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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Mixed connective tissue disease (MCTD) 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 antiU1 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 • 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

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Rheumatology Osteoarthritis: x-ray changes X-ray changes of osteoarthritis • decrease of joint space • subchondral sclerosis • subchondral cysts • osteophytes forming at joint margins

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Osteoarthritis: management • 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 intraarticular 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.

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Rheumatology

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

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 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

Rheumatology

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 Typically, 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 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 nonmechanical 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 • Europid 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 (Δ 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

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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 supplemention 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 DS 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

• 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

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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 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/m) 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 highdose 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

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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

Rheumatology Supplementary notes on treatment • Bisphosphonates Oral bisphosphonates (alendronic 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 (alendronic 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 Alendronic 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.

Rheumatology 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 ≥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.)

Rheumatology

Paget's disease of the bone 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 disorganised 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

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• 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.

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

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Pseudogout 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/μL 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

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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. 1. asymmetric oligoarthritis (most common) (43%). 2. symmetric polyarthritis (33%) proximal interphalyngeal joint involvement.

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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 Psoariatic 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 • Psoariatic 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:
6. Current psoriasis (assigned a score of 2)
7. history of psoriasis (in the absence of current psoriasis; assigned a score of 1)
8. family history of psoriasis (in the absence of current psoriasis and history of psoriasis; assigned a score of 1)
9. Dactylitis (assigned a score of 1)
10. Juxta-articular new-bone formation (assigned a score of 1)
11. RF negativity (assigned a score of 1)
12. 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:

1. presence of dactylitis and
2. 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.

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Rheumatology Notice the nail changes on this image as well X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxtaarticular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.

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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 progresion towards a 'pencil-in-cup' changes.