors for Paget’s disease.
2. What other bones are commonly affected in Paget’s disease?
3. Apart from bone pain, name five other complications that can arise from Paget’s disease.
4. How should this patient be managed pharmacologically?
5. How would you monitor the response to treatment?

Answers to self-assessment questions are to be found in Appendix A.