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Chapter 8

Rheumatology

(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

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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• Preferred medications (if required) NSAIDs: may be used until 32 weeks but after this time should be withdrawn due to the risk of early close of the ductus arteriosus.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) TNFα 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.

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

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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

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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:

1. 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

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Ankylosing spondylitis 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 tramline 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 • Ossification or calcification of the annulus fibrosus or a spinal ligament Radiographic features • Symmetrical, vertical growth, directly from vertebral body to vertebral body • Full manifestation: "bamboo spine" Etiology • Inflammatory spine disease (e.g., AS) Notes & Notes for MRCP
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• Lipping of vertebral bodies • Horizontal growth • Degenerative spine disease (e.g., diffuse idiopathic skeletal hyperostosis)

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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: Sacroilitis 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 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

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• 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 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) 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)

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 sleepwake 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.

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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 reticulated 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

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Rheumatology 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

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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

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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

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

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• 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/µL with > 50%

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

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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

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 IL-1 blockers
 European Medicines Agency approved anti-IL-1β 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. • 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 ≥ 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 µmol/L). Urate-lowering therapy (ULT) • Xanthine oxidase inhibitors (XOIs): Allopurinol and Febuxostat (the preferred firstline 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 secondchoice 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 Monitor for myotoxicity when prescribing colchicine with statins. Reduce dose of pravastatin, atorvastatin, and simvastatin when prescribed concomitantly.

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 Interactions Purine analogs (e.g., azathioprine, 6-mercaptopurine) combined with XOIs 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 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. The combination

of allopurinol and azathioprine leads to increased bone marrow toxicity

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Rheumatology 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 (↑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

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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 paraesthetica 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 of 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

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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 • 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 • 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. Pauciarticular JIA refers to cases where 4 or less joints are affected. It accounts for around 60% of cases of JIA Features of pauciarticular JIA • 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

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Lateral epicondylitis 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

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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 • 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 • 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 • 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 • 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 • (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:

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Rheumatology

 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.