

Third edition

Notes & Notes

For MRCP part 1 & 2

By

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Rheumatology

Updated 2022

The 10 Golden Tips for MRCP written exams you will ever need

1. For MRCP, do not read hard; read smart.
2. Three to six months is usually enough for preparation.
3. Practice the best of the five questions as much as possible.
4. The few days before the exam date, stop revising questions and concentrate on your MRCP notes and top tips.
5. Remember, you are getting ideas and concepts from the questions.
6. Time factor in the exam room is the leading killer after poor preparation.
7. Manage your time wisely.
8. Read the end of the question first; if you can answer it without reading the whole scenario, it will save your time for the other tuff question (long scenario, .what is the action of imatinib?)
9. Take care for any single word in the question, e.g. (the initial test, the diagnostic test, the best test, the next step)
10. Practice, practice and practice.



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Third edition

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Rheumatology

Updated 2022

Bone markers

Bone remodeling

- Cells involved
 - ⇒ Osteoclasts: degrade bone tissue by secreting collagenase and H⁺
 - ⇒ Osteoblasts:
 - Build bone tissue by secreting type I collagen
 - Activity assessed by an increase in bone ALP, osteocalcin, and type I procollagen propeptides.

Bone markers are useful for:

- prediction of prognosis
- prediction of fracture risk
- assessing suitability for therapy and
- monitoring the success of therapy.

Markers of bone formation (measured in serum)	Markers of bone resorption (measurable in serum or urine)
<ul style="list-style-type: none"> • Bone-derived alkaline phosphatase (ALP). • Osteocalcin • Procollagen type 1 propeptides. 	<ul style="list-style-type: none"> • Telopeptides • Pyridinium cross-linking molecules • Tartrate-resistant acid phosphatase (TRAP) • Hydroxyproline.

Rheumatoid factor

Rheumatoid factor is an IgM antibody against IgG

Overview

- Rheumatoid factor (RF) is a circulating antibody (usually IgM) which reacts with the Fc portion of the patients own IgG.
- **Rheumatoid factor is an antibody with reactivity to the heavy chain of IgG.**
- The rheumatoid factor may be of IgM, IgG or IgA class.
- The conventional (agglutination) test, detects only IgM RF.
- high titre levels are associated with severe progressive disease (but NOT a marker of disease activity).

A positive rheumatoid factor is associated with:

- **More severe erosive disease**
- Extra-articular manifestations including subcutaneous nodules and
- Increased mortality.

Conditions associated with a positive RF include:

- Sjogren's syndrome (around 100%)
- Felty's syndrome (around 100%)
- Mixed cryoglobulinemia (types II and III) - 40 to 100%

- rheumatoid arthritis (70-80%)
- Mixed connective tissue disease - 50 to 60%
- infective endocarditis (= 50%)
- SLE (= 20-30%)
- systemic sclerosis (= 30%)
- Polymyositis/dermatomyositis - 5 to 10%
- general population (= 5%)

Rheumatoid arthritis

Rheumatoid arthritis - HLA DR4

Rheumatoid arthritis - TNF is key in pathophysiology

- Around 70% of patients with rheumatoid arthritis are HLA-DR4.
- Patients with Felty's syndrome (a triad of rheumatoid arthritis, splenomegaly and neutropaenia) are even more strongly associated with 90% being HLA-DR4

Epidemiology

- Prevalence = 1%
- F:M ratio = 3:1
- Peak onset = 30-50 years, although occurs in all age groups

Aetiology

- Idiopathic inflammatory autoimmune disorder of unknown etiology
- Genetic disposition: associated with HLA-DR4 and HLA-DR1

Pathophysiology

- Autoimmune — inflammation induces **formation of pannus** (proliferative granulation tissue), which erodes articular cartilage and bone.
- Citrullinated proteins (converted from arginine to citrulline) are recognized as foreign → Activation and migration of CD4+ T cells to synovial joints → recruitment of macrophages → secretion of cytokines (**TNF- α , IL-1, IL-6**) → inflammation and proliferation → **pannus** and synovial hypertrophy → invasion, progressive destruction, and deterioration of cartilage and bone
- **TNF is an important in the pathogenesis of rheumatoid arthritis.**
- **Rheumatoid factor (RF)**
 - ⇒ Antibodies against Fc portion of IgG (rheumatoid factor, RF) are produced to aid in removing autoantibodies and immune complexes.
 - ⇒ RF excess triggers formation of new immune complexes and **type III hypersensitivity reaction**
 - ⇒ Individuals with positive RF are more likely to develop extraarticular manifestations.

Rheumatoid arthritis - TNF is key in pathophysiology

Diagnosis

- **The diagnosis of RA is clinical**

- NICE have stated that clinical diagnosis is more important than criteria such as those defined by the American College of Rheumatology.
- Consider RA in patients with arthralgia, joint stiffness, and synovitis lasting ≥ 6 weeks

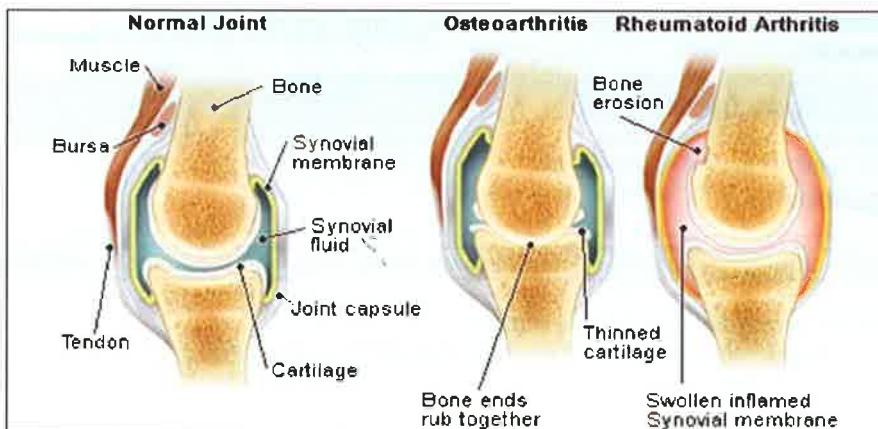
2010 American College of Rheumatology criteria

- Target population. Patients who:
 - have at least 1 joint with definite clinical synovitis
 - with the synovitis not better explained by another disease
- Classification criteria for rheumatoid arthritis (add score of categories A-D; **a score of 6/10 is needed definite rheumatoid arthritis**)

Factor	Scoring	
A. Joint involvement		
1 large joint	0	
2 - 10 large joints	1	
1 - 3 small joints (with or without involvement of large joints)	2	
4 - 10 small joints (with or without involvement of large joints)	3	
10 joints (at least 1 small joint)	5	
B. Serology (at least 1 test result is needed for classification)		
Negative rheumatoid factor (RF) and negative anti-cyclic citrullinated peptide (Anti-CCP)	0	
Low-positive RF or low-positive Anti-CCP	2	
High-positive RF or high-positive Anti-CCP	3	
C. Acute-phase reactants (at least 1 test result is needed for classification)		
Normal CRP and normal ESR	0	
Abnormal CRP or abnormal ESR	1	
D. Duration of symptoms		
< 6 weeks	0	
> 6 weeks	1	

Articular manifestations

- **Polyarthralgia**
 - ⇒ Symmetrical pain and swelling of affected joints (also at rest)
 - ⇒ Frequently affected joints
 - Metacarpophalangeal (MCP) joints
 - Proximal interphalangeal (PIP) joints (**DIP joints are NOT typically affected in RA.**)
 - Wrist joints
- **Morning stiffness** (often > 30 min) that usually improves with activity
- **Joint deformities**
 - ⇒ **Swan neck deformity:** PIP hyperextension and DIP flexion
 - ⇒ **Boutonniere deformity:** PIP flexion and DIP hyperextension.
 - ⇒ **Hitchhiker thumb deformity (Z deformity of the thumb):** hyperextension of the interphalangeal joint with fixed flexion of the MCP joint
 - ⇒ **Ulnar deviation of the fingers**
 - ⇒ **Piano key sign:** dorsal subluxation of the ulna
 - ⇒ **Atlanto-axial subluxation:** A loss of ligamentous stability between the atlas (C1) and axis (C2), which **can result in compression of the spinal cord**, medulla, and/or vertebral arteries by the odontoid process, especially upon neck flexion. Most commonly caused by Down syndrome, rheumatoid arthritis, and trauma.



The earliest manifestation of rheumatoid arthritis in the feet → swelling of the metatarsophalangeal joints

Extraarticular manifestations

- **Constitutional symptoms:** Low-grade fever, myalgia, malaise, fatigue, weight loss
- **Rheumatoid nodules:**
 - ⇒ Nontender, firm, subcutaneous swellings (2 mm–5 cm). Commonly occur in areas exposed to higher pressure, e.g., extensor side of the forearm, bony prominences
 - ⇒ Rheumatoid pulmonary nodules may be accompanied by fibrosis and pneumoconiosis (Caplan syndrome).
 - ⇒
- **Lungs:**
 - ⇒ pleuritis, pleural effusions, interstitial lung disease (e.g., organizing pneumonia)
 - ⇒ **rheumatoid pleural effusion: characterised by → low glucose level**
 - ⇒ cricoarytenoid arthritis:

- seen in up to 75% of patients with RA
- It can cause **stridor**, but is often asymptomatic.
- **symptoms can rapidly worsen in the post-operative period.**
- **the most helpful diagnostic test → Spirometry with flow-volume loop**
- Patients can need urgent tracheostomy and steroids, both orally and via joint injection.
- **Eye:**
 - ⇒ keratoconjunctivitis sicca (dry eyes) (**most common**)
 - ⇒ scleritis, and episcleritis
- **Endocrine** and exocrine glands: secondary Sjogren syndrome
- **Hematological**
 - ⇒ Anemia of chronic disease (normocytic anemia)
 - NSAIDs and/or steroids → increased risk of GI bleeding → iron deficiency anemia (microcytic anemia)
 - Methotrexate → decreased folate level → macrocytic anemia
 - ⇒ Neutropenia
 - ⇒ Splenomegaly
- **Heart:**
 - ⇒ Pericarditis and myocarditis, **constrictive pericarditis is the commonest cardiac complication of rheumatoid arthritis**
 - ⇒ ↑↑ risk of myocardial infarction, stroke.
- **Musculoskeletal:** Tenosynovitis and bursitis, Carpal tunnel syndrome
- **Vascular:**
 - ⇒ Peripheral vasculitis, manifests as livedo reticularis
 - ⇒ Raynaud phenomenon

Investigations

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

- Specific parameters (serological studies)
 - ⇒ **Anti-cyclic citrullinated peptide (Anti-CCP) antibodies**
 - It has sensitivity similar to RF (70-80%) with a much higher specificity of 90-95%.
 - a prognostic marker.
 - ⇒ Rheumatoid factor (RF)
 - IgM autoantibodies against the Fc region of IgG antibodies
 - Present in 70–80% of patients, but not specific to RA
 - ⇒ Serological studies may be negative (i.e., seronegative RA): **Up to 30% of patients with RA are negative for Anti-CCP and RF.**
- Radiographic features
 - ⇒ **X-ray of both hands and feet: initial test**
 - **Early findings** : soft tissue swelling, **osteopenia** (juxta-articular)
 - **Late findings:** joint space narrowing, marginal erosions of cartilage and bone, osteopenia (generalized), subchondral cysts
- Typical RA findings on x-rays may be subtle or absent upon diagnosis in many patients with early RA; therefore, ultrasound or MRI may be more informative, as they have higher sensitivity for detecting early signs of inflammation and erosion.
- Analysis of synovial fluid
 - ⇒ Sterile specimen with leukocytosis (WBC count 5000–50,000/mcL)
 - ⇒ **Abundant neutrophils.**
 - ⇒ **High protein levels.**

Anti-cyclic citrullinated peptide antibodies are associated with rheumatoid arthritis

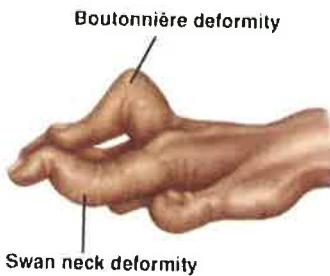
The radiographic features of rheumatoid arthritis can be remembered by the mnemonic **LESS**: Loss of joint space, Erosions, Soft tissue swelling, and Soft bones (osteopenia)

Early x-ray findings	Late x-ray findings
<ul style="list-style-type: none"> loss of joint space juxta-articular osteoporosis soft-tissue swelling 	<ul style="list-style-type: none"> periarticular erosions subluxation

Differential diagnosis

- Rheumatoid arthritis typically affects the metacarpophalangeal and proximal interphalangeal joints symmetrically. Psoriatic arthritis affects the distal interphalangeal joints and tends to be asymmetrical.
- Rheumatoid arthritis VS osteoarthritis

	Rheumatoid arthritis	Osteoarthritis
pathophysiology	autoimmune (inflammatory)	degenerative due to ↑ wear and tear on joints → loss of cartilage (non-inflammatory)
Age of starting	At any age	Usually later in life
Speed of onset	Rapid, over weeks to months	Slow, over years
Pain	improves with movement	worse with movement and better with rest
Primary joint affected	Proximal interphalangeal	Distal interphalangeal
	Metacarpophalangeal	Carpometacarpal
Heberdens nodes	Absent	Present
Joint characteristics	Soft, warm and tender	Hard and bony (little or no swelling)
Stiffness	Worse after resting (morning stiffness)	If present, worse after effort, may be described as evening stiffness
	Usually > 1 hour	Usually <1 hour
Systemic symptoms	Present (eg: fatigue)	Absent
RF and anti-CCP	Positive	Negative
ESR and C-reactive protein	Elevated	Normal
x-ray	Osteophytes absent	Osteophytes may be present



Referral

- Indications for urgent referral for specialist opinion: any person with suspected persistent synovitis of undetermined cause. **Refer urgently** if any of the following apply:
 - the small joints of the hands or feet are affected
 - more than one joint is affected
 - there has been a delay of 3 months or longer between onset of symptoms and seeking medical advice.

Prognosis: poor prognostic features:

- Anti-CCP antibodies (The poorest prognostic factor)**
- Rheumatoid factor positive
- HLA DR4
- Insidious onset : Acute or Sudden onset is not a poor prognosis.
- Poor functional status at presentation
- X-ray: early articular erosions (e.g. within the first 6 months of presentation and in less than < 2 years)
- Extra articular features e.g. nodules
- Female sex.

Rheumatoid arthritis: patients have an increased risk of IHD

✓ Popliteal cysts ('Baker's cysts') may occur in rheumatoid arthritis following persistent effusion into the knee joint.

✓ Which micro-organisms may be associated with the development of rheumatoid arthritis in susceptible patients? → **Proteus mirabilis**

✓ Felty's syndrome (RA + splenomegaly + low white cell count)

✓ Poorly controlled rheumatoid arthritis + proteinuria and hypoalbuminaemia raises the possibility of systemic amyloidosis → **Rectal biopsy**

MRCPUK-part-1-September- 2009 exam: MRCPUK-part-1-jan-2018:

Which (HLA) types is most associated with rheumatoid arthritis?

⇒ **HLA DR4**

A patient of RA on etanercept, scheduled for elective surgery. What advice regarding his medication should be given prior to surgery? → Stop etanercept 2–4 weeks prior to surgery

Updated British Society for Rheumatology (BSR) guidelines (January 2005) for prescribing tumour necrosis factor (TNF- α) blockers in adults with RA recommend:

- **withholding etanercept and other TNF- blockers (infliximab and adalimumab) for 2–4 weeks prior to a major surgical procedure.**
- restarted postoperatively if there is no evidence of infection and once wound healing is satisfactory.

Rheumatoid arthritis: Management

Approach

- **Acute anti-inflammatory treatment**
 - ⇒ Temporary (< 3 months) symptomatic treatment with glucocorticoids and/or NSAIDs is indicated for disease flares (i.e., episodes of increased disease activity and symptom worsening).
 - ⇒ Glucocorticoids (prednisone)
 - Short-term (i.e., < 3 months) therapy at the lowest effective dose is preferred.
 - Longer term therapy only used in patients with highly active RA who do not respond to maximum doses of DMARDs.
 - Glucocorticoids should be used at the lowest effective dose and only for short periods of time to reduce the risk of their many adverse effects (e.g., hypertension, osteoporosis, infections).
 - ⇒ NSAIDs and selective COX-2 inhibitors: relieve symptoms, but do not improve the prognosis.
- **Long-term treatment**
 - ⇒ Initiation of treatment: all patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible.
 - ⇒ Consider short-term concomitant use of acute anti-inflammatory therapy (i.e., glucocorticoids and/or NSAIDs) for symptom control until the onset of action of DMARDs (e.g., ≥ 6 weeks).

Disease-modifying anti-rheumatic drugs (DMARDs)

- DMARD therapy reduces RA mortality and morbidity by up to 30%.
- If DMARD therapy induce disease control → reduce drug doses to levels that still maintain disease control.
- **Methotrexate (MTX)**
 - ⇒ first-line treatment in patients with moderate to high disease activity
 - ⇒ All patients should be co-prescribed **folic acid** supplementation at a minimal dose of 5 mg once weekly to minimize adverse effects.
 - ⇒ Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis.
 - ⇒ Other important side-effects include pneumonitis
- **Azathioprine (AZA)**
 - ⇒ Patients should have baseline **thio-purine methyl-transferase (TPMT)** status assessed
- **Sulfasalazine**
 - ⇒ Consider in patients with low disease activity if MTX is contraindicated, e.g., during pregnancy.

- ⇒ Adverse effects: diarrhea, agranulocytosis, cutaneous hypersensitivity reactions
- **Hydroxychloroquine (HCQ)**
 - ⇒ Consider in patients with low disease activity.
 - ⇒ **Adverse effects:** hyperpigmentation and retinopathy
 - ⇒ Patients should have baseline formal **ophthalmic examination**, ideally including objective retinal assessment for example using optical coherence tomography, within 1 year of commencing an antimalarial drug
- **Leflunomide**
 - ⇒ Consider if all other conventional DMARDs are contraindicated.
 - ⇒ **Mechanism of action:** reversibly inhibits dihydroorotate dehydrogenase → impaired pyrimidine synthesis → inhibition of T-cell proliferation
 - ⇒ Other indications: psoriatic arthritis

Monitoring rheumatoid arthritis

- **Recommended DMARD Blood Monitoring Schedule when Starting or Adding a New DMARD** (BSR guidelines February 2017)
 - ⇒ Check FBC, creatinine/calculated GFR, ALT and/or AST and albumin
 - **every 2 weeks** until on stable dose for 6 weeks;
 - then once on stable dose, **monthly** for 3 months;
 - thereafter, at least **every 12 weeks**.
 - ⇒ Contact rheumatology team **urgently** and **consider interruption in treatment** if any of the following develop:
 - white cell count $<3.5 \times 10^9/l$;
 - mean cell volume $>105 fL$;
 - neutrophils $<1.6 \times 10^9/l$;
 - creatinine increase $>30\%$ over 12 months and/or calculated GFR $<60 \text{ ml/min}$;
 - unexplained eosinophilia $>0.5 \times 10^9/l$;
 - ALT and/or AST $>100 \text{ U/l}$;
 - platelet count $<140 \times 10^9/l$;
 - unexplained reduction in albumin $<30 \text{ g/l}$
 - ⇒ **In the setting of acute infection, most DMARDs (except hydroxychloroquine) should be discontinued until the infectious process has resolved.**
- Measure CRP and key components of disease activity (using a composite score such as DAS28) regularly (**monthly until treatment has controlled the disease**) to inform decision-making about:
 - ⇒ increasing treatment to control disease
 - ⇒ cautiously decreasing treatment when disease is controlled.

The first-line treatment for newly diagnosed active RA → combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as soon as possible, ideally within 3 months of the onset of persistent symptoms.

TNF-inhibitor

- The current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- **Examples** of anti-TNF alpha agents:
 - ⇒ Etanercept: SC administration twice weekly
 - ⇒ Infliximab: IV administration
 - ⇒ Adalimumab: SC administration
- Adverse effects of TNF blockers include:
 - ⇒ reactivation of latent tuberculosis and demyelination.
 - ⇒ The risk of TB reactivation is most pronounced in the first 3 months of treatment.

- ⇒ BTS guidelines therefore recommend a clinical examination, and chest radiograph to check for TB.
- ⇒ In the UK, patients have a baseline CXR and assessment of risk of infection with *Mycobacterium tuberculosis* prior to starting treatment with anti-TNF α.
- Any **patient with active TB**,
 - ⇒ should receive standard chemotherapy.
 - ⇒ **They must complete two months full treatment before starting anti-TNF alpha treatment.**
- **Patients with past TB**,
 - ⇒ who have received previous adequate therapy → can be started on anti-TNF alpha therapy but need to be monitored regularly.
 - ⇒ TB not previously adequately treated, → chemoprophylaxis should be given before commencing anti-TNF alpha treatment.
 - ⇒ **What is the optimal TB screening test in patient with previous TB?**
 - **Interferon gamma release assay**
 - ❖ The test is not altered by previous TB or previous BCG vaccination.
 - ❖ Positive testing indicates a need for anti-tuberculous treatment alongside golumumab, for example isoniazid.
 - ❖ Mantoux testing is less indicative of prior infection because it is likely to evoke a positive reaction in patients with previous TB or who have received BCG vaccination.
- **Patients with a normal chest radiograph who have not started immunosuppressive therapy** → a tuberculin test is helpful.
- **Patients with a normal chest radiograph + already on immunosuppressive treatment**,
 - ⇒ the result of the tuberculin test is damped and it is therefore not useful.
 - ⇒ An individual risk assessment should be made: **if the annual risk of TB is greater than that of drug-induced hepatitis then chemoprophylaxis should be given.** If not, the patient should be monitored and investigated early if symptoms consistent with TB develop.
 - ⇒ Chemoprophylaxis is generally with isoniazid for 6 months.
- Patients who test positive with either of Quantiferon Gold test and Elispot tests should be treated with chemoprophylaxis (either isoniazid for 6 months, or dual therapy Rifampicin + INH for 2 months) at the same time as being started on anti-TNF alpha treatment.
- **TNF-inhibitors should be stopped 2-4 wks before any major operation.**

Rituximab

- **Action**
 - ⇒ **Anti-CD20 monoclonal antibody, results in B-cell depletion.**
- **Prescription**
 - ⇒ Two doses of 1g intravenous infusions are given two weeks apart.
- **Indications**
 - ⇒ rheumatoid arthritis
 - **Nice guidelines of RA** → **Rituximab in combination with methotrexate** is recommended as an option for treatment of rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.
 - ⇒ non-Hodgkin lymphoma (The primary clinical use)
 - ⇒ idiopathic thrombocytopenic purpura.
- **Follow up**
 - ⇒ Treatment with rituximab plus methotrexate should be continued only if:
 - There is an adequate response following initiation of therapy.
 - An adequate response is defined as an improvement in disease activity score

(DAS28) of 1.2 points or more.

- Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months.

- **Side effects:**

⇒ **risk of reactivation of hepatitis B,**

- patients should be screened for previous exposure to hepatitis B prior to starting rituximab;
- those with lone anti-hep B core antibodies should be treated with chemoprophylaxis (eg lamivudine) prior to rituximab.
- ⇒ Risk of Progressive multifocal leukoencephalopathy

Biologic DMARDs

- **Indication:**

⇒ persistent moderate or severe disease activity after 3 months of conventional DMARD therapy

- **Agents**

⇒ TNF- α inhibitors: e.g., adalimumab, infliximab, etanercept (see also "Contraindications to anti-TNF- α treatment")

⇒ Others: rituximab (anti-CD20), anakinra (IL-1 receptor antagonist, particularly for Still disease), tocilizumab (**IL-6 receptor antagonist**)

- **Adverse effects** include:

⇒ Infections

⇒ **TB reactivation**

⇒ Hepatitis B reactivation

Rheumatoid arthritis: Management in pregnancy

Key points

- patients with early or poorly controlled RA should be advised to defer conception until their disease is more stable
- RA symptoms tend to improve in pregnancy but only resolve in a small minority. Patients tend to have a flare following delivery
- patients should be referred to an obstetric anaesthetist due to the risk of atlanto-axial subluxation

Effect of pregnancy on rheumatoid arthritis

- 50 to 70% of women with rheumatoid arthritis (RA) **improve during pregnancy**
- 50% of patients eventually **flare during the postpartum period**, usually within the first three months.
- The risk of developing RA increased in the first three months postpartum

Effect of RH on pregnancy

- RA does not increase fetal losses.
- Higher rate of intrauterine growth restriction, pregnancy-induced hypertension, and cesarean delivery

Medications in pregnancy

- **Contraindicated in pregnancy**

⇒ **Methotrexate (teratogenic):** needs to be stopped at least 3 months before conception

⇒ leflunomide

- **Preferred medications (if required)**

- ⇒ **NSAIDs:** may be used until 32 weeks but after this time should be withdrawn due to the risk of early close of the ductus arteriosus. Considered category B earlier in the pregnancy
- ⇒ **Corticosteroids**
- ⇒ Sulfasalazine
- ⇒ hydroxychloroquine

- **Medications relatively safe to use (require individualized approach)**

- ⇒ TNF α inhibitors
- ⇒ Azathioprine

Medications in breast feeding

- Breast feeding is not recommended with azathioprine.
- Prednisolone and hydroxychloroquine may be taken whilst breast-feeding.
- Azathioprine, cyclophosphamide, methotrexate and cyclosporine are contraindicated in breast-feeding mothers.

RA during pregnancy → continue current dose of azathioprine and add folic acid

Felty's syndrome

Definition

- a severe subtype of RA characterized by neutropenia and splenomegaly
- It is considered an extra-articular manifestation of rheumatoid arthritis.

Epidemiology

- occur in less than 1% of patients with rheumatoid arthritis.

Risk factors

- usually occurs in patients with long-standing seropositive RA.
- HLA subtype (**HLA DRW4**) is found in 95% of patients with Felty syndrome compared with 70% of patients with rheumatoid arthritis alone.

Feature

- **Triad of arthritis, splenomegaly, and neutropenia** (absolute neutrophil count <2000/microL)
- Neutropenia increases risk of recurrent bacterial infections.
- **ANA is positive in more than 90% of patients**

Treatment

- **Most appropriate initially → Pulsed corticosteroid therapy**
- First line → Disease-modifying anti-rheumatic drugs (DMARDs): methotrexate
- Second line (If no response to methotrexate) → rituximab (RTX)
- **granulocyte colony-stimulating factor (G-CSF, filgrastim)** to stimulate production of granulocytes.
- Splenectomy : usually reserved for patients with severe neutropenia and recurrent infections who fail to respond to medical intervention.

Felty's syndrome → Triad of arthritis, splenomegaly, and neutropenia

Seronegative spondyloarthropathies

Common features

- associated with HLA-B27
- rheumatoid factor negative - hence 'seronegative'
- peripheral arthritis, usually asymmetrical
- sacroiliitis
- enthesopathy: e.g. Achilles tendonitis, plantar fasciitis
- extra-articular manifestations: uveitis, pulmonary fibrosis (upper zone), amyloidosis, aortic regurgitation

Spondyloarthropathies

- ankylosing spondylitis
- psoriatic arthritis
- Reiter's syndrome (including reactive arthritis)
- enteropathic arthritis (associated with IBD)

Adhesive capsulitis

Overview

- Adhesive capsulitis (frozen shoulder) is a common cause of shoulder pain. aetiology of frozen shoulder is not fully understood.

Risk factors

- Adhesive capsulitis is a recognised musculoskeletal complication of diabetes** (40% of diabetic patients developing this problem at some stage.)
- occurs more commonly in women after age 50

Features

- Severe restriction of both active and passive range of movement of the glenohumeral joint in all planes (especially external rotation)
- Dull shoulder pain

Diagnosis

- Radiographs of the shoulder show osteopenia.
- The diagnosis is confirmed by arthrography.

Management

- no single intervention has been shown to improve outcome in the long-term
- treatment options include NSAIDs, physiotherapy, oral and intra-articular corticosteroids

Prognosis

- Self-limiting condition that usually resolves within 18 to 24 months

Ankle injury: Ottawa rules

- The Ottawa Rules for ankle x-rays have a **sensitivity approaching 100%**
- An ankle x-ray is required only if there is any pain in the **malleolar zone** and any one of the following findings:
 - bony tenderness at the lateral malleolar zone** (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)

2. bony tenderness at the medial malleolar zone (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)
 3. inability to walk four weight bearing steps immediately after the injury and in the emergency department
- There are also Ottawa rules available for both foot and knee injuries

Ankylosing spondylitis

Ankylosing spondylitis features - the 'A's

- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis

Ankylosing spondylitis - x-ray findings: subchondral erosions, sclerosis and squaring of lumbar vertebrae

Definition

- Seronegative spondyloarthropathy that involves chronic inflammatory disease of the spine and sacroiliac joints.

Pathophysiology

- Autoimmune disorder, 90–95% of patients are HLA-B27 positive
- It has a polygenic inheritance.

Epidemiology

- Typically presents in males (sex ratio 3:1)
- Age: 20 – 40 years

Features

Typically a young man who presents with lower back pain and stiffness of insidious onset

- Articular manifestations
 - ⇒ Spinal joint pain
 - Features of inflammatory back pain (most common presenting symptom)
 - Morning stiffness > 30 minutes that improves with activity
 - usually worse in the morning and improves with exercise
 - Pain is independent of positioning
 - Tenderness over the sacroiliac joints (positive Mennell's sign)
 - Reduced spinal mobility, reduced lateral flexion
 - Reduced forward flexion → positive Schober's test (restriction in the lumbar flexion when patient asked to touch his toes while keeping the knees straight.)
 - Accentuated thoracic kyphosis
 - Loss of lumbar lordosis

⇒ **Extraspinal joint pain**

- Inflammatory enthesitis (the point where a tendon attaches to a bone)
- **Dactylitis** (an inflammation of the fingers and/or toes)
- Arthritis outside the spine, peripheral arthritis (25%, more common in female)

• **Extraarticular manifestations**⇒ **Anterior uveitis**

- The most common extra-articular manifestations (in around 40% of patients)
- Usually acute, unilateral anterior uveitis
- more common in B27 positive than B27 negative patients.

⇒ **Fatigue**

⇒ Restrictive pulmonary disease → **↓ chest expansion on deep breathing** due to decreased mobility of the thoracic spine and costovertebral joints

⇒ GIT symptoms of inflammatory bowel disease (diarrhea with blood) (5%)

⇒ **Aortic root inflammation** and subsequent aortic valve insufficiency, atrioventricular blocks

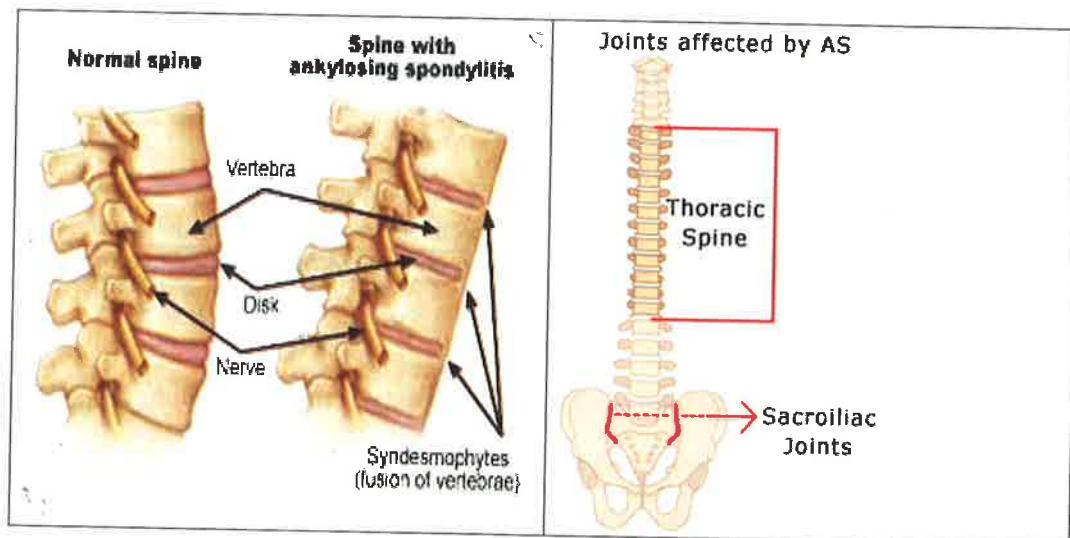
⇒ IgA-nephropathy

Ankylosing spondylitis: Diagnostic criteria

⌚ Lower back pain for **> 3 months** in patients **< 45 years of age** and **one of the following:**

⦿ **Sacroiliitis confirmed on x-ray or MRI and ≥ 1 typical clinical or laboratory finding**

⦿ **A positive HLA-B27 test and ≥ 2 typical clinical or laboratory findings**



Investigations

the best option to confirm a diagnosis of ankylosing spondylitis → Sacroiliac joints x ray

- Inflammatory markers (ESR, CRP) are typically **raised** although normal levels do not exclude ankylosing spondylitis.
- HLA-B27 is of little use in making the diagnosis because it is positive in 90% of patients with ankylosing spondylitis and 10% of normal patients. **The likelihood of a positive test depends on the racial and ethnic background of the patient**
 - ⇒ **The commonest subtype HLA associations** are:
 - **HLA B*2705** (Caucasians)
 - **B*2704** (Chinese, Japanese)
 - **B*2702** (Mediterranean).
 - The B*2706 subtype is weakly associated and commonly found in normal south east Asian individuals.
- Autoantibodies (e.g., rheumatoid factor, antinuclear antibodies) are **negative**
- Radiographs
 - ⇒ **Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis.**
 - ⇒ Radiographs may be normal early in disease, later changes include:
 - sacroilitis: subchondral erosions, sclerosis
 - squaring of lumbar vertebrae
 - 'bamboo spine' (vertebral fusion) (late & uncommon)
 - **Syndesmophytes**: due to ossification of outer fibers of annulus fibrosus (**the tramine appearance** is due to syndesmophyte growth between the margins of the vertebrae)
 - ❖ Syndesmophytes grow vertically, as opposed to spondylophytes, which grow horizontally
 - Chest x-ray: apical fibrosis

Syndesmophytes grow vertically, as opposed to osteophytes, which grow horizontally

Syndesmophytes vs. osteophytes		
	Syndesmophytes	Osteophytes
Definition	<ul style="list-style-type: none"> • Ossification or calcification of the annulus fibrosus or a spinal ligament 	<ul style="list-style-type: none"> • Lipping of vertebral bodies
Radiographic features	<ul style="list-style-type: none"> • Symmetrical, vertical growth, directly from vertebral body to vertebral body • Full manifestation: "bamboo spine" 	<ul style="list-style-type: none"> • Horizontal growth
Etiology	<ul style="list-style-type: none"> • Inflammatory spine disease (e.g., AS) 	<ul style="list-style-type: none"> • Degenerative spine disease (e.g., diffuse idiopathic skeletal hyperostosis)



40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

- **MRI: More sensitive than x-ray** (Best method for early detection)
 - ⇒ Shows:
 - **Bone marrow edema** (The **earliest change** visible on MRI)
 - **Squaring of the vertebrae**,
 - Erosion of apophyseal joint
 - Obliteration of sacroiliac joint
- **Spirometry** may show a **restrictive defect** due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

Diagnosis → New York criteria

- Current British Society for Rheumatology recommendations state that the modified New York criteria should be used to diagnose ankylosing spondylitis:
 - ⇒ **Clinical criteria:**
 - Low back pain, present for more than three months, improved by exercise but not relieved by rest
 - Limitation of lumbar spine motion in both the sagittal and frontal planes
 - Limitation of chest expansion relative to normal values for age and sex.
 - ⇒ **Radiological criteria:**
 - Sacroiliitis on x ray.
 - ⇒ **Diagnosis:**
 - Definite AS if the radiological criterion is present plus at least one clinical criterion

- Probable AS if three clinical criteria are present alone or if the radiological criterion is present but no clinical criteria are present.

Management

- **Non-pharmacological:** encourage regular exercise such as swimming, physiotherapy
- **Pharmacological**
 - ⇒ **First-line** pharmacotherapy in most patients: **NSAIDs**
 - ⇒ Second-line : TNF- α inhibitors (e.g., etanercept, adalimumab)

Avascular necrosis (AVN)

Definition

- death of bone tissue due to interruption of blood supply; most commonly affects the epiphysis of long bones such as the femur.

Causes

- **long-term steroid use**
- **sickle cell disease**, Gaucher disease
- Cellular toxicity (e.g., **chemotherapy**, radiotherapy, alcohol excess)
- trauma

Features

- initially asymptomatic
- pain in the affected joint

Investigation

- plain x-ray findings may be normal initially
- **MRI is the investigation of choice.** It is more sensitive than radionuclide bone scanning

Treatment

- Joint replacement (e.g., hip, shoulder, knee)

Behcet's syndrome

Oral ulcers + genital ulcers + anterior uveitis = Behcet's

Definition

- Behcet's syndrome is a systemic vasculitis that is characterized by autoimmune mediated inflammation of the arteries and veins.
- affects small and large vessels (venous and arterial).

Pathophysiology

- Autoimmune (involves mainly the T helper cells) and infectious triggers (e.g., precipitating HSV or parvovirus infection)
- Strong **HLA-B51** association
 - ⇒ HLA B5 is associated with ocular disease;
 - ⇒ **HLA B12 is associated with recurrent oral ulcers.**

Epidemiology

- More common in the eastern Mediterranean (e.g. Turkey)
- More common and more severe in men
- Tends to affect young adults (e.g. 20 - 40 years old)
- Around 30% of patients have a positive family history

Features

- Recurrent painful oral aphthous ulcers: (95–100%): Usually last about 1–4 weeks
- Recurrent genital ulcerations
- Ocular disease (50–80%) → Uveitis

- Skin lesions (35–85%)
- Erythema nodosum
- Vasculopathy: Superficial thrombophlebitis, DVT
- Seronegative arthritis: Usually asymmetric arthritis.
- Neurological involvement (e.g. aseptic meningitis)
- GI: abdominal pain, diarrhoea, colitis
- Pathergy (development of pustules at venepuncture sites).
- Fever

Behcet's syndrome: The classic triad of symptoms are:

1. Oral ulcers
2. Genital ulcers
3. Anterior uveitis (iritis)

Behcet's syndrome → PATHERGY

Positive pathergy test, Aphthous mouth ulcers, Thrombosis (arterial and venous), Hemoptysis (pulmonary artery aneurysm), Eye lesions (uveitis, retinal vasculitis), Recurrent Genital ulcers, Young at presentation (3rd decade)

Diagnosis

- No definitive test. Diagnosis based on clinical findings
- **Positive pathergy test** is suggestive (puncture site following needle prick becomes inflamed with small pustule forming) → **specific to Behcet's disease**. It involves intradermal injection of skin with a 20-gauge needle under sterile conditions. It is considered **positive if an erythematous sterile papule develops within 48 hours**.
- Autoantibodies (e.g., ANA, ANCA, rheumatoid factor) are **usually absent**.
- **Diagnostic criteria** (International Study Group criteria)
 - ⇒ Recurrent oral ulceration at least three times within a 12-month period AND ≥ 2 of the following
 - Recurrent genital ulceration
 - Eye lesions
 - Skin lesions
 - Positive pathergy test

Treatment

- **Oral ulcers and/or genital ulcers:** topical corticosteroids, topical lidocaine for pain relief
- **Arthritis or Erythema nodosum:** **Colchicine is the first line treatment.**
- **Ocular disease, CNS disease, and/or vasculopathy**
 - ⇒ Systemic corticosteroids
 - ⇒ Immunosuppressant therapy (e.g., azathioprine, infliximab, cyclosporine A, cyclophosphamide, IFN-α, methotrexate)

Chronic fatigue syndrome

Definition

- Diagnosed after at least **4 months** of **disabling fatigue** affecting mental and physical function more than **50% of the time** in the absence of other disease which may explain symptoms.
- also known as myalgic encephalomyelitis

Epidemiology

- More common in **females** and young to middle-aged adults.
- Past psychiatric history has **NOT** been shown to be a risk factor

Fatigue is the central feature, other recognised features include

- Sleep problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep-wake cycle
- Muscle and/or joint pains
- Headaches
- **Painful lymph nodes without enlargement**
- Recurrent sore throat
- Cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
- Physical or mental exertion makes symptoms worse
- General malaise or 'flu-like' symptoms
- Dizziness
- Nausea
- Palpitations

To confirm a diagnosis of fatigue the following main features need to be present:

- Must be new in onset, persistent or recurrent and unexplained by other conditions.
- Should be characterised by post-exertional malaise.
- Should result in a substantial reduction in activity level.

Red flag symptoms which suggest another diagnosis include:

- Significant weight loss
- Inflammatory arthropathy or connective tissue disease
- Localising or focal neurological signs.

Investigation

- NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin* (*children and young people only), coeliac screening and also urinalysis

Management

- **Treatment of choice: graded exercise therapy**
 - ⇒ a formal supervised program,
 - ⇒ not advice to go to the gym
 - ⇒ 'pacing' - organising activities to avoid tiring
- Cognitive behaviour therapy - very effective,
- Low-dose amitriptyline may be useful for poor sleep
- Referral to a pain management clinic if pain is a predominant feature

Prognosis

- The short-term prognosis for recovery of function is generally poor. The long-term prognosis appears to be better
- Better prognosis in children

Chronic fatigue syndrome (also known as myalgic encephalomyelitis) → unexplained, persistent, and relapsing fatigue.

Compartment syndrome

Pain with passive stretching of the muscles, is the earliest clinical indicator of compartment syndrome.

Pathophysiology

- External or internal forces as initiating event → increased compartment pressure → obstruction of venous outflow and collapse of arterioles → decreased tissue perfusion → lower oxygen supply to muscles → irreversible tissue damage (necrosis) to muscles and nerves after 4–6 hours of ischemia

Features

- Early presentation**
 - ⇒ Pain
 - Often out of proportion to the extent of injury
 - Worse with passive stretching or extension of muscles**
 - Very tight, wood-like muscles that are extremely tender to touch
 - ⇒ Sensory deficit in the distribution of the peripheral nerve(s) passing through that compartment
 - Paresthesia (e.g., pins and needles)
 - Decreased 2-point discrimination is the most consistent early finding**
 - in acute anterior lower leg compartment syndrome, the first sign to develop may be numbness between the first 2 toes (superficial peroneal nerve).
 - ⇒ Soft tissue swelling
- Late presentation**
 - ⇒ Muscle weakness to paralysis
 - ⇒ Cold peripheries
 - ⇒ Pallor
 - ⇒ Absent (or weak) distal pulses

Complications

- Muscle and soft tissue necrosis
- Nerve lesions (esp. the tibial nerve and peroneal nerve) with sensory and motor deficits or paralysis
- Rhabdomyolysis with potential Crush syndrome

Investigations

- A **Creatine phosphokinase (CPK)** concentration of 1000–5000 U/mL or greater or the presence of **myoglobinuria** can suggest compartment syndrome.
- Compartment pressure measurement (initial and confirmatory test)**

Risk factors

- Trauma
- Anticoagulation therapy and bleeding disorders (eg, hemophilia)
- Vigorous exertion (has been found in soldiers and athletes without any trauma).

Treatment

- Surgical** → **Urgent decompression is required to prevent severe ischaemia.**
 - ⇒ Fasciotomy (tissue and fascia incisions): relieves the pressure, thus restoring perfusion
 - ⇒ Escharotomy: in the case of circumferential compression by a burn eschar

Acute compartment syndrome is a surgical emergency and requires an early fasciotomy. Elevated positioning may worsen ischemia by reducing blood flow.

Complex regional pain syndrome (CRPS)

Epidemiology

- Three times more frequent in females than males

Pathophysiology

- Unknown. Proposed mechanisms include classic inflammation, neurogenic inflammation, and maladaptive changes in pain perception at the level of the central nervous system.

Precipitating factors

- injury and surgery (fractures and soft tissue injuries.): most common
- CRPS seldom occurs in the absence of an identifiable trigger.

Features

- Severe pain out of proportion to the original injury**
- Sensory changes, motor impairments, autonomic symptoms, and trophic changes in the affected limb.
 - ⇒ **Allodynia** (perception of pain from a nonpainful stimulus)
 - ⇒ **Hyperalgesia** (an exaggerated sense of pain)

A repeat X-ray is the most appropriate next investigation looking for patchy osteoporosis in patient developed clinical features consistent with complex regional pain syndrome type 1 (CRPS1)

Cryoglobulinaemia

consumption of C4 + strongly positive rheumatoid factor → cryoglobulinaemia.

Overview

- Cryoglobulins are abnormal immunoglobulins which precipitate when cooled below 37°C (maximum precipitate formation takes place at +4°C) and redissolve in plasma when warmed back to 37°C (**reversible precipitation at low temperatures**)
- The precipitated clump can block blood vessels and cause toes and fingers to become gangrenous.
- Cryoglobulins usually consist of IgM directed against the Fc region of IgG.
- Common causes: hepatitis C, multiple myeloma, SLE, rheumatoid arthritis, Idiopathic (one third of cases)

Pathophysiology

- Immune deposition** on the wall of small vessels result in generalized **vasculitis**, which presents with a reticular skin pattern of **micro-thrombosis** and areas of gangrene.
- cryoglobulins → form an immune complexes → activate the complement system, resulting in ↓complement levels (**Hypocomplementemia**)

Three types

- Type I** (25%):
 - ⇒ monoclonal (IgG or IgM)
 - ⇒ associated with haematological diseases such as myeloma and Waldenstrom's.
- Type II** (25%):
 - ⇒ **Mixed** monoclonal and polyclonal: usually with RF
 - ⇒ Composed of a **monoclonal IgM** rheumatoid factor plus **polyclonal IgG**
 - ⇒ Associations: **hepatitis C**, RA, Sjogren's, lymphoma

- most importantly, hepatitis C infection which should always be excluded.
 - ❖ If serological testing is negative, then the cryoprecipitate should be checked for HCV RNA by PCR.
 - ❖ **Membranoproliferative glomerulonephritis (also known as mesangiocapillary glomerulonephritis) is the characteristic histological finding on biopsy where there is renal involvement.**
 - ❖ For hepatitis C associated mixed cryoglobulinaemia, **interferon alpha is the treatment of choice**, although rapidly progressive disease may require immunosuppressive therapy.
- Type III (50%):
 - ⇒ polyclonal: usually with RF
 - ⇒ composed of a **polyclonal IgM** rheumatoid factor plus **polyclonal IgG**.
 - ⇒ associations: RA, Sjogren's

Mixed cryoglobulinemia

- Types **II and III** cryoglobulinemia
- both type II and III cryoglobulinaemia have rheumatoid factor reactivity
- represent 80% of all cryoglobulins.
- contain rheumatoid factors (RFs) which are usually IgM
- closely associated with **hepatitis C** virus (HCV)

Symptoms (if present in high concentrations)

Meltzer's triad (seen in cryoglobulinaemia (types II/III) → palpable purpura, arthralgia and myalgia

- Raynaud's only seen in type I
- Cutaneous: vascular purpura, distal ulceration
 - ⇒ **skin is most commonly involved organ** (over 90%), with purpura, leg ulcers and acrocyanosis.
- Arthralgia (seen in 70%).
- Renal involvement (diffuse glomerulonephritis)
 - ⇒ Glomerular disease is common in types 2 and 3 (mixed types) and occurs in around 50–55% of cases.
- **Axonal peripheral neuropathy**
 - ⇒ **cryoglobulins → small-vessel vasculitis → axonal peripheral neuropathy**
 - ⇒ may be sensorimotor, or purely sensory.
 - ⇒ Neurological involvement (polyneuropathy) is seen in 40% of patients.
- Pulmonary embolism, arterial and venous thrombosis are common.
- The gastrointestinal tract is affected in 30%.

A vasculitic rash and neuropathy in a patient with hepatitis C is suggestive of cryoglobulinaemia.

Tests

- **low complement (esp. C4):** occurs in about 90% of patients with mixed cryoglobulinaemia (Type II) as a result of classic pathway activation.
- Since they precipitate at low temperatures, cryoglobulins should always be transported to the lab at 37°C. Failure to do this will result in a false negative result as the cryos will precipitate and be removed with the clot.
- High ESR

Treatment

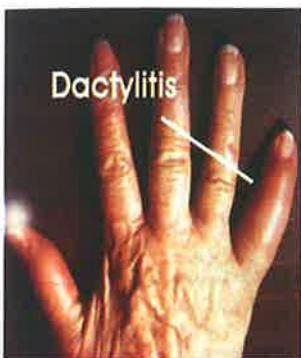
- immunosuppression (high dose steroids and cyclophosphamide).
- Plasmapheresis

Hypocomplementemia is seen in many conditions, including:

- Lupus,
- **Mixed cryoglobulinemia**,
- Membranoproliferative glomerulonephritis, and
- Hereditary angioedema.

Dactylitis

- Dactylitis describes the inflammation of a digit (finger or toe).
- **A 'sausage-shaped' digit is a classical description of dactylitis**
- **Causes** include:
 - ⇒ spondyloarthritis: e.g. **Psoriatic** and **reactive arthritis**
 - ⇒ sickle-cell disease
 - ⇒ other rare causes include tuberculosis, sarcoidosis and syphilis



De Quervain's tenosynovitis

- De Quervain's tenosynovitis is a common condition in which the sheath containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed.
- It is a common pathology which consists of a stenosing tenosynovitis of the first dorsal compartment of the wrist.
- It typically affects females aged 30 - 50 years old

Causes

- commonly caused by **occupational** or avocational repetitive movement of the thumb
- also associated with RA, psoriatic arthritis, direct trauma, pregnancy, and the post-partum period.

Features

- **pain on the radial side of the wrist**
- tenderness over the radial styloid process
- abduction of the thumb against resistance is painful
- **Finkelstein's test:**
 - ⇒ Used to confirm the diagnosis
 - ⇒ the patient is asked to bring the thumb across the palm and clasp the fingers around it. The examiner then pulls it in the ulnar direction, which elicits a sharp pain.

Management

- analgesia
- steroid injection
- immobilisation with a thumb splint (spica) may be effective
- surgical treatment is sometimes required

Scaphoid fractures

- are relatively common,
- typically occurring following a fall onto outstretched hand.
- The proximal portion lacks its own blood supply, so **avascular necrosis** can occur if a fracture leaves it isolated from the remainder of the scaphoid.
- produces **pain and tenderness of the radial side of the wrist**, classically in the **anatomical snuffbox**, exacerbated by wrist movement.
- Preiser's disease is avascular necrosis of scaphoid

Gout

The vast majority of gout is due to decreased renal excretion of uric acid

Gout: start allopurinol if ≥ 2 attacks in 12 month period

Definition

- An inflammatory crystal arthropathy that is caused by the precipitation and deposition of uric acid crystals in synovial fluid and tissues. It is typically associated with hyperuricemia, but can also occur if uric acid levels are normal.

Epidemiology

- Gout is the most prevalent form of inflammatory arthropathy.
- Sex: ♂ > ♀ (3:1)
- Age of onset: 2 peaks of incidence (at 30–39 years and at 60 years of age)

Pathophysiology

- Uric acid is an end-product of purine metabolism that is excreted by the kidneys, predisposes to gout
- Chronic hyperuricaemia (uric acid $> 0.45 \text{ mmol/l}$) → intraarticular uric crystal precipitation (deposition of **monosodium urate** monohydrate in the synovium) → release of inflammatory mediators and enzymes → aggregations of urate crystals and giant cells (tophi) → local joint inflammation (microcrystal synovitis), arthritis and deformities

Causes

- **Decreased uric acid excretion via the kidney** → **most common cause (90%)**
 - ⇒ Medications (e.g., pyrazinamide, aspirin, loop diuretics, thiazides, niacin, cytotoxic agents)
 - **Aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels**
 - If diuretics are being used to treat hypertension an alternative antihypertensive should be considered, but they should not be stopped in the presence of heart failure.
 - ⇒ Chronic renal insufficiency
 - ⇒ Ketoacidosis; due to, e.g., starvation → ↑ lactic acid → impairs the kidneys' ability to excrete uric acid → ↑ risk of gout)

- ⇒ Postmenopause
- **Increased uric acid production (10%)**
 - ⇒ High cell turnover, e.g.:
 - Tumor lysis syndrome
 - Hemolytic anemia
 - Psoriasis
 - Myeloproliferative neoplasms
 - ⇒ Enzyme defects, e.g.:
 - Lesch-Nyhan syndrome
 - Phosphoribosyl pyrophosphate synthetase overactivity
 - von Gierke disease
 - ⇒ Diet rich in protein and especially purine (e.g., red meat, seafood)
 - ⇒ Obesity
 - ⇒ Hypercholesterolemia, hypertriglyceridemia
 - ⇒ Hypertension
- **Combined decreased excretion and overproduction:** high alcohol consumption
 - ⇒ Organic acids from alcohol metabolism compete with uric acid to be excreted by the kidneys.
- **Can be idiopathic (primary hyperuricemia):** Primary hyperuricemia can be aggravated by poor dietary habits.

Drugs associated with gout: aspirin, thiazides, niacin, pyrazinamide, loop diuretics.

Lesch-Nyhan syndrome

- **hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency**
- x-linked recessive therefore only seen in boys
- features: gout, renal failure, neurological deficits, learning difficulties, **aggressiveness**, self-mutilation (for example, biting of finger tips and/or lips).

What is the most common cause of acute gout in association with G-6PD deficiency?

- **Increased production of pentose sugars**
 - ⇒ Glucose-6-phosphate dehydrogenase (G6PD) → converts (G6P) to glucose.
 - ⇒ (G6PD) Deficiency → accumulation of G6P → enters the hexose monophosphate shunt → **↑ production of pentose sugars**. (These act as a substrate for phosphoribosyl pyrophosphate (PRPP) synthetase) → **↑ production of purines** → uric acid.
 - ⇒ Hypoglycaemia in G6PD deficiency → **↑ catecholamine levels** → **↑ glycogenolysis** in muscles → **↑ lactic acidosis** → **↓ urate excretion** (competes with uric acid for excretion)

Features

- **Acute gouty arthritis**
 - ⇒ Acute severe pain with overlying erythema, decreased range of motion, swelling, warmth
 - Symptoms are more likely to occur at night, typically waking the patient.
 - peak after 12–24 hours
 - ⇒ Desquamation of the skin
 - ⇒ Location: Usually monoarthritis during first attacks
 - Asymmetrical distribution is common if more than one joint is affected
 - **Metatarsophalangeal joint (MTP joint) inflammation of the big toe (the most common site)**
 - Knee, finger, ankle; wrist

- **Chronic gouty arthritis**
 - ⇒ **Progressive joint destruction**
 - ⇒ **Tophi formation:** Multiple painless hard nodules with possible joint deformities, appear yellow or white. Ulceration and discharge (chalky white substance) may occur
 - Bone tophi: urate crystal deposition in bones (e.g., elbows, knees, extensor surfaces of forearms)
 - Soft tissue tophi: urate crystal deposition in the pinna of the external ear, subcutis, tendon sheaths (e.g., at the Achilles tendon), or synovial bursae (e.g., olecranon bursa)
 - ⇒ **Uric acid nephrolithiasis and uric acid nephropathy**

Investigations

- WBC and ESR are typically elevated
- Serum urate
 - ⇒ often elevated (hyperuricemia); may also be normal or low; (**normal urate concentration does not rule out a diagnosis of gout**).
 - ⇒ Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout
- X-ray: the **bony erosions are typically punched out** with sclerotic margins and overhanging edges, sometimes termed rat bite erosions.
- Joint aspiration → Presence of long needle-shaped Crystals (uric acid crystal)
 - ⇒ **gold standard for diagnosing gout**
 - ⇒ Findings
 - **Needle-shaped monosodium urate crystals that are negatively birefringent**
 - Synovial fluid cell count: WBC > 2000/ μ L with > 50% neutrophils



There is well defined **punched-out** juxta-articular erosions related to both sides of the first metatarsal bone. This is a classical site for gout.

Management

- **Lifestyle modifications may help reduce the risk of flares.**
 - ⇒ Limit alcohol consumption
 - ⇒ Limit intake of purines (e.g., red meat and shellfish)
 - ⇒ Weight loss if patient is overweight
- **Acute gout flare** → First-line agents: NSAIDs, colchicine or glucocorticoids
 - ⇒ **NSAIDs** (Naproxen: indomethacin, ibuprofen)
 - Add a proton pump inhibitor to reduce the risk of gastrointestinal ulcers.
 - **Should be avoided in elderly patients taking warfarin** due to the risk of a life-threatening gastrointestinal haemorrhage.
 - **Contraindicated in renal impairment** (use colchicine in mild to moderate CKD and prednisolone in severe CKD)
 - Relatively contraindicated in congestive cardiac failure
- ⇒ **Colchicine**
 - **Mechanism of action:** binds and stabilizes tubulin subunits → inhibits microtubule polymerization → inhibits phagocytosis of urate crystals, neutrophil activation, migration, and degranulation
 - **Useful in patients taking warfarin as combined NSAID is harmful to GIT.**
 - Can be used in mild and moderate CKD (not severe CKD). The BNF advises to reduce the dose by up to 50% if creatinine clearance is less than 50 ml/min and to avoid if creatinine clearance is less than 10 ml/min.
 - May be increased up to a dose of 3mg, divided in 600mcg portions to cope with the acute attack.
 - **The most appropriate management for patient on colchicine 600mcg daily presented with acute gout and mild renal impairment → Increase his colchicine to cope with the exacerbation**
 - **Side effects**
 - ⇒ Diarrhea (**the main side-effect**)
 - ⇒ Myopathy, rhabdomyolysis
 - ⇒ Polyneuropathy
 - ⇒ CNS symptoms (e.g., fatigue, headache)
 - ⇒ Myelosuppression
 - ⇒ Cardiac toxicity, arrhythmias
 - **Contraindications: Severe CKD**
 - **Drug interactions**
 - ⇒ Statins: Consider reducing dose of pravastatin, atorvastatin, or simvastatin when prescribed concomitantly.
 - ⇒ Potent cytochrome P450 3A4 substrates or inhibitors
 - ⇒ Reduce colchicine dose when prescribed concomitantly.
 - ⇒ Avoid in patients with CKD or hepatic impairment.
- ⇒ **Glucocorticoids** (prednisolone, methylprednisolone, or intraarticular administration)
 - Glucocorticoids are preferable **if there are contraindications (e.g., CKD), intolerance, or inadequate response to NSAIDs or colchicine.**
 - A recent trials found that oral prednisolone (30 mg/day for 5 days) had analgesic effectiveness equivalent to that of indomethacin and naproxen.
 - Avoided in diabetics because it would adversely affect diabetic control.
 - intraarticular steroid are preferred for NPO patients

⇒ **IL-1 blockers**

- European Medicines Agency approved anti-IL-1 β monoclonal antibody canakinumab (150 mg subcutaneously, one dose) **for patients with contraindication to colchicine, NSAIDs and steroids**
- Current infection is a contraindication to the use of IL-1 blockers.

⇒ **Rest the affected joints**

Low-dose aspirin can decrease uric acid excretion and trigger recurrent gout flares but it should not be stopped in patients taking it for specific indications (e.g., coronary artery disease, cerebrovascular disease), regardless of the severity of gout.

Monitor for myotoxicity when prescribing colchicine with statins. Reduce dose of pravastatin, atorvastatin, and simvastatin when prescribed concomitantly.

• **Chronic gout → Urate-lowering therapy (ULT)**

- ⇒ **First-line:** xanthine-oxidase inhibitors (allopurinol)
- ⇒ **Second-line:** uricosurics (probenecid)
- ⇒ **Third-line:** recombinant uricase (pegloticase)
- ⇒ **Absolute indications**
 - Damage due to chronic gout seen on imaging
 - Tophi development
 - Frequent gout attacks (≥ 2 per year)
- ⇒ **Relative indications**
 - < 2 gout attacks per year
 - First episode of acute gout flare in patients with any of the following risk factors:
 - CKD \geq stage 3
 - Serum uric acid > 9 mg/dL
 - History of urolithiasis
- ⇒ **Contraindications to all ULT agents**
 - Acute gout flare (in the absence of the above-mentioned risk factors). **If the patient is already taking allopurinol it should be continued.**
 - Asymptomatic hyperuricemia
- ⇒ **Timing of initiating ULT:** at least one week after initiating anti-inflammatory prophylaxis as ULT may trigger, prolong, or worsen an acute gout flare.
- ⇒ **Target of serum uric acid:** < 6 mg/dL (360 μ mol/L).

Urate-lowering therapy (ULT)• **Xanthine oxidase inhibitors (XOIs): Allopurinol and Febuxostat (the preferred first-line agent)**⇒ **Action:**

- Allopurinol is a competitive inhibitor.
- Febuxostat is a non-purine, selective inhibitor of xanthine oxidase that is metabolized in the liver. **Recommended by NICE guidance as second-choice to prevent gout when allopurinol has not been tolerated or is contraindicated.**

⇒ **Contraindications**

- **Allopurinol:** Presence of the HLA-B*5801 allele
- **Febuxostat:** History of cardiovascular disease

⇒ **Side effects**

- **Allopurinol:** Stevens-Johnson syndrome/toxic epidermal necrolysis
- **Febuxostat:** Nausea, diarrhea, **transaminitis**

- ⇒ **Interactions**
 - Purine analogs (e.g., azathioprine, 6-mercaptopurine) combined with XOLs can cause bone marrow toxicity
 - Probenecid and thiazides decrease the efficacy of allopurinol
 - **Allopurinol increase INR by inhibiting the metabolism of warfarin.**
- **Uricosurics: Probenecid (the second line)**
 - ⇒ Action: **Inhibition of uric acid reabsorption** along renal proximal convoluted tubules → increased renal elimination
 - ⇒ **Contraindications**
 - Nephrolithiasis
 - Moderate to severe CKD
 - ⇒ **Side effects:** Urolithiasis (uric acid stones)
 - ⇒ **Interactions:** Inhibits penicillin secretion in the proximal convoluted tubule
- **Recombinant uricase: Pegloticase (the third line)**
 - ⇒ Action: **breakdown of uric acid to allantoin** (allantoin is water-soluble and therefore can be renally excreted)
 - ⇒ **Contraindications:** G6PD deficiency, Congestive heart failure

The combination of allopurinol and azathioprine leads to increased bone marrow toxicity

Rasburicase

- recombinant urate oxidase
- **may be given during the acute attack of gout**, to allow allopurinol therapy to be commenced without the initial worsening of symptoms.
- But it is **not currently licensed for the treatment of acute gout** associated with other conditions.
- **The best choice for warfarinsed patient**

Acute gout pain with congestive cardiac failure and renal impairment, developed severe diarrhoea with colchicine. The treatment of choice → Prednisolone

Most patients with hyperuricaemia never develop gout or stones. Treatment of these patients is not recommended.

Allopurinol

- **Allopurinol therefore**
- **Inhibit xanthine oxidase**
- **Reduces both purine breakdown and synthesis.**
- **Can be used even in moderate-severe renal failure with dose reduction**
- **NSAID or colchicine cover should be used when starting allopurinol**

Allopurinol, Azathioprine interaction

- Azathioprine metabolised to active compound 6-mercaptopurine
- xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
- Allopurinol can therefore lead to high levels of 6-mercaptopurine
- A much-reduced dose (e.g. 25%) must therefore be used if the combination cannot be avoided
- **Allopurinol Increases toxicity and effects of azathioprine and 6-mercaptopurine. So reduce dose of azathioprine and 6-mercaptopurine to one quarter of usual dose.**

Antihypertensive drugs and gout

- Antihypertensive either increase serum **uric acid levels** (e.g., diuretics, β -blockers) or **decrease serum uric acid levels** (e.g., **calcium-channel blockers, losartan**).
- **Losartan** has a specific uricosuric action (\uparrow excretion of uric acid in the urine, thus reducing the serum uric acid) and may be particularly suitable for the many patients who have coexistant hypertension

Prognosis

- Gout appears to be an independent risk factor for cardiovascular mortality and morbidity
- Hyperuricaemia may be associated with both hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

Hip pain in adults

The table below provides a brief summary of the potential causes of hip pain in adults

Condition	Features
Osteoarthritis	Pain exacerbated by exercise and relieved by rest Reduction in internal rotation is often the first sign Age, obesity and previous joint problems are risk factors
Inflammatory arthritis	Pain in the morning Systemic features Raised inflammatory markers
Referred lumbar spine pain	Femoral nerve compression may cause referred pain in the hip Femoral nerve stretch test may be positive - lie the patient prone. Extend the hip joint with a straight leg then bend the knee. This stretches the femoral nerve and will cause pain if it is trapped
Greater trochanteric pain syndrome (Trochanteric bursitis)	Due to repeated movement of the fibroelastic iliotibial band Pain and tenderness over the lateral side of thigh Most common in women aged 50-70 years
Meralgia paraesthesia	Caused by compression of lateral cutaneous nerve of thigh Typically burning sensation over antero-lateral aspect of thigh
Avascular necrosis	Symptoms may be of gradual or sudden onset May follow high dose steroid therapy or previous hip fracture or dislocation
Pubic symphysis dysfunction	Common in pregnancy Ligament laxity increases in response to hormonal changes of pregnancy Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. A waddling gait may be seen
Transient idiopathic osteoporosis	An uncommon condition sometimes seen in the third trimester of pregnancy Groin pain associated with a limited range of movement in the hip Patients may be unable to weight bear ESR may be elevated

Hip problems in children

The table below provides a brief summary of the potential causes of hip problems in children

Condition	Notes
Development dysplasia of the hip	Often picked up on newborn examination Barlow's test, Ortolani's test are positive Unequal skin folds/leg length
Transient synovitis (irritable hip)	Typical age group = 2-10 years Acute hip pain associated with viral infection Commonest cause of hip pain in children
Perthes disease	Perthes disease is a degenerative condition affecting the hip joints of children, typically between the ages of 4-8 years. It is due to avascular necrosis of the femoral head Perthes disease is 5 times more common in boys. Around 10% of cases are bilateral Features <ul style="list-style-type: none"> • hip pain: develops progressively over a few weeks • limp • stiffness and reduced range of hip movement • x-ray: early changes include widening of joint space, later changes include decreased femoral head size/flattening
Slipped upper femoral epiphysis	Typical age group = 10-15 years More common in obese children and boys Displacement of the femoral head epiphysis postero-inferiorly Bilateral slip in 20% of cases May present acutely following trauma or more commonly with chronic, persistent symptoms Features <ul style="list-style-type: none"> • knee or distal thigh pain is common • loss of internal rotation of the leg in flexion
Juvenile idiopathic arthritis (JIA)	Preferred to the older term juvenile chronic arthritis, describes arthritis occurring in someone who is less than 16 years old that lasts for more than three months. Pausiarticular JIA refers to cases where 4 or less joints are affected. It accounts for around 60% of cases of JIA Features of pauciarticular JIA <ul style="list-style-type: none"> • joint pain and swelling: usually medium sized joints e.g. knees, ankles, elbows • limp • ANA may be positive in JIA - associated with anterior uveitis
Septic arthritis	Acute hip pain associated with systemic upset e.g. pyrexia. Inability/severe limitation of affected joint

Lateral epicondylitis

Lateral epicondylitis: worse on resisted wrist extension/supination whilst elbow extended

Lateral epicondylitis typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow'). It is most common in people aged 45-55 years and typically affects the dominant arm.

Features

- pain and tenderness localised to the lateral epicondyle
- pain worse on wrist extension against resistance with the elbow extended or supination of the forearm with the elbow extended
- episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks

Management options

- advice on avoiding muscle overload
- simple analgesia
- steroid injection
- physiotherapy

Lower back pain

- Lower back pain (LBP) is one of the most common presentations seen in practice.
- Whilst **the majority of presentations will be of a non-specific muscular nature** it is worth keeping in mind possible causes which may need specific treatment.
⇒ musculogenic (strain) etiology is the most common cause of low back pain.

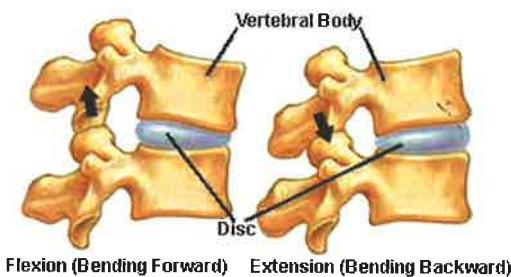
Red flags for lower back pain

- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

Facet joint	<ul style="list-style-type: none"> • May be acute or chronic • Pain worse in the morning and on standing • On examination there may be pain over the facets. • The pain is typically worse on extension of the back
Spinal stenosis	<ul style="list-style-type: none"> • Usually gradual onset • Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down. • Pain may be described as 'aching', 'crawling'. • Relieved by sitting down, leaning forwards and crouching down • Clinical examination is often normal • Requires MRI to confirm diagnosis
Ankylosing spondylitis	<ul style="list-style-type: none"> • Typically a young man who presents with lower back pain and stiffness • Stiffness is usually worse in morning and improves with activity • Peripheral arthritis (25%, more common if female)
Peripheral arterial disease	<ul style="list-style-type: none"> • Pain on walking, relieved by rest • Absent or weak foot pulses and other signs of limb ischaemia • Past history may include smoking and other vascular diseases

Facet Joints in Motion



- (also known as zygapophyseal, apophyseal, or Z-joint)
- are synovial joints between the spinal vertebrae
- Function: guide and limit movement of the spinal motion segment.

Assessment

- Do risk stratification for new cases
 - ⇒ such as the **STarT Back risk assessment tool**
- do not request imaging unless serious underlying pathology is suspected.

STarT Back Screening Tool

1. My back pain has spread down my leg(s) at some time in the last 2 weeks
 2. I have had pain in the shoulder or neck at some time in the last 2 weeks
 3. I have only walked short distances because of my back pain
 4. In the last 2 weeks, I have dressed more slowly than usual because of back pain
 5. It's not really safe for a person with a condition like mine to be physically active
 6. Worrying thoughts have been going through my mind a lot of the time
 7. I feel that my back pain is terrible and it's never going to get any better
 8. In general I have not enjoyed all the things I used to enjoy
 9. Overall, how bothersome has your back pain been in the last 2 weeks? Not at all (0), Slightly, (0), Moderately (0), Very much (1), Extremely (1)
- **STarT Back scoring:**

- ⇒ For questions 1-8, score 1 for agreement, 0 for disagreement
 - Low risk = total score 0-3;
 - high risk = score 4-5 of questions 5-9 only;
 - the rest are medium risk.

Management (NICE: November 2016)

- **Non-pharmacological**
 - ⇒ Self-management
 - encouragement to continue with normal activities.
 - ⇒ Exercise
 - ⇒ Manual therapies (spinal manipulation, mobilisation or soft tissue techniques such as massage)
 - Traction is NOT recommended
 - ⇒ Psychological therapy (cognitive behavioural)
 - ⇒ Acupuncture and Electrotherapies are NOT recommended
- **Pharmacological**
 - ⇒ NSAIDs
 - ⇒ Do not offer paracetamol alone for managing low back pain.
 - ⇒ Consider weak opioids (with or without paracetamol) for managing **acute** low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.
 - ⇒ Do not offer opioids for managing **chronic** low back pain.
 - ⇒ Antidepressants and anticonvulsants are not recommended
- **Invasive non-surgical treatments**
 - ⇒ Spinal injections are not recommended for treatment.
 - except for 'radiofrequency denervation'.
 - ❖ To determine whether these people will benefit from this procedure, they may be offered a diagnostic block of the nerves that supply the joints between the vertebrae.
 - ⇒ If they experience significant pain relief they may then be offered radiofrequency denervation in an attempt to achieve longer-term relief.
 - ⇒ **Radiofrequency denervation**
 - for chronic low back pain if:
 - 1) non-surgical treatment has not worked **and**
 - 2) the main source of pain is thought to come from structures supplied by the **medial branch nerve and**
 - 3) they have moderate or severe pain
 - Only performed after a positive response to a diagnostic medial branch block.
 - ⇒ **epidural injections** of local anaesthetic and steroid in people with acute and severe sciatica.
 - **Invasive surgical treatments:**
 - ⇒ **spinal decompression**
 - for sciatica when non-surgical treatment has not improved pain
 - ⇒ Spinal fusion and disc replacement are NOT recommended in treatment of low back pain.

Mixed connective tissue disease (MCTD)

Anti-ribonuclear protein (anti-RNP) = mixed connective tissue disease

Definition

- MCTD is an overlap syndrome characterised by combinations of clinical features of SLE, systemic scleroderma and polymyositis (**e.g. arthralgia, myositis and Raynaud's**).

Feature

- The presenting symptoms of MCTD are most often:
 - ⇒ Raynaud's phenomenon
 - ⇒ puffy hands
 - ⇒ arthralgias
 - ⇒ myalgias
 - ⇒ fatigue.

Diagnosis

- Anti-RNP positive
 - ⇒ A defining feature of MCTD is the presence of antibodies against the U1 ribonucleoprotein (U1 RNP) complex, and hence the presence of high titre anti-U1 RNP will confirm the clinical diagnosis of MCTD.

Prognosis

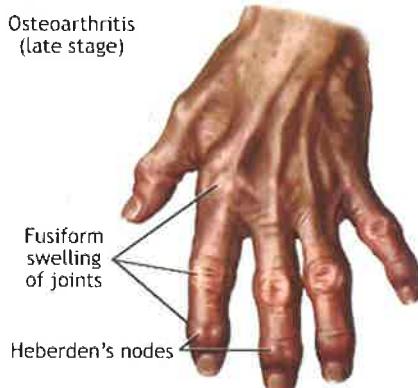
- Most deaths are due to heart failure caused by pulmonary arterial hypertension.

Osteoarthritis

The trapezio-metacarpal joint (base of thumb) is the most common site of hand osteoarthritis

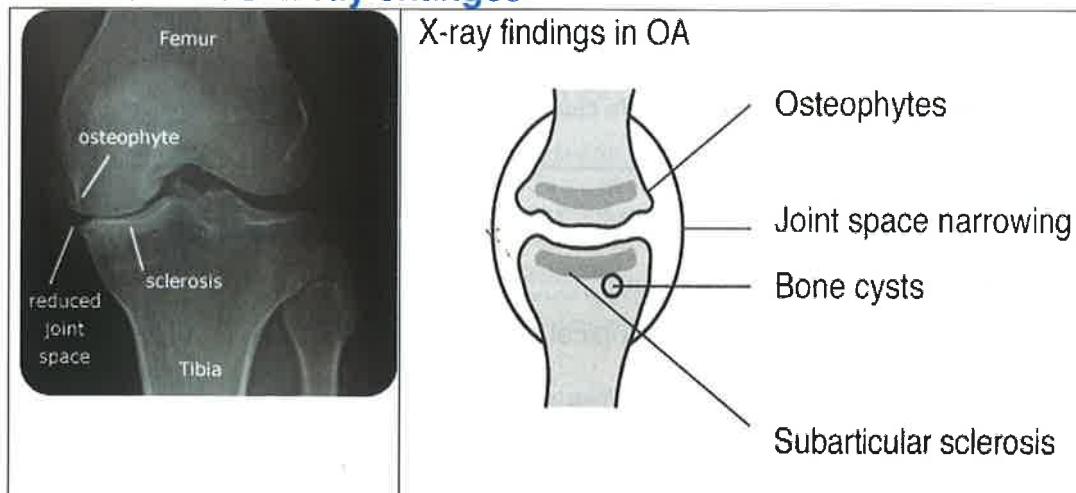
Osteoarthritis - paracetamol + topical NSAIDs (if knee/hand) first-line

- Pathogenesis involves the localised loss of cartilage, with remodelling of adjacent bone.
- Osteoarthritis characteristically affects the **distal interphalangeal** as well as the proximal interphalangeal and first metacarpophalangeal joints.
- The carpometacarpal (CMC) joint is classically involved
- Joint swelling is bony in nature**, unlike the boggy swelling which occurs in inflammatory arthritis.
- Thenar wasting occurs in OA of the first CMC joint due to disuse.
- pain is exacerbated by exercise and relieved by rest, although in advanced disease rest and night pain can develop.
- Obesity is one of the commonest causes for the early appearance of osteoarthritis**
- Osteoarthritis may be secondary to haemochromatosis → do Ferritin**



Typical findings in the hand are bony enlargement of the proximal interphalangeal joints (Bouchard's nodes) and the distal interphalangeal joints (Heberden's nodes)

Osteoarthritis: x-ray changes



X-ray changes of osteoarthritis

- decrease of joint space
- subchondral sclerosis
- subchondral cysts
- osteophytes forming at joint margins

The gull-wing or inverted-T pattern of erosions is typical of erosive inflammatory osteoarthritis.

GULL WING SIGN

DIP jts showing central erosions and marginal osteophytes in EROSION
OSTEOARTHRITIS.



Osteoarthritis: management

Osteoarthritis - paracetamol + topical NSAIDs (if knee/hand) first-line

NICE recommend co-prescribing a PPI with NSAIDs in all patients with osteoarthritis

- all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- paracetamol and topical NSAIDs are first-line analgesics. **Topical NSAIDs are indicated only for OA of the knee or hand**
- second-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. A proton pump inhibitor should be co-prescribed with NSAIDs and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin
- non-pharmacological treatment options include supports and braces, **Transcutaneous Electrical Nerve Stimulation (TENS)** and shock absorbing insoles or shoes
- if conservative methods fail then refer for consideration of joint replacement

What is the role of glucosamine?

- normal constituent of glycosaminoglycans in cartilage and synovial fluid
- a systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported significant short-term symptomatic benefits including significantly reduced joint space narrowing and improved pain scores
- more recent studies have however been mixed
- the 2008 NICE guidelines suggest it is not recommended
- a 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to limited evidence of cost-effectiveness

Studies have shown that paracetamol 1 g combined with **codeine at dose of 60 mg** have the best analgesic outcomes.

The guiding principle in the management of osteoarthritis is to treat the symptoms and disability, not the clinical or radiological appearances. Educating the individual about the disease and its effects reduces pain, distress and disability and increases compliance with treatment. Psychological or social factors alter the impact of the disease.

The following table compares osteoarthritis with rheumatoid arthritis.

	OA	RA
Morning stiffness	< 30 minutes	> 1 hour
DIP	Yes	No
PIP	Yes	Yes
MCP	No	Yes
RF, anti-CCP	No	Yes
Joint fluid leukocyte count	< 2,000	5,000–50,000

Osteomyelitis

Osteomyelitis: MRI is the imaging modality of choice

If no other information is available about a patient with **osteomyelitis**, the causative bacteria is ***Staphylococcus aureus*** until proven otherwise.

Patients with sickle cell disease have a predisposition to develop osteomyelitis due to *Salmonella* species.

Definition

- Osteomyelitis: infection of bone marrow and bone
- Acute form: develops within days or weeks
- Chronic form: develops slowly (over months or years) and is associated with avascular bone necrosis and sequestrum formation within the bone

Causes

- ***Staph. aureus* is the most common cause** followed by *Pseudomonas*
- *Pseudomonas aeruginosa* is more common in intravenous drug users.
- ***Salmonella* species is the commonest cause in patients with sickle-cell anaemia.**
- *Pasteurella multocida*
 - ⇒ seen in cases caused by cat and dog bites
- **Haematogenous osteomyelitis:**
 - ⇒ most commonly involves the vertebrae, but infection may also occur in the **metaphysis** of the long bones, pelvis, and clavicle.
 - The lumbar spine is most commonly affected, followed by the thoracic and cervical regions.
 - ⇒ the location is usually **metaphyseal**
 - The metaphysis is commonest site of osteomyelitis, because:

- ❖ Is highly vascular
- ❖ Has a hair pin like arrangement of capillaries
- ❖ Has sluggish blood **flow**
- ❖ has relatively fewer phagocytic cells than the physis or diaphysis, allowing infection to occur more easily in this area
- ❖ thin cortex
- Posttraumatic osteomyelitis
 - ⇒ typically found in the tibia.
- Contiguous-focus osteomyelitis
 - ⇒ direct inoculation of bacteria via trauma
 - ⇒ Infection usually results approximately one month after inoculation.

Predisposing conditions

- diabetes mellitus
- sickle cell anaemia
- intravenous drug user
- immunosuppression due to either medication or HIV
- alcohol excess

Investigations

- **MRI is the imaging modality of choice**, with a sensitivity of 90-100%
 - ⇒ show → cortical destruction, bone marrow inflammation, soft tissue involvement
- Bone scintigraphy (Gallium bone scan) if MRI is contraindicated (metal foreign body implants) → detects sites of infection
- X-ray shows:
 - ⇒ still provide the best initial **screening** test for acute and chronic osteomyelitis.
 - ⇒ **Early stages (< 2 weeks of symptoms onset): typically no pathological findings**
 - ⇒ Later stages: bone destruction, **sequestrum** formation, periosteal reactions
 - ⇒ lytic lesion with sclerotic margins (**Brodie's abscess**)
 - a form of **chronic osteomyelitis**
 - thickened bone with irregular and patchy sclerosis that gives a honeycombed appearance.
 - Sequestra are seen as dense loose fragments lying within a cavity in the bone.
 - insidious onset (eg: 6-month history of gradually progressive swelling and pain)
 - often near the site of the metaphysis,
 - Deep 'boring' pain is often the predominant symptom.
 - ⇒ Osteomyelitis can cause a raised **periosteum** which is part of the radiographic sign known as the **Codman triangle**.
- Bone biopsy
 - ⇒ **confirmatory test**
 - ⇒ Detects both osteonecrosis and the pathogen → confirms the diagnosis and helps guide more specific therapy



The x ray shows lucent defects in the head of the humerus with loss of the normally well-corticated surface. This is consistent with osteomyelitis.

Differential diagnosis

- Septic arthritis
 - ⇒ Infection of the joint; in contrast to osteomyelitis, involvement of the metaphysis is rare
- Ewing sarcoma
 - ⇒ x-ray: lytic bone lesions, onion skin appearance of the periosteum

Management

- flucloxacillin for 6 weeks
- clindamycin if penicillin-allergic
- Beta-lactams and vancomycin are commonly used as initial empiric therapy.
- *Osteomyelitis from contiguous spread of infection*
 - ⇒ *Piperacillin-tazobactam*
 - ⇒ *Patients with penicillin allergy* → Clindamycin or metronidazole plus ciprofloxacin
 - ⇒ If MRSA is suspected: → Add vancomycin (or linezolid if allergic to vancomycin)

Skull base osteomyelitis

- Risk factors
 - ⇒ Usually osteomyelitis of the skull is **preceded by a local infection**, for example:
 - Sinusitis extending to the sphenoid sinuses and involving frontal bone may have serious complications such as cavernous sinus thrombosis
 - Mastoid cell infection and occipital bone osteomyelitis
 - Necrotising otitis externa, complicated by petrous bone osteomyelitis with cranial nerve involvement (most common site of skull base osteomyelitis).
 - ⇒ people with compromised immunity (**eg: diabetic patient with otitis externa**)
- Causative pathogens
 - ⇒ Pseudomonas aeruginosa is the causative pathogen.
 - ⇒ Less common pathogens are *Proteus mirabilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*.
- Features
 - ⇒ The clinical scenario depends on the affected part of the skull base in its most common form, that is, petrous bone involvement.
 - ⇒ Patients suffer from **chronic otitis externa with otalgia and otorrhoea**, which, if **untreated**, **progress** and cause **unilateral headache, cranial nerve palsies, most**

commonly IX, X, XI (jugular foramen content) and include also XII nerve form, Villaret's syndrome.

- **Investigations**

- **Investigations**
 - ⇒ The usual biochemical picture is raised erythrocyte sedimentation rate (ESR) and normal white cell count (WCC) and C reactive protein (CRP).
 - ⇒ The typical imaging finding are signs of bone destruction especially clivus, shown as hypointensity of bone marrow in the clivus and preclival soft tissue infiltration on MRI T1 weighted images.
 - ⇒ **Diagnosis is confirmed by** fine needle aspiration (FNA) of tissue and cultures.

- **Treatment** with antibiotics.

Discitis

- *Staphylococcus aureus* is the commonest cause of bacterial discitis in adults.
- infection should be considered for patients with a history of **fever**, weight loss, and **non-mechanical back pain** (i.e., pain that occurs even without motion, particularly at rest and at night); hx of intravenous drug use, **immunosuppression**, or **diabetes**
- **localised tenderness** present particularly with percussion;
- neurological findings absent

Differential diagnosis

- epidural abscess
 - ⇒ Unlike discitis, epidural abscess presents with neurological signs in the lower limbs.
- Osteoporotic spinal fracture
 - ⇒ Osteoporotic spinal fractures present with acute pain, however in these patients the plain x ray film demonstrates vertebral collapse.
- Acutely painful spinal metastases are unlikely in the absence of plain film x ray changes.

Osteomalacia

The symptoms of proximal bone pain with hypocalcaemia and low phosphate suggest a diagnosis of osteomalacia

↓↓ Ca ↓↓ P ↓ vit D + ↑↑ ALP → osteomalacia

Basics

- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion
- occurs more commonly in patients of **South Asian origin**, particularly those who have a cultural tendency to spend more time inside.
- more common in ethnic groups who are dark-skinned, or cover themselves up so that cholesterol cannot be converted to vitamin D in the skin.
- Asians who eat chapattis are also at risk, as the phytic acid in the chapattis chelates vitamin D and calcium
- European ethnic origin is associated with a reduced risk of osteomalacia versus populations with increased skin pigmentation.

Causes

- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- vitamin D resistant; inherited
- renal failure
- liver disease, e.g. cirrhosis

- drug induced e.g. anticonvulsants
- **Mercury poisoning** or any heavy metal poisoning causes an acquired Fanconi syndrome with proximal (type 2) renal tubular acidosis.

Features

- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia:
 - ⇒ bone pain, particularly around the hips and lower back,
 - ⇒ fractures,
 - ⇒ muscle tenderness,
 - ⇒ proximal myopathy

Investigation

- low calcium, phosphate, 25(OH) vitamin D
- raised alkaline phosphatase as it is released from bone reflecting osteoblastic activity.
- Serum PTH is also usually elevated and normalises gradually on response to treatment.
- There is also acidosis which is caused by the inhibition of phosphate, bicarbonate, and sodium reabsorption by PTH.
- x-ray:
 - ⇒ children - cupped, ragged metaphyseal surfaces;
 - ⇒ adults - translucent bands (**Looser's zones (Linear areas of low density)** (pseudofractures))
 - Looser's zones characterised by **low-density bands extending from the cortex inwards in the shafts of long bones.**

Treatment

- calcium with vitamin D tablets

May 2013 exam: A 58-year-old woman C/O aches and pains in her bones. Generally weak and lethargic. Low calcium, phosphate and vitamin D levels combined with a raised alkaline phosphatase and parathyroid hormone level. What is the most appropriate management?

- ⇒ Start vitamin D3 supplementation ($\Delta \rightarrow$ osteomalacia)

Osteopetrosis

Overview

- also known as marble bone disease
- rare disorder of **defective osteoclast function** resulting in failure of normal bone resorption
- results in dense, thick bones that are prone to fracture
- bone pains and neuropathies are common.
- calcium, phosphate and ALP are normal
- stem cell transplant and interferon-gamma have been used for treatment

Osteoporosis

In osteoporosis, there is **decreased bone mass**, but mineralization is normal.

Causes

- unknown (95%)
- **Advancing age and female sex.**

⇒ Prevalence increases from 2% at 50 years to more than 25% at 80 years in women.

Risk factors: the most 'important' ones are risk factors that are used by major risk assessment tools such as FRAX:

- history of glucocorticoid use
- rheumatoid arthritis
- alcohol excess
- history of parental hip fracture (**family history of osteoporotic fracture**)
- low body mass index
- current smoking

Other risk factors

- sedentary lifestyle
- premature menopause
 - ⇒ Early menarche and late menopause are associated with reduced risk of fracture.
- Caucasians and Asians
- endocrine disorders: hyperthyroidism, hypogonadism (e.g. Turner's, testosterone deficiency), growth hormone deficiency, hyperparathyroidism, diabetes mellitus
- multiple myeloma, lymphoma
- gastrointestinal disorders: inflammatory bowel disease, malabsorption (e.g. Coeliac's), gastrectomy, liver disease
- chronic kidney disease
- osteogenesis imperfecta, homocystinuria

Risk factors for post-menopausal osteoporosis, include

- Early onset (<45 years) menopause
- Absence of hormone replacement therapy, calcium and vitamin D supplementation and
- Low body weight.

Medications that may worsen osteoporosis (other than glucocorticoids):

- SSRIs
- antiepileptics
- proton pump inhibitors
- glitazones
- long term heparin therapy
- aromatase inhibitors e.g. anastrozole (used for breast cancer in postmenopausal women and gynecomastia in men. aromatase, which converts androgens into estrogens by a process called aromatization.)

feature

- Classically, osteoporosis in the absence of fracture, **does not cause pain**. Many patients with osteoporosis have concomitant disorders such as osteomalacia and osteoarthritis which cause bone pain.
- Patients with osteoporosis may have no warning signs until the first **fracture** occurs.
- Gradual height loss and dorsal kyphosis may result from microfractures or complete fractures of vertebral bodies.

Investigations for secondary causes

If a patient is diagnosed with osteoporosis or has a fragility fracture further investigations may be warranted. NOGG recommend testing for the following reasons:

- exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);
- identify the cause of osteoporosis and contributory factors;
- assess the risk of subsequent fractures;
- select the most appropriate form of treatment

The following investigations are recommended by NOGG:

- History and physical examination
- Blood cell count, sedimentation rate or C-reactive protein, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
- Thyroid function tests
- Bone densitometry (DXA)

Other procedures, if indicated

- Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
- Protein immunoelectrophoresis and urinary Bence-Jones proteins
- 25OHD
- PTH
- Serum testosterone, SHBG, FSH, LH (in men),
- Serum prolactin
- 24 hour urinary cortisol/dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies (coeliac disease)

- Isotope bone scan
- Markers of bone turnover, when available
- Urinary calcium excretion

So from the first list we should order the following bloods as a minimum for all patients:

- full blood count
- urea and electrolytes
- liver function tests
- bone profile
- CRP
- thyroid function tests

DEXA scan

Basics

- T score: based on bone mass of young reference population (compare the patient's bone mineral density (BMD) with that of a healthy young adult)
- T score of -1.0 means bone mass of one standard deviation below that of young reference population
- Z score is adjusted for age, gender and ethnic factors (Z-scores compare the individual's BMD with that of a population of peers)
 - ⇒ The Z-score is not routinely used in the diagnosis of osteoporosis
 - ⇒ It can be used to investigate the possibility of osteoporosis in premenopausal women, men under the age of 50 and children.
 - ⇒ It is most useful when the bone mineral density is less than 2 standard deviations below the normal.

T score

- > -1.0 = normal
- -1.0 to -2.5 = osteopaenia
- < -2.5 = osteoporosis

Osteoporosis diagnosis according to the WHO and International Osteoporosis Foundation criteria:

diagnosis	T score	definition
normal	(≥ -1)	hip BMD greater than the 1 SD below the young adult reference mean
osteopaenia	(-1 to -2.5)	hip BMD between 1 and 2.5 SD below the young adult reference mean
osteoporosis	(≤ -2.5)	hip BMD 2.5 SD or more below the young adult reference mean
Severe osteoporosis	(≤ -2.5 PLUS fracture)	hip BMD 2.5 SD or more below the young adult reference mean + one or more fragility fractures

May
2016

What percentage of young adults have a T score between -2.0 to +2.0?

95%

The T score is calculated based on the young adult mean bone density. Given bone density is normally distributed, a T score between -2.0 and +2.0 spans two standard deviations above and below the mean, which covers 95% of the population.

- 5% of young adults lie outside the boundaries of T score -2.0 to +2.0
- 2.5% of young adults have a T score above +2.0 & 2.5% of young adults have a T score below -2.0
- 99.7% of young adults have a T score between -3.0 to +3.0
- 68% of young adults have a T score between -1.0 to +1.0

Osteoporosis: glucocorticoid-induced

- Steroids cause a decrease in calcium absorption from the gut, increased urinary calcium excretion, and also causes bone resorption, resulting in osteoporosis.
- The risk ↑↑ with prednisolone 7.5mg a day for 3 or more months.
- patients should be managed in an anticipatory, i.e. if it likely that the patient will have to take steroids for at least 3 months then we should start bone protection straight away, rather than waiting until 3 months has elapsed.
- A good example is a patient with newly diagnosed polymyalgia rheumatica. As it is very likely they will be on a significant dose of prednisolone for greater than 3 months bone protection should be commenced immediately.

Management of patients at risk of corticosteroid-induced osteoporosis

The RCP guidelines divide patients into two groups.

1. age > 65 years **or** H/O previously fragility fracture → give bone protection.
 - ⇒ Fragility fracture - defined by The WHO as resulting from a mechanical force equivalent to a fall from standing height or less which should not ordinarily cause a fracture.
2. age < 65 years → bone density scan

T score	Management
Greater than 0	Reassure
Between 0 and -1.5	Repeat bone density scan in 1-3 years
Less than -1.5	Offer bone protection

The first-line treatment is alendronate. Patients should also be calcium and vitamin D replete.

Osteoporosis: Assessing patients following a fragility fracture

- The management of patients following a fragility fracture depends on age.

Patients ≥ 75 years of age

- Patients ≥ 75 years + fragility fracture → start first-line therapy (an oral bisphosphonate), **without DEXA scan**.
- For example, a 79-year-old woman falls over on to an outstretched hand and sustains a Colles' fracture (fracture of the distal radius). Given her age she is presumed to have osteoporosis and therefore started on oral alendronate 70mg once weekly. No DEXA scan is arranged.
- the 2014 NOGG guidelines have a different threshold, suggesting treatment is started in all women > 50 years who've had a fragility fracture - '*although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women.*'

Patients < 75 years of age

- patient < 75 years + fragility fracture → DEXA scan should be arranged.
- These results can then be entered into a FRAX tool to assess ongoing fracture risk.

Osteoporosis: assessing risk

Osteoporosis in a man - check testosterone

Who should be assessed for fragility fracture?

- all women aged ≥ 65 years and all men aged ≥ 75 years.
- Younger patients + presence of risk factors, such as:

- ⇒ previous fragility fracture
- ⇒ current use or frequent recent use of oral or systemic glucocorticoid
- ⇒ history of falls
- ⇒ family history of hip fracture
- ⇒ other causes of secondary osteoporosis
- ⇒ low body mass index (BMI) (< 18.5 kg/m²)
- ⇒ smoking
- ⇒ alcohol (> 14 units/week for women and > 21 units/week for men).

Methods of risk assessment

- NICE recommend using a clinical prediction tool such as FRAX or Q Fracture to assess a patient's 10-year risk of developing a fracture. This is analogous to the cardiovascular risk tools such as QRISK.

FRAX

- estimates the 10-year risk of fragility fracture
- valid for patients aged 40-90 years
- based on international data so use not limited to UK patients
- assesses the following factors:
 1. age,
 2. sex,
 3. weight,
 4. height,
 5. previous fracture,
 6. parental fracture,
 7. current smoking,
 8. glucocorticoids,
 9. rheumatoid arthritis,
 10. secondary osteoporosis,
 11. alcohol intake
- bone mineral density (BMD) is optional, but clearly improves the accuracy of the results.
- NICE recommend arranging a DEXA scan if FRAX (without BMD) shows an intermediate result

Q Fracture

- estimates the 10-year risk of fragility fracture
- developed in 2009 based on UK primary care dataset
- can be used for patients aged 30-99 years (this is stated on the Q Fracture website, but other sources give a figure of 30-85 years)
- includes a larger group of risk factors e.g. cardiovascular disease, history of falls, chronic liver disease, rheumatoid arthritis, type 2 diabetes and tricyclic antidepressants

DEXA scan

- There are some situations where NICE recommend arranging BMD assessment (i.e. a DEXA scan) rather than using one of the clinical prediction tools:
 - ⇒ before starting treatments that may have a rapid adverse effect on bone density (for example, sex hormone deprivation for treatment for breast or prostate cancer).
 - ⇒ in people aged under 40 years who have a major risk factor, such as history of multiple fragility fracture, major osteoporotic fracture, or current or recent use of high-dose oral or high-dose systemic glucocorticoids (more than 7.5 mg prednisolone or equivalent per day for 3 months or longer).
- Indicators of low BMD are:
 - ⇒ low body mass index (defined as less than 22 kg/m²),
 - ⇒ medical conditions such as ankylosing spondylitis, Crohn's disease,
 - ⇒ conditions that result in prolonged immobility, and
 - ⇒ untreated premature menopause

Interpreting the results of FRAX

- If the FRAX assessment was done **without a bone mineral density (BMD) measurement** the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:
 - low risk: reassure and give lifestyle advice
 - intermediate risk: offer BMD test
 - high risk: offer bone protection treatment
- If the FRAX assessment was done **with a bone mineral density (BMD) measurement** the results (10-year risk of a fragility fracture) will be given and categorised automatically into one of the following:
 - reassure
 - consider treatment
 - strongly recommend treatment
- If you use Q Fracture instead patients are not automatically categorised into low, intermediate or high risk. Instead the 'raw data' relating to the 10-year risk of any sustaining an osteoporotic fracture. This data then needs to be interpreted alongside either local or national guidelines, considering certain factors such as the patient's age.

When should we reassess a patient's risk (i.e. repeat the FRAX/Q Fracture)?

- if the original calculated risk was in the region of the intervention threshold for a proposed treatment and only after a minimum of 2 years, or
- when there has been a change in the person's risk factors

Osteoporosis: management

- **secondary prevention of osteoporotic fractures in postmenopausal women (NICE guidelines 2008). Key points include**
 - osteoporotic fragility fractures in postmenopausal women + confirmed osteoporosis (a T-score of -2.5 SD or below) → treatment.
 - In women aged ≥ 75 years, a DEXA scan may not be required
 - vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
 - **If osteoporosis is established, the treatment includes 1500 mg/day of calcium and 400-800 pg /day of vitamin D**
 - Dietary intake of calcium should be:
 - ❖ 800-1000 mg/day in childhood through early adulthood
 - ❖ 1000-1200 mg/day in the middle years
 - ❖ 1500 mg/day in the elderly
 - **alendronate is first-line**
 - around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
 - strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)
- **Treatment criteria for patients not taking alendronate:** for patients who do not tolerate alendronate, the most important thing to remember is:
 - the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
 - if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
 - the strictest criteria are for denosumab

Supplementary notes on treatment

- **Bisphosphonates**
 - ⇒ **Oral bisphosphonates** (alendronate acid, ibandronic acid and risedronate sodium) are recommended for treating osteoporosis only if:
 - the 10- year probability of osteoporotic fragility fracture is **at least 1%**.
 - ⇒ **Intravenous bisphosphonates** (ibandronic acid and zoledronic acid) are recommended for treating osteoporosis only if:
 - the 10- year probability of osteoporotic fragility fracture is **at least 10% or**
 - the 10- year probability of osteoporotic fragility fracture is at least 1% **and** the person has difficulty taking oral bisphosphonates (alendronate acid, ibandronic acid or risedronate sodium) or these drugs are contraindicated or not tolerated.
 - ⇒ alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
 - ⇒ reduce the risk of both vertebral and non-vertebral fractures
 - ⇒ alendronate, risedronate may be superior to etidronate in preventing hip fractures
 - ⇒ Alendronate acid
 - tablets, 10 mg once a day
 - tablets, 70 mg once a week
 - ⇒ Risedronate sodium
 - tablets, 5 mg once a day
 - tablets, 35 mg once a week
 - ⇒ Etidronate is an oral bisphosphonate
 - administered in 90-day cycles, with each cycle consisting of etidronate (400 mg/day) for 14 days followed by calcium carbonate (1.25 g/day) for the remaining 76 days.
 - ⇒ Zoledronic acid
 - intravenous infusion, 50 micrograms/ml once a year
 - ⇒ ibandronate is a once-monthly oral bisphosphonate
 - ⇒ Ibandronic acid:
 - tablets, 150 mg once a month
 - injection, 3 mg/ml once every 3 months
 - ⇒ Instructions for administration
 - Alendronate and risedronate must be taken with 200 ml and 120 ml of water, respectively.
 - Before and immediately after administration patients should not eat or drink, and must remain upright for stipulated time periods.
 - Etidronate should be taken with water at the midpoint of a 4-hour fast (that is, 2 hours after and 2 hours before food, vitamins with mineral supplements such as iron, calcium supplements, laxatives containing magnesium, or antacids containing calcium or aluminium).
 - ⇒ **contraindicated in patients with a GFR less than 35 ml/min**
 - Data from randomised controlled trials supports use of bisphosphonates down to GFRs as low as 30-35 ml/min. Below this level RCT evidence is unavailable, and the risk of adynamic bone disease associated with renal impairment is significantly elevated.
 - ⇒ **Bisphosphonate induce osteonecrosis of the jaw** (associated with dental extraction surgery and increased with underlying malignancy, especially multiple myeloma)
 - Most cases have been associated with **zoledronic acid** and pamidronate given intravenously for metastatic bone disease.
 - The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.
 - Dental disease is a recognised predisposing factor.

- The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.
- **Vitamin D and calcium**
 - ⇒ poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients
- **Raloxifene - selective oestrogen receptor modulator (SERM)**
 - ⇒ (SERMs) are drugs with selective activity in various organ systems, acting as weak oestrogen-receptor agonists in some systems and as oestrogen antagonists in others.
 - ⇒ prevent bone loss
 - ⇒ reduce risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
 - ⇒ increase bone density in the spine and proximal femur
 - ⇒ less effective in preventing loss of bone mineral density versus bisphosphonates or denosumab.
 - ⇒ disadvantages
 - may worsen menopausal symptoms
 - increased risk of thromboembolic events
 - ⇒ contraindicated in:
 - history of venous thromboembolism (VTE),
 - hepatic impairment,
 - cholestasis,
 - severe renal impairment,
 - unexplained uterine bleeding or endometrial cancer.
 - Raloxifene should not be co-administered with systemic oestrogens,
 - in patients with breast cancer it should not be used for osteoporosis treatment or prevention until treatment of the breast cancer, including adjuvant treatment, has been completed.
 - ⇒ advantage:
 - may decrease risk of breast cancer
- **Strontium ranelate**
 - ⇒ Action
 - 'dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
 - ⇒ Indication
 - secondary prevention of osteoporotic fragility fractures in postmenopausal women who are:
 - ❖ unable to take alendronate and risedronate due to contraindication, intolerance or unable comply with the special instructions for the administration. **And**
 - ❖ have a combination of T-score, age and number of independent clinical risk factors for fracture (see denosumab indications below).
 - ⇒ Dose and administration
 - The dose is 2 g once daily in water, preferably at bedtime.
 - **Advice to avoid food for 2 hours before and after taking granules**, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules.
 - Treatment with strontium ranelate should be discontinued during treatment with oral tetracycline or quinolone antibiotics.
 - it is not recommended in patients with severe renal impairment
 - should be used with caution in patients at increased risk of VTE.

⇒ Disadvantages

- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care
- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- **increased risk of cardiovascular events:** any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
- **increased risk of thromboembolic events:** a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

● Denosumab

- ⇒ human monoclonal antibody that **inhibits RANK ligand**, which in turn **inhibits the maturation of osteoclasts**
 - RANK occurs on the surface of osteoclast precursors and osteoclasts. Inhibiting it leads to reduced osteoclast formation, function and survival. This leads to reduced bone reabsorption in both cortical and trabecular bone.
- ⇒ given as a single subcutaneous injection **every 6 months**
 - therefore, tolerated by patients who don't want a daily subcutaneous injection
 - ⇒ initial trial data suggests that it is effective and well tolerated
 - ⇒ (NICE guidelines 2010) state that: it is recommended only in postmenopausal women at increased risk of fractures:
 - who are unable to comply with alendronate and either risedronate or etidronate, or have an intolerance of, or a contraindication to, those treatments **and**
 - ❖ who have a combination of T-score, age and number of independent clinical risk factors for fracture
 - ❖ **independent clinical risk factors for fracture are:**
 - ⇒ parental history of hip fracture,
 - ⇒ alcohol intake of 4 or more units per day, and
 - ⇒ rheumatoid arthritis.
 - ⇒ The recommended dosage is 60 mg subcutaneous **injection once every 6 months**.
 - ⇒ Side effects:
 - Like bisphosphonates it is associated with **osteonecrosis of the jaw**, but **not other adverse events such as reflux oesophagitis**.
 - The risk of a dynamic bone disease may be less for denosumab versus bisphosphonates because it does not accumulate in bone.

● Teriparatide

- ⇒ is a recombinant fragment of human parathyroid hormone and, as an anabolic agent, it stimulates new formation of bone and increases resistance to fracture.
- ⇒ Action
 - **Increased osteoblast activity** (the main effect)
 - **increased calcium absorption from the gut and**
 - **reduced calcium excretion from the kidney.**
- ⇒ Indications
 - an alternative treatment option for the secondary prevention of osteoporotic fragility fractures in postmenopausal women who are:

- ❖ unable to take alendronate and risedronate, or strontium ranelate due to contraindication, intolerance or unsatisfactory response **and**
 - ❖ age \geq 65 years and have a T-score of ≤ -4.0 SD, **or** a T-score of ≤ -3.5 SD **plus** more than two fractures, **or**
 - ❖ age 55–64 years and have a T-score of ≤ -4 SD **plus** more than two fractures.
- ⇒ Disadvantage
- Although this synthetic parathyroid hormone (PTH) analogue is an effective option for the treatment of severe osteoporosis, it is a **daily injectable**, and therefore, not considered by many patients, particularly those who don't likely injectables.
- ⇒ Dose
- The recommended dose is 20 micrograms administered once **daily** by subcutaneous injection in the thigh or abdomen.
 - the maximum total duration of treatment was restricted, by the marketing authorisation, to 18 months.
- ⇒ Contraindications include:
- pre-existing hypercalcaemia,
 - severe renal impairment,
 - metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of bone),
 - unexplained elevations of alkaline phosphatase, and
 - previous radiation treatment to the skeleton.
- **Hormone replacement therapy**
 - ⇒ has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
 - ⇒ due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms
 - **Hip protectors**
 - ⇒ evidence to suggest significantly reduce hip fractures in nursing home patients
 - ⇒ compliance is a problem
 - **Falls risk assessment**
 - ⇒ no evidence to suggest reduced fracture rates
 - ⇒ however, do reduce rate of falls and should be considered in management of high risk patients

Raloxifene and teriparatide are second line treatments if bisphosphonates are not tolerated, ineffective or unsuitable for the patient.

(Ref: NICE guidelines . Last updated: 09 August 2017)

Pathophysiology of bone diseases

- **Osteoporosis** → decreased bone mass, but mineralization is normal.
- **Osteomalacia** → Decreased bone mineralization (due to vitamin D deficiency)
- **Paget's disease** → Disorder of bone remodeling (excessive bone resorption, followed by disorganized bone formation occurs, producing thickened but weak bone.)

Paget's disease of the bone

Paget's disease - old man, bone pain, raised ALP

The constellation of bony pain, unilateral hearing loss, and an isolated raised ALP should point you in the direction of Paget's disease of the bone.

Disease localization

- most commonly involves the axial skeleton, **the pelvis being the most common**, but it can affect any area.
- In the majority of patients, the disease affects at least two bones**, but in one third of patients only one bone is affected.

Epidemiology

- Second most prevalent skeletal disease after osteoporosis
- (UK prevalence 5%) but symptomatic in only 1 in 20 patients
- more common in men (sex ratio 3:2 men: women).
- Age of onset: > 55 years

Pathophysiology

- increased but uncontrolled bone turnover
- It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity.**
- it is a focal disorder of bone remodelling characterized by an increase in the number and size of osteoclasts in affected skeletal sites while the rest of the skeleton is spared.
- ↑osteoclasts → ↑bone resorption → subsequent increase in new bone formation and altered bone architecture.
- The structure of the new bone is disorganized and mechanically weaker and therefore liable to pathological fracture and deformity.

Predisposing factors

- increasing age
- male sex
- northern latitude
- family history

Clinical features - only 5% of patients are symptomatic

- most commonly no symptoms.**
 - ⇒ The diagnosis is typically found incidentally on radiographs and laboratory investigations.
 - ⇒ Paget disease should be considered in an asymptomatic patient who presents with isolated ALP elevation that cannot be explained by any other means (e.g., cholestasis or bone metastases)
- bone pain (e.g. pelvis, lumbar spine, femur)
 - ⇒ **Bone pain is typically increased with rest and on weight bearing.**
 - ⇒ Unlike osteoarthritis, pagetic bone pain usually increases with rest, on weight bearing, when the limbs are warmed, and at night.
- classical, untreated features: bowing of tibia, bossing of skull

Complications

- deafness (cranial nerve entrapment)
 - ⇒ In the skull, the 8th nerve can be compressed, resulting in hearing loss. This is one of the more common complaints, being present in 37% of respondents in a recent survey of 2000 patients with Paget's disease .

- **bone sarcoma** (1% if affected for > 10 years)
 - ⇒ Although the risk of osteogenic sarcoma is 30 times that of patients without Paget's, the risk of sarcoma development is still small → **Less than 1%**
 - ⇒ Symptoms of osteogenic sarcoma include increased pain localised to one particular area and pathological fracture.
 - ⇒ tumor arising from mesenchymal stem cells (osteoblasts)
 - ⇒ Most common primary bone malignancy
 - ⇒ x-ray
 - **Sunburst appearance of lytic bone lesions** and/or codman triangles (a ridge of sub-periosteal new bone is raised by an underlying tumor)
 - ⇒ Treatment
 - Surgery (definitive resection) with adjuvant polychemotherapy
 - usually resistant to radiation therapy
- Pathological fractures
- Spinal cord compression
- skull thickening
 - ⇒ (A classic symptom: a hat which no longer fits)
- high-output cardiac failure
 - ⇒ (due to AV shunts in bone)

Diagnosis

- Raised alkaline phosphatase (ALP) - **calcium* and phosphate are typically normal**
 - ⇒ **the Best initial test**
 - ⇒ * **calcium** is usually normal but hypercalcaemia may occur with prolonged immobilisation
- X-ray:
 - ⇒ eg: (skull x-ray) thickened vault, osteoporosis circumscripta
 - ⇒ Osteolysis and new bone formation typical of the disease.
 - ⇒ **Radiographic features** in the mixed lytic and sclerotic phase of Paget's disease include:
 - bone expansion,
 - cortical thickening and
 - **trabecular bone thickening**.
- **the best investigation to confirm the diagnosis → Skeletal survey**
 - ⇒ Recent evidence has suggested that limited **skeletal survey is superior to bone scan** for the assessment of the disease because, when there is significant osteoclastic resorption of bone, **bone scanning underestimates the extent of disease activity and still requires plain radiography for confirmation.**
- Bone biopsy
 - ⇒ abnormal "**mosaic**" pattern in woven and lamellar bone.

Treatment

- **Indications for treatment include:**
 - ⇒ **bone pain**,
 - ⇒ **skull or long bone deformity**,
 - ⇒ **fracture**,
 - ⇒ **periarticular Paget's**
- **The mainstay of treatment for Paget's disease is bisphosphonate therapy**, which is proven to **relieve symptoms of pain** and has been shown to **reduce the risk of pathological fracture** in long bones **and complications of Paget's such as deafness**.
 - **bisphosphonate (either oral risedronate or IV zoledronate)**
 - Unless contraindicated, all patients on bisphosphonates should be given supplements of calcium and Vitamin D to avoid symptomatic hypocalcaemia.
 - ⇒ In patients who cannot tolerate these, calcitonin is second-line therapy.
 - calcitonin is less commonly used now

- the most appropriate way to monitor disease activity is → 6-monthly alkaline phosphatase levels



The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.

Paget's Disease




X-ray of affected bones show
Cortical thickening with a coarse
Thickened trabecular pattern

Often called "cotton wool"
Appearance

Mixed areas of radiolucency &
radiopaque areas

Penicillamine

Mechanism of action

- largely unknown
- thought to reduce IL-1 synthesis and prevent the maturation of newly synthesized collagen

Uses

- rheumatoid arthritis

Adverse effects

- rashes
- disturbance of taste
- proteinuria

Pseudogout

Pseudogout - positively birefringent rhomboid shaped crystals

Chondrocalcinosis in a question is most likely to indicate → **Pseudogout**

Definition

- Pseudogout is a form of microcrystal synovitis **caused by the deposition of calcium pyrophosphate dihydrate in the synovium**

Risk factors

- hyperparathyroidism
- hypothyroidism
- haemochromatosis
- acromegaly
- low magnesium, low phosphate
- Wilson's disease

Features

- knee, wrist and shoulders most commonly affected
- joint aspiration:
 - ⇒ Polar light microscopy: weakly-positively birefringent **rhomboid shaped crystals**
 - ⇒ Synovial fluid findings: 10,000-50,000 WBCs/ μ L with > 90% neutrophils
- x-ray: chondrocalcinosis
 - ⇒ (cartilage called due to deposition of calcium pyrophosphate dihydrate crystals in the large joints, particularly the knees.)

Management

- aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

Psoriatic arthropathy

If first-degree relatives of patients with psoriasis have joint problems, psoriatic arthritis should be considered

- Chronic progressive seronegative inflammatory arthritis occurring in patients with underlying psoriasis.
- most commonly a seronegative **oligoarthritis** found in patients with psoriasis
 - ⇒ **Oligoarthritis** (most common, accounting for 70% of cases)
- autoimmune disease , associated with an increased frequency of **HLA-B7 and HLA-B27**.

Epidemiology

- affects men and women equally
- the range of age of onset between 35–55 years.
- Around 10-20% percent of patients with skin lesions develop an arthropathy**

Types

- Five subsets of psoriatic arthritis have been described based on the pattern of joint involvement, with an increased prevalence of the **spondylitic form in males** and the **rheumatoid form in females**.
 - asymmetric oligoarthritis (most common) (43%).
 - symmetric polyarthritis (33%)
 - proximal interphalangeal joint involvement.

- 3. sacroilitis
- 4. DIP joint disease
 - associated with nail pitting, and onycholysis (separation of nail from nail bed)
- 5. arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers') (rare)

The relation between skin lesion and Psoriatic arthritis

- **Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions.**
 - ⇒ Psoriasis precede psoriatic arthritis in 60-80% of patients (usually by less than 10 years)
 - ⇒ **In 15-20% of patients, arthritis appears before the psoriasis**
 - Small plaques should be looked for on the elbows and scalp.

Feature

- Psoriatic arthritis tends to affect the **distal interphalangeal joints (DIP)**.
- can present with or without associated psoriatic skin lesions or only with nail malformations.
- If no obvious skin lesions are visible, the clinician must look for psoriasis in hidden sites such as the scalp, intergluteal cleft and umbilicus.
- Nail involvement includes onycholysis, transverse ridging and nail pitting.
- vertebrae may be asymmetrically affected and there may be involvement of the atlantoaxial joint with erosion of the odontoid and consequent subluxation.
- Dactylitis with sausage digits is seen in 35% of patients
- **Extra-articular features include:**
 - ⇒ **Ocular involvement may occur in 30% of patients, including:**
 - conjunctivitis (in 20%)
 - acute anterior uveitis (in 7%);
 - ❖ in patients with uveitis, 43% have sacroiliitis
 - ⇒ **Synovitis affecting flexor tendon sheaths**, (with sparing of the extensor tendon sheath)

Investigations

- ↑ (ESR) and C-reactive protein level
- Negative rheumatoid factor
- Low levels of circulating immune complexes (in 56% of patients)
- High Serum immunoglobulin A levels (in two thirds of patients)
- **Radiography**
 - ⇒ **asymmetric "pencil-in-cup" deformity** in the distal interphalangeal joints of the fingers.

Diagnostic criteria

- established inflammatory articular disease with at least 3 points from the following features:
 1. Current psoriasis (assigned a score of 2)
 2. history of psoriasis (in the absence of current psoriasis; assigned a score of 1)
 3. **family history of psoriasis** (in the absence of current psoriasis and history of psoriasis; assigned a score of 1)
 4. Dactylitis (assigned a score of 1)
 5. Juxta-articular new-bone formation (assigned a score of 1)
 6. RF negativity (assigned a score of 1)
 7. Nail dystrophy (assigned a score of 1)

Differential diagnosis

- The condition can be distinguished from the sacroilitis seen in ankylosing spondylitis by the presence of the other clinical signs in the nails and the skin and by differences in the patterns of vertebral involvement.

- Polyarticular psoriatic arthritis distinguished from rheumatoid arthritis by:
 - presence of dactylitis and
 - absence of anticyclic citrullinated peptide antibodies.

Management

- treat as rheumatoid arthritis but better prognosis
- limited disease → NSAIDs usually sufficient
 - ⇒ **do not prevent progressive joint damage**
- Patients with progressive peripheral arthritis (polyarthritis, joint erosions) or oligoarthritis refractory to NSAIDs and/or intra-articular corticosteroids require disease-modifying antirheumatic disease therapy (e.g., methotrexate) early in the disease course.
 - ⇒ **methotrexate will improve both the joint and skin problems**
- Sulfasalazine** is safe to use in pregnancy and there is no need to stop it.
 - ⇒ **Sulphasalazine tends to only improve joint symptoms and not improve the psoriasis.**
- Tumour necrosis factor (TNF)-alpha inhibitors may be considered as **second-line** therapy for most disease manifestations.
 - ⇒ If not respond to an adequate trial of two DMARDs (for example, leflunomide, methotrexate, sulfasalazine) → **anti-TNF agents**
- Apremilast** (Nice guidelines February 2017)
 - ⇒ phosphodiesterase 4 (PDE4) inhibitor.
 - ⇒ ↓ anti-inflammatory cytokines and mediators associated with psoriatic arthritis (including [TNF]-alpha and interleukin [IL]-23).
 - ⇒ Apremilast, alone or in combination with (DMARDs), is recommended for psoriatic arthritis only if:
 - they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
 - not responded to adequate trials of at least 2 standard DMARDs.
 - ⇒ Adverse effects
 - (GI) disorders (most commonly diarrhoea and nausea);
 - upper respiratory tract infections;
 - headache; and tension headache.
 - ⇒ Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate response
- Hydroxychloroquine → exacerbate psoriatic skin lesions
- In patients with cutaneous psoriasis, systemic corticosteroids predispose to pustular psoriasis, and may result in a flare of skin psoriasis when they are stopped.



Notice the nail changes on this image as well



X-ray showing some of changes seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular perostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.



Psoriasis involvement of the nail produces pitting and yellowing, which can be mistaken for onychomycosis.



This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progression towards a 'pencil-in-cup' changes.

Reactive arthritis (Reiter syndrome)

Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

'Can't see, pee or climb a tree'

Urethritis + arthritis + conjunctivitis = reactive arthritis

- Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.
⇒ the presence of bacterial infection on joint aspiration would count against it.
- Reactive arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies.
- It encompasses **Reiter's syndrome**, a term which described a classic triad of urethritis, **conjunctivitis** and arthritis following a dysenteric illness during the Second World War.
- Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA).

Eye diseases in Reiter's syndrome:

- **Most common** → conjunctivitis (50%)
- **Less common** → iritis (12%)

Epidemiology

- post-STI form much more common in men (e.g. 10:1)
- post-dysenteric form equal sex incidence

The table below shows the **organisms that are most commonly associated with reactive arthritis:**

Post-dysenteric form	Post-STI form
<i>Shigella flexneri</i> <i>Salmonella typhimurium</i> <i>Salmonella enteritidis</i> <i>Yersinia enterocolitica</i> <i>Campylobacter</i>	<i>Chlamydia trachomatis</i>

Features

- typically develops within 4 weeks of initial infection
⇒ symptoms generally last around 4-6 months
- arthritis is typically an **asymmetrical** oligoarthritis of lower limbs
⇒ mainly affecting the large weight-bearing joints (usually knee and ankle).
- dactylitis
- symptoms of urethritis
- eye:

- ⇒ **conjunctivitis (seen in 50%),**
- ⇒ anterior uveitis
- skin:
 - ⇒ circinate balanitis (painless vesicles on the coronal margin of the prepuce),
 - ⇒ **Keratoderma blenorragica** (waxy yellow/brown papules on palms and soles)

Management

- usually self-limiting
- symptomatic: analgesia, NSAIDS, intra-articular steroids
- sulfasalazine and methotrexate are sometimes used for **persistent disease**

Prevention

- Antibiotics given at the time of the non-gonococcal venereal infection will **reduce the likelihood of that person developing reactive arthritis.**
 - ⇒ Appropriate treatment during the acute stage would be **doxycycline 100 mg bd if Chlamydia infection is confirmed.**

Prognosis

- Prognosis with respect to long-term complications is better when **dysenteric** infection is the precipitant factor rather than **Chlamydial** infection.
- arthritis usually resolves in 3 months
- In general, symptoms last from a few weeks to around 6 months in total.
 - ⇒ symptoms rarely last more than 12 months
- **Around 25% of patients have recurrent episodes**
- **10% of patients develop chronic disease**
- In **HLA-B27-positive** patients, **ankylosing spondylitis** may develop in up to **50%** of patients who have suffered an episode of **reactive arthritis**.
- HIV infection is associated with a higher risk of reactive arthritis
 - ⇒ **HLA-B27** is found in 80–90 % of **Caucasians** with HIV-associated reactive arthritis,
 - ⇒ while studies of **Africans** with HIV-associated reactive arthritis have found nearly all to be **HLA-B27-negative**
- Rarer **long-term complications** include:
 - ⇒ urethral stricture,
 - ⇒ cataracts, and
 - ⇒ aortic root necrosis.



Keratoderma blenorragica

Amyloidosis

Amyloidosis should always be considered in a patient with a long-standing inflammatory and/or infectious disease who presents with kidney, liver, or GI involvement.

Overview

- amyloidosis describes the extracellular deposition of an insoluble **fibrillar protein** termed amyloid
- amyloid also contains a **non-fibrillary protein** called:
 - ⇒ amyloid-P component, derived from the acute phase protein serum amyloid P
 - ⇒ apolipoprotein E
 - ⇒ heparan sulphate proteoglycans
- the accumulation of amyloid fibrils leads to tissue/organ dysfunction

Causes

- Amyloidosis may be inherited or acquired; acquired form is associated with long standing chronic illnesses (DM, Rheumatoid Arthritis).

Feature

- unexplained weight loss,
- fatigue,
- oedema resistant to diuretic therapy.
- joint pains and stiffness, usually upper limbs more than lower limbs.

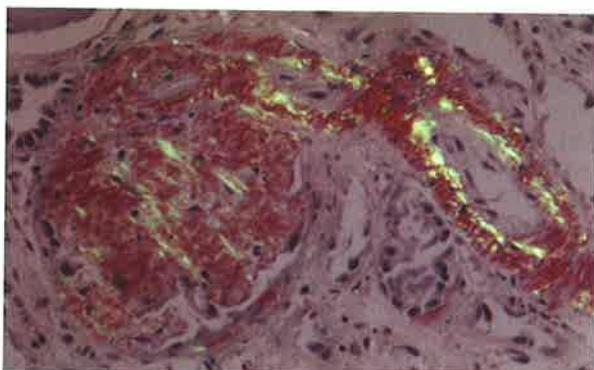
Types

- **Light-chain amyloidosis (AL-amyloidosis)**
 - ⇒ Most common form of amyloidosis in developed nations
 - ⇒ Aetiology:
 - primary disease caused by plasma cell dyscrasias e.g., :
 - ❖ multiple myeloma,
 - ❖ Waldenström's macroglobulinemia,
 - ❖ non-Hodgkin lymphoma
 - ⇒ Pathophysiology:
 - increased production of the light chains of immunoglobulins → deposition of AL (amyloid light chain) protein in various organs
 - ⇒ Features: rapidly progressive clinical course
 - Heart:
 - ❖ restrictive cardiomyopathy,
 - ❖ atrioventricular block
 - ⇒ An ECG is required in all patients to look for conduction abnormalities.
 - Kidney:
 - ❖ nephrotic syndrome,
 - ❖ type II renal tubular acidosis,
 - ❖ nephrogenic diabetes insipidus
 - Tongue:
 - ❖ **macroglossia** → obstructive sleep apnea
 - Nervous system:
 - ❖ Amyloid peripheral neuropathy
 - ⇒ carpal tunnel syndrome
 - ⇒ only seen in AL, never seen in AA
 - ❖ autonomic neuropathy
 - Gastrointestinal tract:
 - ❖ malabsorption
 - **periorbital ecchymoses**
 - **Enlargement of the submandibular salivary glands**

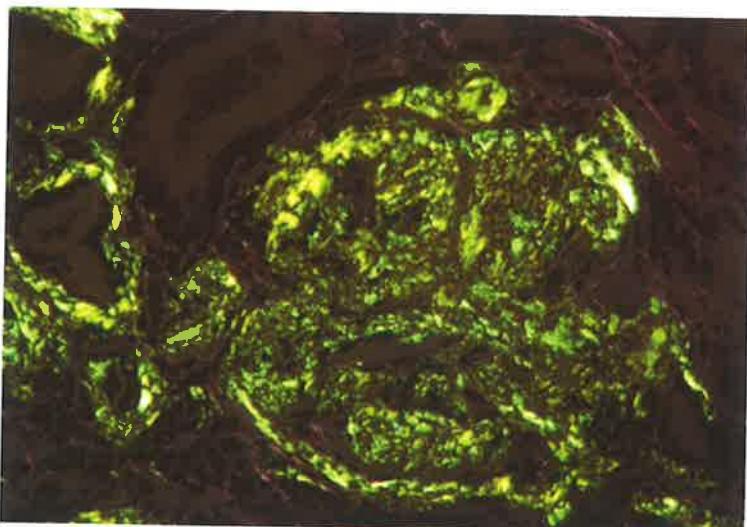
- shoulder pad sign due to periarticular infiltration with amyloid and pseudohypertrophy is specific for AL
 - Bleeding disorders
- **Reactive amyloidosis (AA-amyloidosis)**
 - ⇒ Etiology: secondary disease
 - Chronic inflammatory conditions (e.g., IBD, **rheumatoid arthritis**, SLE, vasculitis)
 - Chronic infectious diseases (e.g., tuberculosis, bronchiectasis, leprosy, osteomyelitis)
 - Certain tumors (e.g., renal cell carcinoma, lymphomas)
 - ⇒ Pathophysiology:
 - chronic inflammatory process → increased production of acute phase reactant SAA (serum amyloid-associated protein) → deposition of **AA** (amyloid-associated) protein in various organs
 - ⇒ Clinical features
 - Kidney: **most common feature → renal involvement**
 - ❖ nephrotic syndrome,
 - ❖ type II renal tubular acidosis,
 - ❖ nephrogenic diabetes insipidus
 - Adrenal glands:
 - ❖ primary adrenal insufficiency
 - Liver and spleen:
 - ❖ hepatomegaly, splenomegaly
 - Gastrointestinal tract:
 - ❖ malabsorption
- **β -2 microglobulin amyloidosis**
 - ⇒ Precursor protein is β -2 microglobulin, part of the major histocompatibility complex
 - ⇒ **Associated with patients on renal dialysis**
 - ⇒ neurological impairment in patients on longstanding dialysis.

Diagnosis

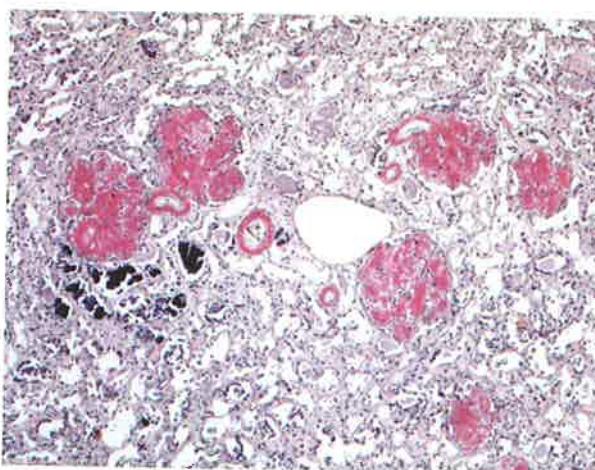
- **Biopsy**
 - ⇒ Biopsy of abdominal wall fat, the **rectum** or a salivary gland can be examined
 - ⇒ The tissue is treated with **Congo red stain** → the amyloid proteins appear **apple-green** birefringence on Light microscopy.
- Tests to diagnose the underlying disease
 - ⇒ Light chain amyloidosis
 - Serum electrophoresis: → monoclonal gammopathy
 - Urine test for Bence-Jones proteins → multiple myeloma
 - ⇒ Reactive amyloidosis: → ESR, CRP, chest x-ray



Renal amyloid with congo red staining - apple-green birefringence



Renal amyloid with congo red staining - apple-green birefringence



Congo red staining. Amyloid deposits are seen in both the arteries/arterioles and within the glomerulus. The deposit of amyloid within the mesangium is not dissimilar to the nodular lesions seen in diabetic nephropathy

Pathological feature of amyloidosis

1. Electron micrography - fibrillar appearance
2. x Ray diffraction pattern - beta pleated sheet structure
3. Haematoxylin and eosin staining - amorphous eosinophilic appearance
4. Congo red histological staining - apple-green birefringence
5. Solubility in water and buffers of low ionic strength.

Treatment

- The only treatment is renal transplantation.
- It can be reduced by using high flux dialysis membranes in patients who are likely to be on dialysis for a prolonged period.

Amyloidosis: cardiac

- Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy, associated with AL Amyloidosis
- **Presentation:** Typical presentation of right heart failure:
 - ⇒ Jugular venous distension
 - ⇒ Peripheral oedema
 - ⇒ Orthopnoea and paroxysmal nocturnal dyspnea are typically absent
- **Diagnosis**
 - ⇒ Combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis.
 - ⇒ **Echocardiographic abnormalities** include:
 - dilatation of atria, thickened interatrial septum, diastolic dysfunction and small-volume ventricles.
 - The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases.
 - Cardiac amyloidosis is associated with a 'global speckled' pattern on echo.



The ECG typically shows low-voltage complexes with poor R wave progression in the chest leads (a pseudoinfarction pattern).

Management of AL

- The most effective treatment is autologous bone marrow transplants with stem cell rescues. However, many patients are too weak to tolerate this approach
- Other treatments can involve application of chemotherapy similar to that used in multiple myeloma. A combination of bortezomib and dexamethasone has been proposed, as has melphalan and dexamethasone.
- Digoxin is contraindicated in cardiac amyloidosis (restrictive cardiomyopathy)

Septic arthritis

Septic arthritis - most common organism: *Staphylococcus aureus*

Septic arthritis: IV flucloxacillin

Causes

- most common organism overall is *Staphylococcus aureus*
 - ⇒ The most likely organisms are staphylococci (70%) and beta-haemolytic streptococci (20%).
- in young adults who are sexually active *Neisseria gonorrhoeae* should also be considered
- The most likely organism to have been aspirated from the **infected hip joint replacement** prosthesis → **Propionibacterium acnes** (PA):
 - ⇒ Gram positive bacilli,

- ⇒ it is poorly virulent,
- ⇒ symptoms of PA infection may occur many years after original arthropathy,
- ⇒ it is sensitive to penicillins, clindamycin and carbapenems.

Feature

- Fifty percent of cases will have an associated bacteraemia.
- Early x-rays are almost always normal.

Management

- synovial fluid should be obtained before starting treatment
- intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends flucloxacillin or clindamycin if penicillin allergic
- antibiotic treatment is normally given for several weeks (BNF states 6-12 weeks)
 - ⇒ ideally these should be intravenous for 2 weeks and then oral for 4 weeks.
- needle aspiration should be used to decompress the joint
- surgical drainage may be needed if frequent needle aspiration is required
- if patient on warfarin, what is the most appropriate management of anticoagulation before joint aspiration and injection?
 - ⇒ If INR is within the therapeutic range → no need to stop the warfarin or change the dose.
 - ⇒ The risk of a thrombotic episode if anticoagulation is changed outweighs any risk associated with injecting joint while taking anticoagulation.

The following table compares synovial fluid cell count values.

Normal	Inflammatory (Gout/Pseudogout)	Infectious
< 2,000 WBCs	2,000–50,000 WBCs	> 50,000 WBCs

Sjögren's syndrome

- Sjögren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces.
- It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around 10 years after the initial onset.
- primary Sjögren's syndrome occurs alone and more likely to have positive anti Ro SSA antibodies than secondary Sjögren's).
- Hypergammaglobulinaemia is present in 80% of individuals.
- Typically secondary Sjögren's has pre-existent rheumatoid or systemic lupus erythematosus before the development of Sjögren's symptoms.
- more common in females (ratio 9:1).
- There is a marked increased risk of lymphoid malignancy (40-60 fold)

Features

- dry eyes: keratoconjunctivitis sicca
- dry mouth
- vaginal dryness
- arthralgia
- Raynaud's,
- myalgia
- sensory polyneuropathy
- renal tubular acidosis (usually subclinical)
- Plasma cell infiltration of salivary and lacrimal glands: Parotid swelling.

Complication

- **higher risk of developing lymphoma**

⇒ These lymphomas are primarily of B cell origin.
 ⇒ High risk factors for lymphoma development in Sjogren's syndrome patients include:

- persistent unilateral or bilateral parotid gland enlargement,
- splenomegaly and lymphadenopathy,
- low C4 complement levels,
- type 2 mixed cryoglobulinaemia

Investigation

- rheumatoid factor (RF) positive in nearly 100% of patients
- ANA positive in 70%
- anti-Ro (SSA) antibodies in 70% of patients with PSS
 - ⇒ **Anti-Ro antibody is associated with:**
 - **congenital complete heart block**
 - **neonatal lupus**
 - ❖ The mother is usually positive for anti-Ro or anti-La antibodies but may not have overt lupus erythematosus.
- anti-La (SSB) antibodies in 30% of patients with PSS
- Hypergammaglobulinaemia (\uparrow IgG) in 80%
- low C4
- Schirmer's test: filter paper near conjunctival sac to measure tear formation
 - ⇒ placement of a standard strip of filter paper on the inside of the lower eyelid.
 - ⇒ **Wetting of less than 5 mm in 5 min indicates defective tear production.**
- **Rose Bengal staining of the eyes** commonly shows punctate or filamentary **keratitis**.
- histology: focal lymphocytic infiltration
- **the most definitive test for Sjögren's syndrome → Labial gland biopsy**

Management

- artificial saliva and tears
- pilocarpine may stimulate saliva production

Other causes of dry eyes, and/or dry mouth include:

- past head and neck radiation
- hepatitis C infection
- acquired immunodeficiency disease
- pre-existing lymphoma
- sarcoidosis
- graft versus host disease, or
- the use of an anticholinergic drugs.

Systemic lupus erythematosus (SLE)

SLE - antibodies associated with congenital heart block = anti-Ro

SLE: C3 & C4 low

- Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder.

Epidemiology

- much more common in females (F:M = 9:1)
- more common in Afro-Caribbeans* and Asian communities

⇒ *It is said the incidence in black Africans is much lower than in black Americans - the reasons for this are unclear

- onset is usually 20-40 years

Pathophysiology

- autoimmune disease
- associated with HLA B8, DR2, DR3
- thought to be caused by immune system dysregulation leading to immune complex formation
- the most likely immunopathological process:
 - Activation of the classical complement pathway
 - complement consumption is common in active SLE (indicated by the low C3 and C4).
 - Activation of the classical complement pathway occurs in (SLE) owing to the large number of double-stranded DNA (dsDNA) and other immune complexes that form and fix complement.
 - These immune complexes deposit in the kidneys and other organs, where they attract other components of the immune system that cause tissue damage.
- immune complex deposition can affect any organ including the skin, joints, kidneys and brain
- SLE can also be described as a type III hypersensitivity reaction

Features

The triad of fever, arthralgia and rash in a woman of childbearing age should suggest the diagnosis of systemic lupus erythematosus (SLE).

General features

The multisystem presentation of fever, arthralgia, pericarditis and nephritis associated with the epidemiological clues (a young black female) suggest a diagnosis of (SLE).

- fatigue
- fever
- mouth ulcers
- lymphadenopathy

Skin



Malar Rash

- malar (butterfly) rash: spares nasolabial folds
- discoid rash:** scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- photosensitivity**
- Raynaud's phenomenon
- livedo reticularis
- non-scarring alopecia

Musculoskeletal

- arthralgia typically affecting the small joints of the hands, wrists and knees.
- non-erosive arthritis

Jaccoud's Arthropathy



- **Jaccoud's arthropathy** → gross deformities of the hands without joint damage or erosions
- **caused by** recurrent episodes of synovitis that damage tendon sheaths and slings resulting in joint deformity
- **seen in:**
 - ⇒ SLE
 - ⇒ Rheumatic fever
 - ⇒ Parkinson's disease, and
 - ⇒ Hypocomplementaemic urticarial vasculitis.

Cardiovascular

- myocarditis

Respiratory

- pleurisy
- fibrosing alveolitis
- Direct pulmonary involvement in (SLE) occurs in 30% (pleuropericarditis, atelectasis, pneumonitis, raised hemidiaphragms and **pulmonary fibrosis**).

Renal

- proteinuria
- glomerulonephritis (**diffuse proliferative glomerulonephritis is the most common type**)

Neuropsychiatric

- anxiety and depression
- psychosis
- seizures

Investigations

Immunology

SLE: ANA is 99% sensitive - anti-Sm & anti-dsDNA are 99% specific

SLE - antibodies associated with congenital heart block = anti-Ro

- **99% are ANA positive (the best screening test for SLE)**
 - ⇒ Almost all patients with SLE have a positive ANA test result.
 - ⇒ ANA test is sensitive but not specific for SLE.
 - ⇒ A negative result argues strongly against a diagnosis of active SLE, but does not exclude the possibility of other autoimmune diseases.
 - ⇒ **Negative ANA has the highest negative predicted value** (The highest negative predicted value implies the test with the greatest sensitivity.)
- 20% are rheumatoid factor positive
- anti-dsDNA: highly **specific** (> 99%), but less sensitive (70%)
- anti-Smith: most specific (> 99%), sensitivity (30%)
 - ⇒ Therefore, absence of anti-DNA or anti-Sm antibodies should not exclude SLE as a diagnosis
- also: anti-U1 RNP, SS-A (anti-Ro) and SS-B (anti-La)
 - ⇒ Anti-Rho and -La antibodies are associated with the development of neonatal lupus.
 - ⇒ Anti-Ro/SS-A antibodies are found in 30% of patients with SLE.
 - ⇒ Anti-Ro antibodies can cross the placenta to cause transient cutaneous lupus in the neonate (5-25% of babies) or permanent congenital heart block (1-3% of babies).

Markers of SLE disease activity

- Early markers of SLE disease activity include:
 - ⇒ **falling C₄ levels,**
 - although congenital C₄ deficiency is itself a predisposing factor for SLE development, so these tests must be interpreted with caution.
 - ⇒ rising immunoglobulins,
 - ⇒ falling haemoglobin (Hb), white cell count (WCC), platelets and albumin.

Monitoring

- ESR: during active disease the CRP is characteristically normal - a raised CRP may indicate underlying infection
- complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement)
- **anti-dsDNA titres can be used for disease monitoring** (but note not present in all patients)

Management

- **Basics**
 - ⇒ NSAIDs
 - ⇒ sun-block
- **Hydroxychloroquine**
 - ⇒ useful for skin disease
- If internal organ involvement e.g. renal, neuro, eye then consider prednisolone, cyclophosphamide

Complication

- Lupus patients are **more prone to infection**.
 - ⇒ Up to two-thirds of lupus patients will have some lung involvement during the course of their disease. The most common manifestations are pleuritis and pleural effusions.

SLE: pregnancy

Overview

- Unlike many autoimmune diseases (**SLE often becomes worse during pregnancy and the puerperium**)
- risk of maternal autoantibodies crossing placenta
- leads to condition termed neonatal lupus erythematosus
- **neonatal complications include congenital heart block**
- **strongly associated with anti-Ro (SSA) antibodies**

Treatment

- **azathioprine**
 - ⇒ A large body of evidence from the use of azathioprine in pregnancy for the treatment of both rheumatological conditions and inflammatory bowel disease, supports its use.
 - ⇒ Although it is less effective in the management of SLE with renal disease versus other options, balance of benefit risk makes it the preferred intervention.
- **Ciclosporin**
 - ⇒ appears to be associated with premature delivery and low birth weight,
 - ⇒ although it does not seem to be associated with malformations, this drives its use as an **alternative to azathioprine** in patients who fail to gain control of their disease.
- Cyclophosphamide, methotrexate and mycophenolate are all contraindicated for use in pregnancy.

Drug-induced lupus erythematosus

Overview

- The pathogenesis of drug-induced lupus is unclear.
- Factors that influence drug metabolism, such as acetylator status, have been implicated.
- In addition, lupus-inducing drugs have been shown to generate a variety of cytotoxic products on exposure to **MPO** released from activated neutrophils.

Epidemiology

- Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbeans, whereas the inverse is true of idiopathic SLE.
- affect the 50-70-year age group most commonly,
- has a male: female ratio of 1:1

Causes

The most commonly associated drugs

- procainamide**
- hydralazine 2,**
- quinidine.**

- Isoniazid (INH) - low risk
- Sulfasalazine - low risk.
- Carbamazepine
- Phenytoin
- Lamotrigine**
- anti-TNF alpha agents,
- Interferons
- Statins
- minocycline.**

⇒ Minocycline associated with the development of long term immunological memory, and therefore exacerbation of symptoms within 12-24 hours of rechallenge.

Risk factors

- strongly positive ANA
- HLA-DR4 phenotype (hydralazine-induced disease)
- slow acetylator status**
 - ⇒ Slow acetylators have increased risk of isoniazid-induced peripheral neuropathy, and hydralazine or procainamide-induced systemic lupus erythematosus (SLE).
- large total daily doses of precipitating drugs

Features

- symptoms are said to appear some 3 weeks to 2 years after the onset of therapy
- In drug-induced lupus not all the typical features of SLE are seen, with renal and nervous system involvement being unusual.
- Lack of cutaneous involvement
 - ⇒ presents with purpuric, erythematous, papular rash. They do not have a malar or discoid rash.
 - ⇒ skin (e.g. malar rash) (seen in 25%)

- ⇒ However, drug induced lupus due to interferon and due to anti-TNF α agents, may present with malar or discoid rash, and may be anti-dsDNA antibody positive.
- joint pains, myalgia and malaise are more common
- pulmonary involvement (e.g. pleurisy) are common
- Raynaud's is seen in around 25%

Laboratory features

- ESR and C reactive protein (CRP) are both markedly elevated,
- ANA is strongly positive (in 100%,)
- hypergammaglobulinaemia.
- Anti-dsDNA antibodies are usually negative;
 - ⇒ positive for anti-ssDNA antibody and typically negative for anti-dsDNA antibody.
- **antihistone antibodies are positive in 95% of drug-induced lupus** (but also 50-80% of idiopathic SLE).
- anti-Ro, anti-Smith positive in around 5%
- **C3/C4 levels are usually normal.**

There are several features which distinguish drug-induced lupus from idiopathic SLE:

- Males and females are equally affected in drug-induced lupus, whereas idiopathic SLE affects females nine times more frequently.
- **Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbeans**, whereas the inverse is true of idiopathic SLE.
- the age of onset is typically older in drug-induced lupus, but this depends on the age at drug exposure.
- Fever, arthralgia, serositis and ANA occur at least as frequently in drug-induced lupus as idiopathic SLE.
- Haematological, renal and central nervous system (CNS) involvement, and double-stranded DNA autoantibodies are rare.

Treatment

- Typically, no further treatment is required after Withdrawal of the precipitating drug
- However, there are situations where corticosteroids or disease modifying antirheumatic drugs (DMARDs) are required to aid resolution.
- The time taken for symptoms to resolve after stopping minocycline is highly variable, from a few days to two years.

Prognosis

- Spontaneous recovery usually occurs promptly



A woman with drug-induced lupus

drugs that induce lupus do not need to be avoided in the idiopathic type of lupus.

MRCPUK-part-2-march-2018: A female diagnosed with epilepsy, suffering from an erythematous rash over sun-exposed areas of her skin. Antihistone antibodies are positive. **Which medication is the most likely cause of her rash?**

- ⌚ **Phenytoin, carbamazepine and lamotrigine** are associated with drug-induced lupus erythematosus

Antiphospholipid syndrome

- Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia.
- It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE).
- A key point for the exam is to appreciate that **antiphospholipid syndrome causes a paradoxical rise in the APTT**. This is due to an ex-vivo reaction of the **lupus anticoagulant autoantibodies** with phospholipids involved in the coagulation cascade

Features

- venous/arterial thrombosis
- recurrent fetal loss
- livedo reticularis
- thrombocytopenia
- prolonged APTT
 - ⇒ (**raised aPTT which fails to correct after the addition of normal human plasma**).
- other features:
 - ⇒ pre-eclampsia,
 - ⇒ pulmonary hypertension
 - ⇒ False positive VDRL testing

Associations other than SLE

- other autoimmune disorders
- lymphoproliferative disorders
- phenothiazines (rare)

Risk factor for thrombosis

- **Lupus anticoagulant is the greatest predictor of future thrombosis in patients with anti-phospholipid syndrome**

Diagnosis

- antiphospholipid antibody syndrome (APAS) can be diagnosed if:

- ⇒ the patient has anticardiolipin antibodies, or lupus anticoagulant on two occasions, over a period of 12 weeks,
- ⇒ and either:
 - has had a thrombus, or
 - a history of recurrent < 10-week pregnancy loss, or one pregnancy loss > 10 weeks in gestation when other causes of pregnancy loss have been excluded.

- **Antibodies**
- the most clinically important autoantibodies directed against phospholipid binding plasma proteins are:
 1. The lupus anticoagulant
 2. Anti-beta-2 glycoprotein I antibodies, and
 3. **The anticardiolipin antibodies.**

Management - based on BCSH guidelines

- initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
 - **Other opinion:** The occurrence of even **a single thrombotic event in a patient with antiphospholipid syndrome warrants lifelong anticoagulation**, as the risk of recurrence is 20-70%.
- recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then increase target INR to 3-4
- arterial thrombosis should be treated with lifelong warfarin with target INR 2-3.

DD of a significantly prolonged APTT:

1. Factor deficiency (factor VIII deficiency, factor IX deficiency and von Willebrand)
2. factor VIII inhibitor
 - factor VIII inhibitors are usually time dependent. As a result, when the initial 50:50 mix is done there is correction of the APTT; but if you repeat the APTT after allowing the 50:50 mix to incubate for two hours, there will be no correction.
3. presence of lupus anticoagulant (LAC)
 - Coagulation tests to demonstrate the presence of the LAC are as follows:
 - Prolongation of a phospholipid-dependent coagulation test, for example, APTT, kaolin clotting time or others.
 - Demonstration of inhibitor by **failing to correct the above coagulation test on 50:50 mixing studies by more than 50%.**
 - ❖ prolonged (APTT), which does not correct by a significant amount when patient's plasma is mixed with normal plasma.
 - Demonstrate phospholipid dependence-correction of the coagulation test used in (1) with phospholipid.

Antiphospholipid syndrome: pregnancy

Antiphospholipid syndrome in pregnancy: aspirin + LMWH

Antiphospholipid syndrome: (paradoxically) prolonged APTT + low platelets

Antiphospholipid syndrome: arterial/venous thrombosis, miscarriage, livedo reticularis

- Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia.
- It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

In pregnancy the following complications may occur:

- recurrent miscarriage
- IUGR
- pre-eclampsia
- placental abruption
- pre-term delivery
- venous thromboembolism

Management

- low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- these interventions increase the live birth rate seven-fold

Juvenile idiopathic arthritis (JIA) (Still's disease)

Definition

- The ACR criteria define juvenile rheumatoid arthritis (JRA) by **age limit (< 16 y)** and the duration of disease (**> 6 weeks**).

Epidemiology

- the most common form of arthritis in children and adolescents.
- Prevalence: 1/1000 children
- Sex: ♀ > ♂

Types

- Oligoarticular JIA
 - ⇒ **Most common form** (accounts for 50% of all JIA cases)
 - ⇒ affects **four joints or fewer** during the **first 6 months**,
 - ⇒ has the highest risk of developing Chronic anterior uveitis (up to 25%)
 - Bilateral eye involvement is common
 - ⇒ RF negative
 - ⇒ ANA positive (~ 70% of cases)
 - ⇒ Treatment
 - NSAIDs
 - Possibly intra-articular steroid injections
 - Possibly methotrexate
- Polyarticular JIA
 - ⇒ 40% of cases
 - ⇒ characterised by inflammatory arthritis affecting **five or more joints** during the **first 6 months** of the disease.
 - ⇒ RF negative
 - ⇒ ANA positive (~ 40% of cases)
 - ⇒ Treatment: Standard therapy with methotrexate and NSAID
- Systemic-onset JIA (Still's disease)
 - ⇒ < 10% of cases
 - ⇒ presents with **fever, arthritis and at least one of the following:**
 - erythematous rash,
 - generalised lymphadenopathy,
 - Hepatosplenomegaly
 - serositis (including pleural and pericardial effusions)

- ⇒ RF negative
- ⇒ ↑ Acute phase reactants (e.g., CRP, ferritin)
- ⇒ Treatment: Poor response to methotrexate and TNF inhibitors (etanercept, adalimumab)

Risk factors

- Exposure to antibiotics during childhood may increase the risk of JIA.

Features

Joint pain, daily spiking fevers, and a 'salmon-pink' rash are classic symptoms.

- persistent non-tender joint swelling → (The cardinal feature)
 - ⇒ The first manifestation of JIA is often limping, especially in young children.
 - ⇒ The persistent swelling most often occurs in the large joints.
 - ⇒ Damage to joints is associated with a T_H1 response.
- Up to 25% of patients have a **positive anti-nuclear antibody**.
- microcytic anaemia which tends to be resistant to iron replacement
- pericarditis is often found.
- hepatosplenomegaly,
- JIA can decrease bone mass and increase the risk of osteoporosis.
- ↑ ESR (usually seen with all forms of JIA).
- Rheumatoid nodules and rheumatoid factor are usually absent
 - ⇒ Rheumatoid factor (RF) is absent in most cases of JIA except seropositive polyarticular JIA.
- **anterior uveitis**
 - ⇒ What eye condition is **most commonly** associated with this presentation? **anterior uveitis.**
 - about 30–50% of children with JIA have uveitis at diagnosis, especially those who are antinuclear antibody (ANA) positive.
 - The uveitis is typically asymptomatic at onset and must be **screened** for with an ophthalmologic **slit lamp examination**.
 - Untreated uveitis can be associated with cataracts, glaucoma and macular oedema
 - about 50–70% of people with severe uveitis develop visual impairment.
 - **If a patient with (JIA) developed new-onset anterior uveitis despite treatment with subcutaneous methotrexate → adalimumab** (as adalimumab is more effective in treating uveitis than etanercept)

Treatment

- Options for pharmacotherapy include NSAIDs, corticosteroids, methotrexate, and anti-TNF biologicals.
- Treatment with **IL-6 receptor antibody** has proved to be successful.
- As per NICE guidance, **if patient had not responded to methotrexate and should be considered for biologic therapy with either adalimumab, etanercept or tocilizumab.**

Prognosis

- Anti-CCP antibodies indicate a poor prognosis.
- Early disease onset is associated with a greater degree of growth impairment and deformity.

Adult onset Still's disease (AOSD) (Adult Still's disease)

Adult-onset Still's disease → triad of persistent high spiking fevers, joint pain, and a distinctive salmon-colored bumpy rash.

- typically affects 16-35-year olds

Features

- arthralgia
- rash: salmon-pink, maculopapular (most prominent with fever)
 - ⇒ occurs in approximately 90% of patients
 - ⇒ often seen only when the patient is febrile and is easily missed.
- pyrexia ($> 39^{\circ}\text{C}$) especially in the afternoon and evening
 - ⇒ described as quotidian or diquotidian returning to 37°C or below between episodes.
- lymphadenopathy
- Hepatosplenomegaly,
- There is often an accompanying sore throat and myalgia.

Rarely there may be:

- Aseptic meningitis
- Cranial nerve palsies
- **Iritis**, and
- Peripheral neuropathy.

Investigation

- neutrophilic leukocytosis, thrombocytosis,
- ↑ serum ferritin
 - ⇒ High serum ferritin, with low glycosylated fraction, are characteristic and **can be used as disease activity markers.**
- ↑ ESR and C-reactive protein.
- Interleukin (IL)-1, IL-6, IL-18, macrophage colony stimulating factor, interferon gamma and TNF-alpha are all elevated.
- rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative

Diagnosis

- Diagnosis is clinical, and should include exclusion of infectious disease, neoplasms and other autoimmune disease.

Treatment

- non-steroidal anti-inflammatory drugs (NSAIDs),
- corticosteroids,
- disease-modifying anti-rheumatic drugs
- biological agents.
- Intravenous immunoglobulin may have a role.

Prognosis

- tends to be better when systemic symptoms predominate.

Adult onset Still's disease is typically **rheumatoid factor negative**

Raynaud's

Raynaud's disease (i.e. primary) presents in young women with bilateral symptoms

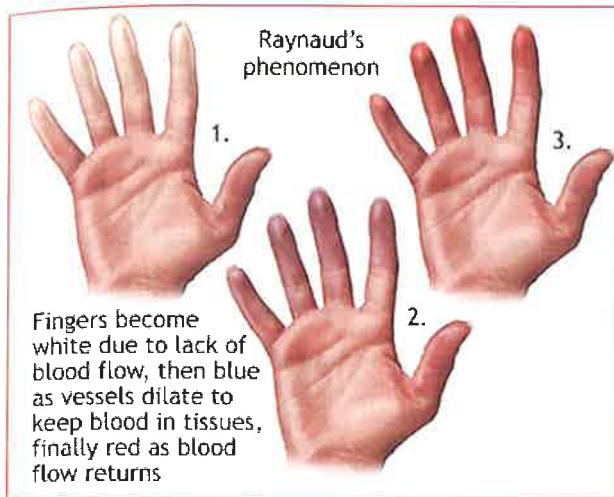
Definition

- Raynaud phenomenon manifests as recurrent vasospasm of the fingers and toes and usually occurs in response to stress or cold exposure.

Types

- Primary Raynaud phenomenon (Raynaud disease).
 - ⇒ Raynaud disease is characterized by the occurrence of the vasospasm alone, with no association with another illness.
 - ⇒ Raynaud's disease typically presents in **young women** (e.g. 30 years old) with **symmetrical attacks**
 - ⇒ Around 2% of women and 6% of men with Raynaud's phenomenon develop systemic sclerosis.
 - ⇒ **Diagnosis:** Primary Raynaud's can be diagnosed if **all the following are present:**
 - Attacks triggered by exposure to cold and/or stress
 - No suspicion of underlying disease
 - Symmetrical episodes affecting both hands, but not necessarily all fingers
 - No tissue necrosis, ulceration, gangrene or severe ischaemia
 - Normal nail-fold capillaries (Normal capillaroscopy findings)
 - Normal ESR and negative anti-nuclear antibodies.
- Secondary Raynaud phenomenon
 - ⇒ Secondary causes
 - connective tissue disorders:
 - ❖ **scleroderma (most common)** (90%)
 - ❖ mixed connective-tissue disease (85%)
 - ❖ rheumatoid arthritis
 - ❖ SLE
 - leukaemia
 - Hyperviscosity: polycythaemia, paraproteinemias (plasmacytoma, Waldenstrom's disease), cryoglobulinemia, cold agglutinin disease
 - use of vibrating tools
 - Vasculitides: e.g., Buerger's disease
 - cervical rib
 - drugs:
 - ❖ oral contraceptive pill,
 - ❖ ergot
 - ❖ methysergide (for intermittent migraine)
 - ❖ beta-blockers
 - ❖ vinblastine
 - ❖ bleomycin
 - ⇒ Factors suggesting underlying connective tissue disease
 - onset after 40 years
 - **Episodes lasting in excess of one hour**
 - ❖ episodes of secondary **Raynaud's** are longer
 - ❖ **Episodes of primary disease typically terminate within 15 minutes** following warming in, but can often be prolonged in secondary disease.
 - unilateral symptoms
 - rashes

- presence of autoantibodies
- features which may suggest rheumatoid arthritis or SLE, for example arthritis or recurrent miscarriages
- digital ulcers,
- calcinosis
- very rarely: chilblains



Investigations

Which investigation would be most useful in determining whether the Raynaud's is related to vasculitis? → Nail fold capillaroscopy

- **The most useful initial assessment** must include **nail fold capillary loop examination**,
 - ⇒ ideally by **capillaroscope** or, if not available, by **ophthalmoscope** using magnification.
 - method
 - ❖ Nailfold capillaroscopy is performed by applying a drop of oil onto the periungual region of the nail and using an ophthalmoscope set to 40 diopter to examine.
 - interpretation
 - ❖ Patients with connective tissue disorder such as systemic sclerosis most often will show → dilated, distorted, paucity or missed nail fold capillary loops.

Management

- For primary Raynaud phenomenon:
 - ⇒ First line → lifestyle measures.
 - **The best initial line**
 - **Advise on lifestyle changes to reduce the frequency of the attacks, such as heated gloves, stopping smoking and avoiding the cold environments**
 - ⇒ Second line → pharmacologic treatment.
 - **First pharmacologic line: calcium channel blockers e.g. nifedipine**
 - **IV prostacyclin infusions:**
 - ❖ **effects may last several weeks/months**
 - ❖ **indications**
 - ⇒ if the patient does not respond to nifedipine Retard or

- ⇒ has developed digital ulceration or ischaemia
- **iloprost** is a synthetic analogue of prostacyclin
 - ❖ **The urgent treatment of severe Raynaud's with threatened or established gangrene is with intravenous iloprost.**
- ⇒ **Third line → non-pharmacologic treatment.**
 - **Digital sympathectomy** should be considered as a last resort when drug therapy has failed or has not been tolerated.
- For secondary Raynaud phenomenon:
 - ⇒ Treatment of underlying disorder
 - ⇒ **ACE inhibitors** also have the best evidence for reno-protection where there is underlying autoimmune pathology.
 - If there is NO underlying autoimmune pathology → ACEi has NO benefit
 - ❖ ACE inhibitors and anti-platelet agents have been trialled in small case series, although no definitive benefit has yet been shown.

Systemic sclerosis (SSc)

- Systemic sclerosis is a chronic autoimmune disease characterised by increased fibroblast activity and fibrosis in a number of different organ systems.
- characterised by hardened, sclerotic skin and other connective tissues.

Epidemiology

- It is four times **more common in females** ($\text{♀} > \text{♂}$)
- Higher incidence in African Americans
- Peak incidence: 30–50 years

Types: There are three patterns of disease:

1. Limited cutaneous systemic sclerosis

Limited (central) systemic sclerosis = anti-centromere antibodies

- The more common type of SSc.
- **Raynaud's may be first sign**
 - ⇒ seen in 90–95% of patients with systemic sclerosis.
- scleroderma **affects face** and distal limbs predominately
 - ⇒ Areas of skin affected include only the face, forearms and lower legs up to the knee.
 - ⇒ It does not affect the upper arms, upper legs, or trunk.
- **associated with anti-centromere antibodies**
- Previously known as CREST syndrome (**Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasia**)
 - ⇒ the most likely cause of this patient's dysphagia? → Esophageal smooth muscle **atrophy and fibrosis**
- **Pulmonary hypertension is one of the more common late complications seen in CREST syndrome**
 - ⇒ **The most common cause of death**
- **Malabsorption is most likely to develop as a further complication**
 - ⇒ Involvement of GIT can occur from mouth to anus
 - can present with both diffuse and limited cutaneous forms.
 - Most GIT manifestations result from dysmotility secondary to infiltration of the intestinal wall with fibrous tissue.
 - can cause life-threatening malabsorption and malnutrition.
 - **Gastric emptying is delayed in 10–75%** of patients and causes symptoms of early satiety, bloating and emesis.
 - ❖ Treatments include metoclopramide and erythromycin.

- small bowel is also involved in 20-60% of patients, due to reduced or absent migrating motor complexes predisposing to bacterial overgrowth.
 - ❖ initial attempts at eradication of bacterial overgrowth with **metronidazole**, ciprofloxacin or co-amoxiclav is appropriate.
- This contributes to malabsorption, as does associated pancreatic insufficiency.
- In the colon there is often development of diverticuli involving all layers of the intestinal wall, or constipation due to reduced motility.

The limited symptoms of scleroderma are referred to as **CREST**

Calcinosis- calcium deposits in the skin



Raynaud's phenomenon- spasm of blood vessels in response to cold or stress



Esophageal dysfunction- acid reflux and decrease in motility of esophagus



Scлеродактиль- thickening and tightening of the skin on the fingers and hands



Telangiectasias- dilation of capillaries causing red marks on surface of skin

2. Diffuse cutaneous systemic sclerosis

- less common.
- scleroderma **affects trunk and proximal limbs predominately** (although face may be involved in either type)
 - ⇒ Skin areas involved include also the upper arms, thighs or trunk.
- **associated with scl-70 antibodies**
- hypertension, **lung fibrosis** and renal involvement seen
 - ⇒ Pulmonary involvement is the second commonest organ involvement after oesophageal disease and is the leading cause of death.
 - ⇒ **Pulmonary fibrosis is associated with anti-Scl-70 antibodies in up to 70% of cases.**
 - ⇒ scl-70 antibodies associated with a higher risk of severe interstitial lung disease
 - ⇒ **Reduced DLCO is the earliest sign of pulmonary disease in systemic sclerosis, often before fibrotic changes manifest clinically.**
- Diffuse cutaneous systemic sclerosis may lead to **scleroderma renal crisis (SRC)** in up to 10% cases.
 - ⇒ The underlying pathology of SRC is vasospasm,
 - ⇒ Features
 - SRC may present with rapid onset renal failure,
 - malignant hypertension,
 - micro-angiopathic haemolytic anaemia with schistocytes.
 - Patients may develop symptoms of fluid overload.
 - ⇒ Other risk factors for SRC include:
 - corticosteroid use (prednisolone more than 15 mg/day),
 - recent onset scleroderma (less than three years), and
 - involvement of other systems.
 - ⇒ Treatment involves starting ACE inhibitors.
- poor prognosis

3. Scleroderma (without internal organ involvement)

- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear





Antibodies

- **ANA positive in 90%**
 - ⇒ therefore, in a negative test → consider an alternative diagnosis
- RF positive in 30%
- **Anti-centromere antibodies** associated with **limited cutaneous systemic sclerosis**
- **Anti-scl-70 antibodies** associated with **diffuse cutaneous systemic sclerosis**
 - ⇒ (anti-Scl-70) also known as **Anti-topoisomerase I antibodies**
 - ⇒ associated with a higher risk of severe interstitial lung disease
- **Anti-RNA polymerase III antibodies**
 - ⇒ found in patients with **diffuse disease**
 - ⇒ associated with:
 - rapidly progressive skin involvement
 - **increased risk for scleroderma renal crisis.**
 - increased risk for cancer

Other investigations

- Serum protein electrophoresis: ↑ γ-globulins

Treatment

- Immunosuppressive therapy: e.g., methotrexate
- **Organ-specific therapy:**
 - gastroesophageal reflux disease → PPIs
 - **Renal crisis → ACE inhibitors**
 - Renal crises result from an acute renal **vasculopathy** with associated hypertension, not glomerulonephritis.
 - ACE inhibitors in the acute setting **improves long term survival**, end organ damage due to hypertension, and can lead to an improvement in renal function even up to 2 years after crisis.
 - **Interstitial lung disease** secondary to underlying diffuse systemic sclerosis:
 - **The most appropriate treatment is cyclophosphamide**
 - Azathioprine is normally used as maintenance therapy following cyclophosphamide.

Prognosis

- **U&Es** have a crucial role with respect to determining prognosis and appropriate therapeutic intervention.

- the most important initial investigation with respect to determining patient outlook?
→ Urea and electrolytes

Scleroderma renal crisis

- A major complication of systemic sclerosis
- Severe and life threatening renal disease develops in approximately 10-15% of patients.
- Features
 - ⇒ severe hypertension, with diastolic BP over 100 mmHg, usually with grade III or IV hypertension retinopathy, together with rapid deterioration of renal function and heart failure;
 - ⇒ symptoms of malignant hypertension, with headaches, blurred vision, fits and heart failure.
 - ⇒ haematological tests often demonstrate a thrombocytopenia and/or **microangiopathic haemolysis**.
- Treatment
 - ⇒ **Hypertension → ACE inhibitor** (calcium channel blockers can be added).
 - While ACE inhibitors are generally avoided in most patients with acute renal failure, **scleroderma renal crisis is an exception to the rule** as long as renal function is closely monitored.
 - ⇒ Renal dialysis may be required.
 - ⇒ An excessive reduction in BP or hypovolemia (should be avoided) → ↓ renal perfusion → acute tubular necrosis. Thus, **parenteral antihypertensive agents (such as intravenous nitroprusside or labetalol) should be avoided**.

Morphea (localised scleroderma)



Definition

- idiopathic inflammatory skin condition which causes excessive collagen deposition and fibrosis.

Types

- Morphea is classified into subtypes according to the clinical presentation and depth of tissue involvement:
 - ⇒ circumscribed morphea,
 - the commonest form, "circumscribed/plaque" morphea.

- This is a well-defined oval to round plaque that fails to meet the criteria for generalised morphea.
 - ⇒ generalized morphea,
 - ⇒ linear morphea
 - ⇒ pansclerotic morphea

Pathophysiology

- autoimmune component is suggested by enhanced **T helper 2** (Th2) dependent **interleukin 4** (IL-4) activity, which in turn upregulates transforming growth factor beta (**TGF-beta**).
- **TGF-beta** stimulates **fibroblast** production of collagen and other extracellular matrix proteins.

Features

- Unlike systemic sclerosis, morphea lacks features such as sclerodactyly, Raynaud phenomenon, nailfold capillary changes, telangiectasias, and progressive internal organ involvement.
- Morphea can present with extracutaneous manifestations, including fever, lymphadenopathy, arthralgias, fatigue, central nervous system involvement,

Investigations

- Hypergammaglobulinaemia ($\uparrow\uparrow$ IgM , IgG)
- peripheral eosinophilia
- $\uparrow\uparrow$ ESR and CRP
- **Anti-Cu/Zn superoxide dismutase** antibodies have been found in up to 90%

Treatment

- Superficial circumscribed morphea
 - ⇒ Tacrolimus 0.1% **ointment** applied twice daily for 12 weeks may be a useful **first-line**
- Generalized, linear, or deep morphea
 - ⇒ combination therapy with oral prednisone and methotrexate
 - ⇒ To minimize the risk of relapse, the recommended treatment duration of MTX is at least 2 years.
 - ⇒ Systemic corticosteroids can be helpful in the inflammatory phases of morphea, but they are not recommended for long-term monotherapy
 - ⇒ Mycophenolate mofetil is a second-line

Prognosis

- generally resolves within 3–5 years, although sometimes a patch may persist for over 25 years.

Polymyalgia rheumatica (PMR)

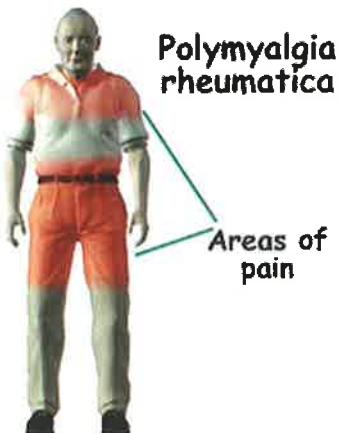
Pathophysiology

- overlaps with temporal arteritis 30% of patients also have giant cell arteritis.
- histology shows vasculitis with giant cells, characteristically 'skips' certain sections of affected artery whilst damaging others
- muscle bed arteries affected most in polymyalgia rheumatica

Epidemiology

- occurring in patients age 50 years or older.
- More common in women

Features



- typically patient > 60 years old
 ⇒ very rarely seen in the under 50s.
- usually rapid onset (e.g. < 1 month)
- **typically presents with pain and stiffness of the shoulder and pelvic girdle muscles.**
- aching, morning stiffness in proximal limb muscles (not weakness)
 ⇒ **Pain and muscle stiffness worst in the mornings**
- mild polyarthralgia, lethargy,
- depression,
- **low-grade fever**, anorexia, night sweats
- **Weight loss**

Investigations

- ESR > 40 mm/hr
 ⇒ **the next best investigation**
 ⇒ a high ESR would prompt immediate treatment with steroids.
- Raised C reactive protein (CRP)
- Alkaline phosphatase is an acute-phase reactant and is raised in approximately a third of patients with polymyalgia rheumatica.
- note CK and EMG normal
- reduced CD8+ T cells
- Normochromic / normocytic anaemia

Differential diagnosis

- **Giant cell arteritis (GCA)**
 - ⇒ GCA and PMR frequently co-exist,
 - ⇒ cranial symptoms including **headache, jaw claudication, and vision symptoms** are **typically absent in patients with PMR.**
 - ⇒ PMR typically has less prominent symptoms than GCA.

Treatment

- prednisolone e.g. 15mg/od - dramatic response
 - ⇒ Response to a moderate dose of steroids can be useful in confirming the diagnosis of PMR.
 - ⇒ The maximum dose of prednisolone should not exceed 20 mg once daily.
 - ⇒ Patients should report 70% improvement in symptoms within three to four weeks, and inflammatory markers should have normalised by this point.

- ⇒ Calcium and vitamin D supplementation should be initiated for all patients with PMR who are starting corticosteroid therapy. Bisphosphonates should be added for long term steroid therapy.
- ⇒ The usual starting dose is 15 mg prednisolone per day.
- ⇒ Patients should expect relief of symptoms within 24-72 hours.
 - One of the best 'tests' for Polymyalgia Rheumatica (PMR) is how patients respond to corticosteroid therapy.
- ⇒ Tapering
 - Tapering should be guided by clinical response.
 - The dose should be increased if symptoms are not well controlled within one week.
 - The effective starting dose should be maintained for two to four weeks after the patient becomes asymptomatic.
 - Generally, the daily dose can be lowered by 1.0-2.5 mg every two to four weeks to find the minimum dose needed to maintain symptom suppression. Once the patient is reduced to 10 mg per day, the daily dose can be tapered by 1 mg every four weeks.
 - Approximately 50-75% of patients can discontinue corticosteroid therapy after two years of treatment.
- ⇒ **Methotrexate and azathioprine**
 - If symptoms relapsed when the dose of prednisolone has been reduced below the current dose, → Continue the current dose of prednisolone and start methotrexate
 - used in patients with corticosteroid intolerance or as corticosteroid-sparing agents.
 - These are generally reserved for patients in whom it has been difficult to reduce the prednisolone after prolonged high dosages (for example, 10 mg or more per day for more than a year).
 - These agents should be added to the prednisolone initially, but with a view to slowly reduce and withdraw prednisolone.
 - As with steroid therapy, azathioprine or methotrexate can be discontinued if there has been sufficient response.

Prognosis

- Rapid improvement often occurs within 24 to 72 hours with low-dose prednisolone.

Temporal arteritis (Giant cell arteritis (GCA))

GCA should always be considered in elderly patients with headaches, ocular symptoms (e.g. acute monocular visual loss), systemic symptoms and high ESR.

Suspected GCA → **glucocorticoids immediately, even before diagnostic evaluation by temporal artery biopsy is complete.**

Overview

- also known as giant cell arteritis (GCA).
- Temporal arteritis is large vessel vasculitis
- overlaps with polymyalgia rheumatica (PMR).
- Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.
- It is a clinical emergency.

Epidemiology

- Sex: ♀ > ♂
- Peak incidence: 70–79 years; rarely seen in patients < 50 years

Features

- typically, patient > 60 years old
 - ⇒ The greatest risk factor for (GCA) is aging.
 - ⇒ almost never occurs before age 50
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- **jaw claudication (65%) is a very specific sign for temporal arteritis.**
- visual disturbances (50%)
 - ⇒ secondary to anterior ischemic optic neuropathy
 - ⇒ 15-20% of patients develop permanent visual loss.
- tender, palpable temporal artery
- features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also, lethargy, depression, low-grade fever, anorexia, night sweats
- Large vessel GCA : Subclinical involvement of the aorta and large arteries is frequent, a clinical consequence of which can be aortic aneurysm (in 10 to 20 % of cases).

Investigations

- Raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
 - ⇒ ESR can be within normal range in 5-10% of GCA cases.
- Temporal artery biopsy:
 - ⇒ **the definitive diagnostic test**
 - ⇒ **skip lesions** may be present (certain sections of affected artery whilst damaging others)
 - ⇒ An adequate length of temporal artery (3 to 5 cm) should be obtained because inflammatory lesions may be present in a segmental fashion.
 - ⇒ A negative temporal artery biopsy can occur in up to 50% of patients, often because the sampled region was not involved in the pathologic process. Therefore, **it is not sensitive enough to rule out temporal arteritis.**
 - ⇒ Treatment should not be delayed while waiting for the biopsy to be performed.
- Note: creatine kinase and EMG normal

Diagnosis

- The American College of Rheumatology 1990 criteria requires 3 of the following for GCA diagnosis:
 1. Age >50 y/o
 2. New onset localised headache
 3. Temporal artery tenderness or decreased pulsation
 4. ESR >50mm/hr
 5. Temporal artery biopsy positive

Treatment

- **High-dose prednisolone**
 - ⇒ there should be a dramatic response, if not the diagnosis should be reconsidered
 - ⇒ **Current BSR guidelines recommend:**
 - Uncomplicated GCA (no jaw or tongue claudication, or visual symptoms)
 - ❖ prednisolone 40-60 mg daily
 - **Complicated GCA: (with visual involvement and/or jaw/tongue claudication)**

- ❖ **Evolving visual loss or history of amaurosis fugax: IV methylprednisolone 500 mg-1 g daily for three days, followed by oral corticosteroids**
- ❖ Established visual loss: at least 60 mg prednisolone daily
- Urgent ophthalmology review.
 - ⇒ Patients with visual symptoms should be seen the same-day by an ophthalmologist.
 - ⇒ Visual damage is often irreversible
- As GCA requires long-term steroid therapy bone sparing agents (**a bisphosphonate and vitamin D**) and a gastroprotective drug (e.g omeprazole) should be prescribed.
- Also, low dose **aspirin** should be considered as it has been shown to reduce the rate of visual loss and cerebrovascular accidents in GCA.

Polyarthritides

Differential diagnosis

- rheumatoid arthritis
- SLE
- seronegative spondyloarthropathies
- Henoch-Schonlein purpura
- sarcoidosis
- tuberculosis
- pseudogout
- viral infection: EBV, HIV, hepatitis, mumps, rubella

Polyarteritis nodosa (PAN)

Definition

- systemic vasculitis of the **medium-sized** vessels, with necrotizing inflammation leading to aneurysm formation and tissue ischaemia;
- most commonly involving skin, peripheral nerves, muscles, joints, gastrointestinal tract, and kidneys .
- any organ with the **exception of the lung** can be affected,

Epidemiology

- Peak incidence: ~ 45–65 years
- Sex: ♂ > ♀
- more common in middle-aged men

Pathophysiology

- diffuse vascular inflammation and ischaemia of the affected organs.
- PAN is a medium-vessel vasculitis that is a type III hypersensitivity reaction.

Association

- hepatitis B infection

Features

- Nonspecific symptoms: (found in 65% to 80% of patients)
 - ⇒ fever, malaise, arthralgia, weight loss
- Neurological involvement: (in 55% of patients)
 - ⇒ polyneuropathy (**mononeuritis multiplex**),
 - ⇒ cerebral ischemia (stroke)
- Skin involvement: (in 44%)
 - ⇒ skin rash,
 - ⇒ Skin ulcers, nodules
 - ⇒ **livedo reticularis**

- Renal involvement : (in 11%)
 - ⇒ hypertension,
 - Hypertension is a manifestation of renal ischaemia via activation of the renin-angiotensin system.
 - ⇒ haematuria
 - but red cell casts are absent because glomerular inflammation is not a feature.
 - ⇒ renal impairment
- Coronary artery involvement ;
 - ⇒ increased risk of myocardial infarction
- GI involvement:
 - ⇒ abdominal pain, nausea, vomiting
 - ⇒ can present with abdominal pain and melena due to involvement of the mesenteric arteries.
- **Testicular pain**
 - ⇒ **testicular pain from ischaemic orchitis is a characteristic feature**
 - ⇒ uncommon presentation
- **Usually spares the lungs**

PAN should be considered in young adults presenting with stroke or myocardial infarction
The diagnosis may be confirmed with a biopsy of involved tissue



Livedo reticularis

Diagnosis

- The American College of Rheumatology (ACR) 1990 criteria
 - ⇒ **Three of the following 10 criteria are required:**
 1. Weight loss ≥4 kg
 2. Livedo reticularis
 3. Testicular pain or tenderness
 4. Myalgias, weakness, or leg tenderness
 5. Mononeuropathy or polyneuropathy
 6. Diastolic blood pressure >90 mmHg
 7. Elevated urea or creatinine
 8. Positivity for hepatitis B virus (HBV) infection
 9. Arteriographic abnormality

10. Biopsy of small- or medium-sized artery containing polymorphonuclear leukocytes.

Investigations

- Hepatitis B surface antigen is positive in 30%,
- p-ANCA is positive **only** in 20%.
 - ⇒ **ANCA is classically negative in PAN.**
- Angiography:
 - ⇒ Conventional angiography is **the imaging modality of choice**, and should be performed if there is a clinical suspicion of PAN.
 - ⇒ typically demonstrates:
 - microaneurysms and
 - focal narrowing in medium-sized blood vessels.
- Biopsy
 - ⇒ should be performed **if angiography is not available or does not conclusively show a medium-vessel vasculitis.**
 - ⇒ Shows:
 - focal and segmental transmural necrotising inflammation with **fibrinoid necrosis** in medium-sized vessels.
 - **pleomorphic cellular infiltrate** of lymphocytes, neutrophils, macrophages, and eosinophils.
 - **granulomas are absent.**

Differential diagnosis

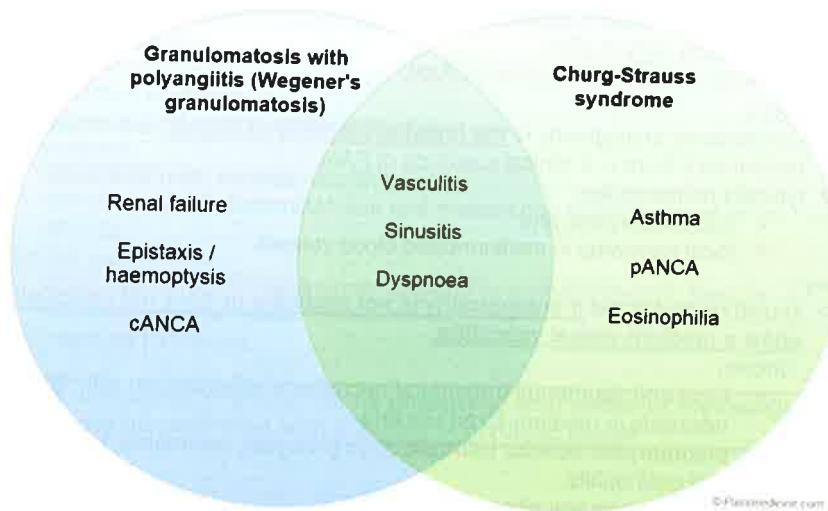
- PAN are differentiated from the other small- and medium-vessel vasculitides by:
 - ⇒ absence of anti-neutrophil cytoplasmic antibodies,
 - ⇒ **Glomerulonephritis is not a feature of PAN**, but it is common in anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis. Making this distinction early by way of urinalysis for protein, blood, and **casts** is a **simple first-line test** that can guide further investigation and treatment.
 - **Red cell casts are absent in PAN**
 - If there is evidence of glomerular inflammation such as urinary casts, then an alternative diagnosis such as microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (Wegener's) (GPA), must be considered.
 - ⇒ lung involvement is not seen in PAN, and abnormal respiratory findings should suggest an alternative diagnosis
 - ⇒ and by confirmation that small vessels (i.e., arterioles, capillaries, venules) are not involved.

Treatment

- idiopathic PAN → corticosteroids and cyclophosphamide
- hepatitis B related disease → plasmapheresis and antiviral agents.
- Azathioprine can be used as maintenance therapy, and typically has fewer side effects than cyclophosphamide.

Cyclophosphamide → causes premature ovarian failure and infertility in both men and women.

Granulomatosis with polyangiitis (Wegener's granulomatosis)



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Overview

- Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis.
- It is an autoimmune condition associated with a necrotizing granulomatous vasculitis, affecting both the upper and lower respiratory tract as well as the kidneys.
- **the classical triad** consists of
 1. necrotising granulomatous inflammation of the respiratory tract,
 2. glomerulonephritis
 3. small-vessel vasculitis.

Features

- upper respiratory tract: epistaxis, sinusitis, nasal crusting
- saddle-shape nose deformity
- lower respiratory tract: dyspnoea, haemoptysis
 - ⇒ **migrating alveolar shadowing**
- rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
 - ⇒ It usually presents with rapidly progressing renal failure (within three months), proteinuria and microscopic haematuria.
- also:
 - ⇒ vasculitis (causing carotid artery tenderness)
 - ⇒ vasculitic rash,
 - ⇒ eye involvement (e.g. proptosis),
 - ⇒ cranial nerve lesions

Investigations

- c-ANCA (PR3-ANCA (targeting peroxidase-3) positive in > 90%, p-ANCA (MPO-ANCA (targeting myeloperoxidase) positive in 25%
 - ⇒ cANCA directed against proteinase-3
 - ⇒ cANCA is highly specific, but is **found in only 50% of patients with disease localised to the respiratory tract** and 95% with generalised Wegener's.

- In active Wegener's disease **with renal involvement cANCA is highly sensitive and specific.**
- ⇒ After disease remission cANCA may remain elevated for years, and is **not useful in evaluating patients for relapse.**
- chest x-ray: wide variety of presentations, including cavitating lesions
- tissue biopsy
 - ⇒ renal biopsy:
 - epithelial crescents in Bowman's capsule
 - Kidneys show vasculitis and glomerulonephritis and **occasional** (NOT always) granulomata
 - ⇒ **Lung biopsy has a high diagnostic yield**
 - show vasculitis and granulomas
 - ⇒ Biopsy of the upper respiratory tract shows granulomas but not vasculitis.

Management

- steroids
 - ⇒ **Prednisolone** is given in doses of around 1 mg/kg per day initially, after which the dose is reduced rapidly, typically at weekly intervals.
 - ⇒ **In case of renal failure with indications for dialysis, the initial management → Methylprednisolone**
 - **Methylprednisolone should be given immediately, followed by haemodialysis and then cyclophosphamide.**
- cyclophosphamide (90% response)
 - ⇒ **The combination of prednisolone and cyclophosphamide is now established as the standard therapy and the treatment of choice for induction of remission in Wegener's granulomatosis**
 - ⇒ **Cyclophosphamide:** Traditionally, oral dose (2 mg/kg per day), but latterly intravenous boluses have proved increasingly popular, given in doses of 0.5-0.75 g/m² body surface area at intervals of 2 weeks (at least for short periods) to 2 months.
 - ⇒ **If a patient had a vasculitic neuropathy. Current practice is to use cyclophosphamide for induction therapy.**
- Both rituximab and methotrexate have also been used for induction therapy in ANCA-associated vasculitis, although they would not be first-line treatment.
- Azathioprine is used as maintenance treatment following cyclophosphamide
- ciclosporin is rarely used in the management of ANCA-associated vasculitis.
- Evidence from controlled trials suggests that once remission is achieved azathioprine or methotrexate may be reasonable alternatives to cyclophosphamide.
- In refractory Wegener's, both infliximab and rituximab have shown some degree of promise.
- plasma exchange
- **in case of decreased conscious level with acute renal failure (with indication for dialysis) and respiratory function is failing. The first immediate step → Endotracheal intubation and positive pressure ventilation, transfer the patient to a critical care setting (especially to protect airway with a GCS 8/15).**

Prognosis

- median survival = 8-9 years

Microscopic Polyangiitis

- ➡ PR3 antibody is associated with Wegener's granulomatosis,
- ➡ MPO antibody is associated with microscopic polyangiitis

- Microscopic polyangiitis is similar to wegener's granulomatosis except in 3 things:

1. it only affects small blood vessels in the lungs or kidneys.
 - No nasopharyngeal damage like wegener's
2. Associated with p-ANCA antibodies.
 - anti-MPO (pANCA, 45%) antibody is strongly positive than anti-PR3 (cANCA, 30%)
3. No granuloma on biopsy

Microscopic polyangiitis is similar to Granulomatosis with polyangiitis (Wegener's granulomatosis) except in 3 things:

1. it only affects small blood vessels in the lungs or kidneys.(No nasopharyngeal damage like wegener's)
2. Associated more with anti-MPO (pANCA, 45%) than anti-PR3 (cANCA, 30%)
3. No granuloma on biopsy

PassOnExam

Churg-Strauss syndrome

- Churg-Strauss syndrome is an ANCA associated small-medium vessel vasculitis.
- also known as Eosinophilic granulomatosis with polyangiitis

Features

- asthma
- paranasal sinusitis
- mononeuritis multiplex
- blood eosinophilia (e.g. > 10%)
- Serum IgE is very commonly elevated and correlates with disease severity.
- pANCA positive in 60%
- Commonly associated with antimyeloperoxidase antibodies.
- Non-fixed pulmonary infiltrates visible on chest radiographs
- Rarely, it can cause ischaemic optic neuropathy, which presents with visual loss.

Leukotriene receptor antagonists may precipitate the disease

Diagnosis

- It is diagnosed **clinically**, although a biopsy should be sought for pathological confirmation.
- **Skin biopsy** reveals small-vessel arteriopathy with **granuloma** formation and is the diagnostic investigation of choice.
 - ⇒ Blood vessels with **extravascular eosinophils** on biopsy.

Treatment

- High-dose methylprednisolone, with or without cyclophosphamide is the treatment of choice

Prognosis

- Without treatment, the 5-year survival rate for Churg-Strauss syndrome is around 25%; with appropriate therapy this rises to over 60%.

Idiopathic pulmonary haemosiderosis

- ▶ pulmonary hemorrhage without immunological features → Idiopathic pulmonary haemosiderosis
- ▶ pulmonary hemorrhage + immunological features → Goodpasture or Wegener's

Definition

- recurrent episodes of diffuse alveolar hemorrhage of unknown aetiology

Prevalence

- rare
- tends to occur in younger people

Features

- pallor,
- weakness, lethargy,
- dry cough and occasional haemoptysis
- **no extrapulmonary features.**
- After recurrent episodes of hemorrhage, pulmonary fibrosis may develop due to iron accumulation.

Investigations

- **no abnormal immunological features, which differentiates it from Goodpasture syndrome and Wegener's**
- Gas transfer is elevated as blood is already in the alveolar space.
- chest radiograph and high resolution computed tomography demonstrate ground glass alveolar opacities that are often bilateral.
- final diagnosis requires lung biopsy documentation of large numbers of hemosiderin-laden macrophages in the alveoli, without evidence of vasculitis, capillaritis, inflammation, granulomas, or deposition of immunoglobulins in any specific pattern.

Treatment

- glucocorticoids +/- another immunosuppressive agent
(eg, azathioprine, or cyclophosphamide)

Henoch-Schonlein purpura

Overview

- Henoch-Schonlein purpura (HSP) is an **IgA mediated** small vessel vasculitis
- involving mainly the blood vessels of the skin, GI tract, the kidneys and the joints.
- 90% of cases of HSP occur in children aged 2-10 years but can occur in any age group.
- In children, (HSP) is the most common cause of vasculitis affecting the kidneys.
- typically commoner in males,
- may follow an infectious agent.
- It can present one to three days following infection of an IgA secreting mucous membrane (commonly following pharyngitis, but can occur following infection of the gastrointestinal tract, bladder or breast).
- An important risk factor in adults → chronic alcohol intake.
- associated with: *Helicobacter pylori*, hepatitis B and malignancy.

Features

HSP is characterised by the **tetrad of:**

- purpura
- abdominal pain
- arthritis, and
- renal involvement (haematuria and proteinuria).

- ⇒ Patients with proteinuria have a worse prognosis than patients with haematuria alone.
- palpable purpuric rash (with localized oedema) over buttocks and extensor surfaces of arms and legs (due to a cutaneous vasculitis)
- abdominal pain (due to gut vasculitis, which may be severe in some cases, leading to bloody diarrhoea)
- polyarthritis (common symptom)
- features of IgA nephropathy may occur e.g. haematuria, renal failure
 - ⇒ HSP nephritis becomes clinically manifest in only 20-30%.
 - ⇒ It usually presents as macroscopic haematuria and proteinuria
 - ⇒ Of those patients with renal involvement, as many as 10% may develop chronic renal failure and end-stage renal disease. However, fewer than 1% of all patients with HSP suffer this poor prognosis.

Diagnosis

- Skin biopsy and immunofluorescence demonstrate **leukocytoclastic vasculitis with IgA deposition**, (meaning lots of white blood cells in the skin around small blood vessels) **which is pathognomonic for HSP**.
 - ⇒ Immunofluorescence studies will reveal → **IgA deposits within blood vessel walls**

Treatment

- analgesia for arthralgia
- treatment of nephropathy is generally supportive.
 - ⇒ **All patients with hypertension and proteinuria (greater than 1 g/day) should be started on an angiotensin-converting enzyme (ACE) inhibitor**, which may control the BP and proteinuria.
 - ⇒ Once the BP has been controlled, patient should have a renal biopsy, and if this showed changes of a crescentic glomerulonephritis (GN), then an immunosuppression regime similar to that used in renal vasculitis should be started (probably with high dose steroids in the first instance +/- cyclophosphamide).
 - ⇒ There is inconsistent evidence for the use of steroids and immunosuppressants
 - ⇒ Management of HSP in adults often involves the use of immunomodulatory or immune-suppressive regimens (in contrast to children where the majority of cases resolve spontaneously).

Prognosis

- usually excellent, HSP is a self-limiting condition, especially in children without renal involvement
- There is often a more complicated course in adults, and 50% of patients who present with renal involvement develop renal insufficiency.
- around 1/3rd of patients have a relapse

Henoch-Schonlein purpura (HSP) is the tetrad of:

1. **Purpura**
2. **Abdominal pain**
3. **Renal involvement (haematuria and proteinuria)**
4. **Arthritis**

Incidence: most common in children <17 years.

Mechanism: IgA mediated small vessel vasculitis.

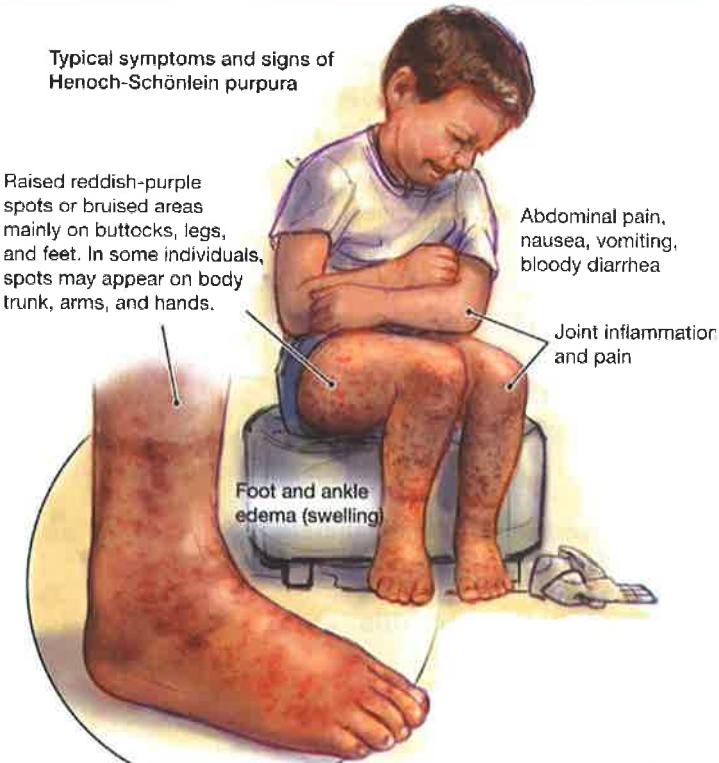
Diagnosis: Skin biopsy → leukocytoclastic vasculitis with IgA deposits within blood vessel walls.

Treatment:

- For pain: 1st line → naproxen. 2nd line → prednisone.
- for hypertension and proteinuria → ACE inhibitor.

Prognosis: self-limited → Full renal recovery.

Typical symptoms and signs of Henoch-Schönlein purpura



MRCPUK-part-1-September 2019 exam: What is the most likely renal outcome in Henoch-Schönlein purpura? Full renal recovery

Kawasaki disease

Overview

- Kawasaki disease is a type of **vasculitis** which is predominately seen in children.
- Whilst Kawasaki disease is uncommon it is important to recognise as it may cause potentially serious complications, including **coronary artery aneurysms**

Features

- high-grade fever which lasts for > 5 days. Fever is characteristically resistant to antipyretics
- conjunctival injection
- bright red, cracked lips
- **strawberry tongue**
- cervical lymphadenopathy
- red palms of the hands and the soles of the feet which later peel

Diagnosis

- Kawasaki disease is a clinical diagnosis as there is no specific diagnostic test

Management

- high-dose aspirin
 - ⇒ Kawasaki disease is one of the few indications for the use of aspirin in children. Due to the risk of Reye's syndrome aspirin is normally contraindicated in children.
- intravenous immunoglobulin
 - ⇒ **Combination therapy with intravenous immunoglobulin (IVIG) and aspirin during the acute phase of Kawasaki disease produces a more marked anti-inflammatory effect and reduction in coronary artery abnormalities than does aspirin alone.**
- echocardiogram (rather than angiography) is used as the initial screening test for coronary artery aneurysms

Complications

- **coronary artery aneurysm (25% of cases)**
- lacayasu1s arter1 t1s

Kawasaki Disease

- Lymphomucocutaneous Disease
- Five Characteristics of Disease (4/5 for diagnosis)
 - Fever >5 days
 - Cervical lymphadenopathy (usually unilateral)
 - Erythema and edema of palms and soles with desquamation of skin
 - Nonpurulent Bilateral Conjunctivitis
 - Strawberry Tongue
- Treatment
 - IVIG and Aspirin

Takayasu's arteritis

Definition

- Chronic inflammatory granulomatous pan-arteritis of the **major arteries**
 - ⇒ It typically causes occlusion of the aorta (the ascending arch of the aorta)
 - ⇒ The subclavian artery is commonly affected, and subclavian steal syndrome may occur
 - ⇒ The brachial, radial and ulnar arteries can also be involved.

Pathology

- continuous or patchy granulomatous inflammatory process involving macrophages, lymphocytes, and multinucleated giant cells which causes progressive occlusive disease of the aorta and its branches.

Epidemiology

- most commonly affects women (the ratio of women to men is 8:1).
- typical age onset of 25-30 years.
- most common in Asia.

Features

- questions commonly refer to an **absent limb pulse**.
- systemic features of a vasculitis e.g. malaise, headache
- unequal blood pressure in the upper limbs
- carotid bruit
- vascular symptoms such as **claudication**. (intermittent claudication)
- systemic symptoms of fever, arthralgia and weight loss.
- neurological symptoms such as transient ischaemic attacks.
- Cardiac features include angina, heart failure, and aortic regurgitation.
- Renal manifestations may include mesangial proliferative glomerulonephritis.
- aortic regurgitation (around 20%)
- ESR and CRP are usually elevated,
- levels of pentraxin 3 may be a useful marker of disease activity.

Associations

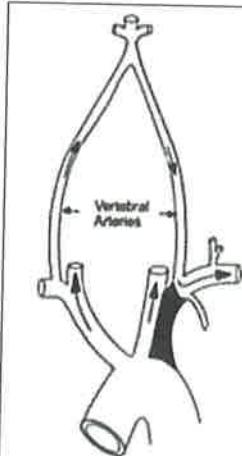
- renal artery stenosis

Treatment

- Corticosteroids with the addition of steroid sparing second agents such as methotrexate or azathioprine are the mainstay of therapy.

Prognosis

- With good care, 15-year survival rates approach 90%.



Subclavian steal syndrome (SSS)

The proximal part of left subclavian is blocked on left side so no flow in vertebral and to left arm. Blood from right vertebral enters left vertebral and flows back to supply left arm

Etiology

- Atherosclerosis
- Cervical rib
- **Takayasu's arteritis**

Features

- Presyncope (sensation that one is about to faint)
- Syncope (fainting)
- Neurologic deficits
- Blood pressure differential between the arms
- severe memory problems
- hands showing circulation problems (hands can have blotchy patches of red and white) (associated with other stigma to vascular disease (e.g. vascular insufficiency ulcers of the foot).

Buerger's disease

Overview

- Thromboangiitis obliterans (Buerger's disease) is a disease of **small and medium-sized arteries and veins** resulting in inflammation and ulceration, in which the **distal vessels** become blocked in the hands and feet.
- There is no excessive atheroma and it does not involve the coronary arteries like atherosclerosis.
- The disease **occurs mainly in cigarette smokers; it has not been documented in non-smokers.**
- Although there is florid histological inflammation within vessels, the disease is not a systemic vasculitis, is not accompanied by any elevation in acute phase markers and does not respond to immune suppression.

Epidemiology

- Prevalence is **higher in men** and people of **Far Eastern origin**.
- seen in young (usually < 40 years) male smokers.

Feature

- symptoms of arterial ischaemia → resulting in **gangrene of the digits**.
 - ⇒ claudication with diminished or absent pulses.
 - ⇒ The feet or legs may be cyanosed or dusky; the skin is thin and without hair.
 - ⇒ Ulcerations occur, and necrosis follows
- **Migratory phlebitis in the superficial vein** is present in 40% of cases.

Diagnosis

- usually clinical.
- Arteriogram will show occlusion of distal arteries of the hands and feet.
- Histopathology
 - ⇒ examination of affected arteries reveals **fresh inflammatory thrombus** within both **small and medium-sized arteries and veins**, **with giant cells surrounding the thrombus**.

Treatment

- Supportive
- **stop smoking.**

Prognosis

- can be excellent (i.e. complete resolution of symptoms) with smoking cessation
- in some cases, however, amputation is unavoidable

IBD-associated arthropathy

- The history of weight loss, diarrhoea and a mono/oligo-arthropathy suggests a diagnosis of inflammatory bowel disease (IBD).
- IBD-associated arthropathy is considered a subtype of seronegative spondyloarthropathy.
- A variety of joint involvement has been described, from large joint pauciarticular arthropathy to a rheumatoid pattern polyarthropathy.
- Peripheral arthritis is generally non-erosive and the oligoarticular variant particularly may correlate with intestinal disease activity.
- Axial arthritis may include inflammatory back pain, sacroilitis, or ankylosing spondylitis and is less likely to correlate with gastrointestinal symptoms.
- mechanisms remain unclear.
- Treatment of the gastrointestinal disease is not always sufficient for control of arthritis, and biologic agents may be indicated.

The description of weight loss, diarrhoea and a mono/oligo-arthropathy suggests a diagnosis of inflammatory bowel disease. (IBD).

Differential diagnoses of arthropathies associated with iron deposition in the joints → brown-stained synovial fluid.

- Haemophilia
- Haemosiderosis from recurrent haemarthrosis
- Haemochromatosis, and
- **Pigmented villonodular synovitis (PVNS).**

SAPHO syndrome

SAPHO is an acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis. It is characterised by osteosclerotic bone lesions, sterile osteomyelitis, and a variety of skin lesions.

- **Synovitis** - may be present rarely, and associates with erosions.
- **Acne** - may be severe (conglobate or fulminans) and recur with new bony involvement.
- **Pustulosis** - palmo-plantar pustulosis occurs in approximately 50% of patients, other skin lesions may include psoriasis, hidradenitis suppurativa, acne, and rarely Sweet's syndrome.
- **Hyperostosis** (increase in bone substance) and **osteitis** (inflammation of the bones) - the bony lesions typically involve the acromioclavicular, and sternoclavicular joints. Other sites include anterior chest wall, sternum, clavicle, pubic symphysis, spine, and mandible. These lesions are visualised on 99m technetium bone scan or MRI.

The cause of the SAPHO syndrome is unknown.

Investigation

- skin lesions are characterised by neutrophilic pseudoabscesses.
- Bone biopsy can reveal sterile osteomyelitis.

Diagnosis should be suspected when there is an association of rheumatic pain with a pustular skin disease.

treatment

- no specific treatment,
- some cases remit spontaneously

- Typical treatment can be used for the arthritic symptoms (i.e. non-steroidal anti-inflammatories and disease modifying anti-rheumatic agents).
- Isotretinoin and acitretin can be used to treat the skin disease.
- In the more severe cases corticosteroids, calcitonin, bisphosphonates and TNF-inhibitors can be used.

Elbow pain

The table below details some of the characteristic features of conditions causing elbow pain:

	Features
Lateral epicondylitis (tennis elbow)	<ul style="list-style-type: none"> pain and tenderness localised to the lateral epicondyle pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks most appropriate to gain short term relief for the patient? → Local steroid/anaesthetic injection
Medial epicondylitis (golfer's elbow)	Features <ul style="list-style-type: none"> pain and tenderness localised to the medial epicondyle pain is aggravated by wrist flexion and pronation symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement
Radial tunnel syndrome	<ul style="list-style-type: none"> Most commonly due to compression of the posterior interosseous branch of the radial nerve. It is thought to be a result of overuse. Features <ul style="list-style-type: none"> symptoms are similar to lateral epicondylitis making it difficult to diagnose however, the pain tends to be around 4-5 cm distal to the lateral epicondyle symptoms may be worsened by extending the elbow and pronating the forearm
Cubital tunnel syndrome	Due to the compression of the ulnar nerve . Features <ul style="list-style-type: none"> initially intermittent tingling in the 4th and 5th finger may be worse when the elbow is resting on a firm surface or flexed for extended periods later numbness in the 4th and 5th finger with associated weakness
Olecranon bursitis	Swelling over the posterior aspect of the elbow. There may be associated pain, warmth and erythema. It typically affects middle-aged male patients.

Shoulder problems

The table below summarises the key features of common shoulder problems:

Condition	Notes
Adhesive capsulitis (frozen shoulder)	Common in middle-age and diabetics Characterised by painful, stiff movement Limited movement in all directions, with loss of external rotation and abduction in about 50% of patients
Supraspinatus tendonitis (Subacromial impingement, painful arc)	Rotator cuff injury Painful arc of abduction between 60 and 120 degrees Tenderness over anterior acromion

Prepatellar bursitis

- The most useful in initial diagnosis of prepatellar bursitis → Crepitus of the knee

Polymyositis

Polymyositis is the commonest cause of inflammatory muscle disease in people under 50-years-old (inclusion body myositis is the commonest in those over 50-years-old).

Anti-Jo-1 antibodies are more common in polymyositis than dermatomyositis

Definition

- Inflammatory disorder causing **symmetrical, proximal, painless** muscle weakness

Pathophysiology

- thought to be a T-cell mediated cytotoxic process directed against muscle fibres

Epidemiology

- Typically affects middle-aged
- Female: male 3:1

Associated conditions

- Connective tissue disorders
- Interstitial lung disease → evaluate with chest x-ray and pulmonary function tests.
- Malignancy, commonly **Adenocarcinomas**, stronger for dermatomyositis, than for polymyositis. **The most appropriate next investigation → CT chest, abdomen and pelvis**

Features

- **Proximal muscle weakness** +/- tenderness
- Raynaud's
- **Mechanics hands** found in a subtype of polymyositis called anti-synthetase syndrome or Jo-1 syndrome → **fissuring and cracking on the distal digital pads of several fingers.**
- Respiratory muscle weakness
- **Interstitial lung disease:** e.g. fibrosing alveolitis or organising pneumonia
- **Dysphagia**, dysphonia

Investigations

- **Elevated creatine kinase** (the initial investigation)
- Electromyography (EMG): abnormal in almost all patients (90%).
 - ⇒ Triad of:
 1. Short, small polyphasia motor units
 2. Fibrillation and sharp waves
 3. Bizarre, repetitive discharges
- Muscle biopsy
 - ⇒ **the definitive investigation to establish the diagnosis**
 - ⇒ Histopathology → **endomysial** mononuclear inflammatory infiltrate with **CD8 T cells (MHC class I)** and muscle fiber **necrosis.**
- Anti-Jo-1 antibodies
 - ⇒ seen in pattern of disease associated with lung involvement, Raynaud's and fever
- **Antinuclear antibody** - Positive in one third

Treatment

- Prednisolone is the mainstay of treatment, at an initial dose of 1 mg/kg/d.
- In patients who fail to show improvement, disease-modifying steroid-sparing agents may be added.
- A high-protein diet and supervised exercise may further improve symptoms.

Prognosis

- Most patients have a favourable response to corticosteroid therapy, and 5-year survival rates approach 80%.

Dermatomyositis

Proximal weakness with normal reflexes and sensation and absence of fasciculations:

- ⇒ without skin lesion → polymyositis
- ⇒ with skin lesion → dermatomyositis

Dermatomyositis antibodies: ANA most common, anti-Mi-2 most specific

Definition

- Dermatomyositis is a variant of an inflammatory myositis causing symmetrical, proximal muscle weakness and characteristic skin lesions, for example a purple **Heliotrope rash** on the cheeks and eyelids or **Gottron's papules**: roughened red papules over extensor surfaces of fingers

Pathophysiology

- Autoantibodies binding to the vasculature, muscle atrophy, and lymphocytic inflammation
- caused by **CD4** T cells that cause perimysial inflammation and atrophy.

Features

- Features of polymyositis (proximal muscle weakness, Raynaud's, respiratory muscle weakness, interstitial lung disease, dysphagia, dysphonia)
- Pathognomonic skin features
 - ⇒ **Heliotrope rash** in the periorbital region
 - a violaceous or erythematous rash in a symmetrical distribution involving periorbital skin.
 - its presence is highly suggestive of dermatomyositis .
 - ⇒ **Gottron's papules**: roughened red papules over extensor surfaces of fingers
- Other skin lesions
 - ⇒ Photodistributed erythema, poikiloderma, nailfold changes
 - ⇒ **Mechanic's hands**: (rough, cracked skin)
 - ⇒ **Fingers telangiectasia**: Nail fold capillary dilatation.
 - ⇒ **Shawl sign**: macular rash over back and shoulder
 - ⇒ **V-neck sig** : Violaceous erythema or poikiloderma involving the anterior chest
- ↑↑ risk of malignancy

Associated features

- Malignancies (**dermatomycotic increases the risk of malignancy more than polymyositis**). typically lung cancer, found in 20-25%
- Interstitial lung disease (ILD) occurs in at least 10%



Investigations

- Elevated creatine kinase → **the most helpful initial test**
- EMG
- Muscle biopsy
 - ⇒ high levels of the complement component **C5b-9 around the capillary vessels**.
 - ⇒ **Perimysial inflammation with lymphocytic infiltrate**
- ANA positive in 60%

- **Anti-Mi-2 antibodies** are highly specific for dermatomyositis, but are only seen in around 25% of patients
- **Screen for malignancy**

Management

- Prednisolone
- Glucocorticoid-sparing agents: azathioprine or methotrexate.

Prognosis

- Relatively good, with **most patients reaching remission after 2–3 years**, except of course where there is an associated underlying malignancy.

Inclusion body myositis (IBM)

Definition

- a syndrome of diffuse, progressive, **asymmetric**, proximal, and distal weakness that is generally **refractory to immunosuppressive treatment**.
- The aetiology of IBM is largely unknown.

Epidemiology

- IBM occurs **more frequently in men than women**.
- More common in older Caucasian males.
- the most common acquired myopathy in **patients older than 50 years**

Features

- Muscle weakness can affect **both proximal and distal muscles**
 - ⇒ unlike **polymyositis and dermatomyositis, asymmetry is common**.
 - ⇒ characteristically early affects quadriceps and finger/wrist flexors are usually more severely
 - ⇒ The onset of muscle weakness in IBM is generally gradual (over months or years).
- Dysphagia is common, occurring in 40-66% of patients
- Difficulties with breathing → the most common cause of death is respiratory system disorders.

Diagnosis

- creatine kinase (CK) levels: no striking elevation (less than 10 times normal)
- anti-**cN1A** autoantibodies
- Muscle biopsy
 - ⇒ shows **intranuclear or cytoplasmic tubofilaments** on electron microscopy.
 - ⇒ The specific finding is the presence of **sarcoplasmic “rimmed” vacuoles**

Treatment

- Optimal treatment for IBM is not known
- In contrast to dermatomyositis and polymyositis, IBM is relatively resistant to standard immunomodulatory therapies.

	Polymyositis	Dermatomyositis	IBM
Onset	Subacute	Subacute	Slow
age	Commonest < 50 years	Commonest < 50 years	commonest > 50 years
Affected muscles	Proximal	Proximal	Proximal and distal
symmetry	symmetrical	symmetrical	Asymmetrical
Common incidence	Female	Female	Male
Skin lesion	NO	Characteristic rash	NO
CK	Highly elevated (up to 50 fold)	Highly elevated (up to 50 fold)	Mild elevated (up to 10 fold) or normal
antibodies	anti-Jo-1 are more common	anti-Mi-2 are highly specific	anti-cN1A autoantibodies
Muscle biopsy	endomysial mononuclear inflammatory infiltrate and muscle fiber necrosis.	perivascular and interfascicular inflammatory infiltrates with adjoining groups of muscle fiber degeneration/regeneration	intranuclear or cytoplasmic tubofilaments
T cell	CD8 T cell	CD4 T cell	
Response to steroids	good	Good	Poor

Painless weakness and wasting with selective involvement of long finger flexors and quadriceps is characteristic of inclusion body myositis.

Inclusion body myositis occurs in older people, has an insidious onset, and does not associate with striking elevations in CK.

Fibromyalgia (FM)

Definition

- Fibromyalgia is a syndrome characterised by widespread pain throughout the body with **tender points at specific anatomical sites**.

Epidemiology

- Prevalence: occur in 1 - 2% of the general population
- **Gender: women are 10 times more** likely to be affected
- Age: typically presents between 30-50 years old

Features

- general symptoms: lethargy
- musculoskeletal symptoms:
 - ⇒ chronic pain: at multiple site, sometimes 'pain all over'
 - ⇒ allodynia: (pain in response to non-painful stimuli)
 - ⇒ Morning fatigue
 - ⇒ morning stiffness
 - ⇒ tissue swelling,
- neurological and psychiatric symptoms:
 - ⇒ sleep disturbance, headaches, dizziness are common
 - ⇒ patients often look unwell and may appear depressed and anxious.
- GIT symptoms:
 - ⇒ 50% of patients with fibromyalgia complain of **diarrhoea and constipation**, often associated with abdominal bloating.

Diagnosis

- The diagnosis of FM should be considered in any patient with >three months of widespread, multisite pain without apparent causative found.
- is clinical → **pain in all four quadrants of the body**, as well as **tenderness** in 11 of 18 anatomically defined trigger areas.
- The **normal ESR** in patients with FM contrasts with the high ESR in elderly patients with polymyalgia rheumatica.
- Other causes of fatigue should be excluded e.g. hypothyroidism, anaemia and other rheumatological diseases

Management

- explanation
- **aerobic exercise: has the strongest evidence base**
- cognitive behavioural therapy
- medication: pregabalin, duloxetine, amitriptyline

Key facts:

- How to diagnose?
 - ⇒ A female, presented with a feature of pain and **tenderness** over multiple area + **normal ESR** and CRP.
- What is the best management?
 - ⇒ aerobic exercise

Dupuytren's contracture

Definition

- progressive painless contracture of the palmar fascial bands, causing flexion deformities of the fingers.
- autosomal-dominant** condition with variable penetrance.

Prevalence

- has a **male**: female predominance of 10:1.
- prevalence rates approaching 25% in elderly Scandinavians.
- most commonly observed in persons of Northern European descent and affects 4-6% of Caucasians worldwide.

Pathophysiology

- fibroblast proliferation**, and collagen deposition leading to contractures of the palmar fascia.
- Interleukin 1 (IL-1)** is the most abundant cytokine
- Normal palmar fascia is primarily composed of type I collagen; Dupuytren disease is associated with an **increase in type III collagen**.

Risk factor

- Alcoholism** (10%),
- diabetes mellitus (8%).
- previous myocardial infarction,
- hand trauma,
- HIV infection,
- cigarette smoking.

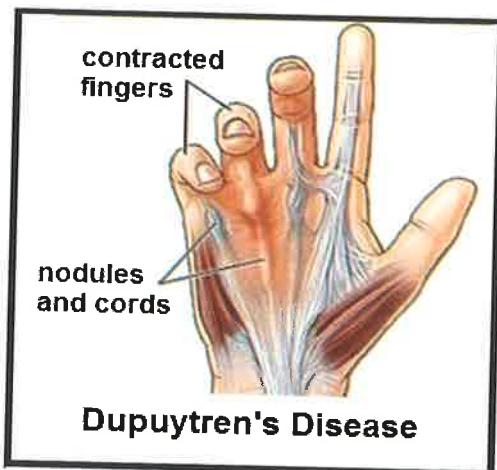
Features

- bilateral in 45%;
- in unilateral cases, the right side is more often affected.
- The ring finger is most commonly involved, followed by the fifth digit and then the middle finger. The index finger and the thumb are typically spared.
- Penile fibromatosis (Peyronie's disease) is seen in about 7-10% of patients.

Rheumatoid arthritis seems to protect against the development of Dupuytren disease.

Management

- Surgery followed by physiotherapy to improve finger function is the recommended course of action.
- Collagenase therapy may be an alternative to surgery in some cases.



Ledderhose disease is involvement of the plantar fascia by a similar process of nodule and cord formation leading to **contraction of the toes**.

Baker cyst

Look for a patient with osteoarthritis or rheumatoid arthritis with a swollen calf. A ruptured Baker's cyst is a "pseudophlebitis." Unruptured cysts can be palpated.

Overview

- A Baker's cyst (popliteal cyst) is a posterior herniation of the synovium of the knee.
- A Baker cyst is the most common mass in the popliteal fossa.
- Since the cyst is an extension from the knee joint, it is lined by synovium.

Causes

- **the most common cause → osteoarthritis**

Investigations

- **Ultrasonography** is the imaging technique of choice in the evaluation of a popliteal mass, but using this technique it may be difficult to show a true connection with the joint space to establish a definitive diagnosis of popliteal cyst.