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Rheumatology

Reactive arthritis (Reiter syndrome) • Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint. the presence of bacterial infection on joint aspiration would count against it. • Reactive arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies. • It encompasses Reiter's syndrome, a term which described a classic triad of urethritis, conjunctivitis and arthritis following a dysenteric illness during the Second World War. • Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA). Eye diseases in Reiter's syndrome: • Most common conjunctivitis (50%) • Less common iritis (12%) Epidemiology • post-STI form much more common in men (e.g. 10:1) • post-dysenteric form equal sex incidence The table below shows the organisms that are most commonly associated with reactive arthritis: Post-dysenteric form Post-STI form Shigella flexneri Salmonella typhimurium Salmonella enteritidis Yersinia enterocolitica Campylobacter Chlamydia trachomatis Features • typically develops within 4 weeks of initial infection symptoms generally last around 4-6 months • arthritis is typically an asymmetrical oligoarthritis of lower limbs mainly affecting the large weight-bearing joints (usually knee and ankle). • dactylitis • symptoms of urethritis • eye:

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 conjunctivitis (seen in 50%), anterior uveitis • skin: circinate balanitis (painless vesicles on the coronal margin of the prepuce), keratoderma blenorrhagica (waxy yellow/brown papules on palms and soles) Management • usually self-limiting • symptomatic: analgesia, NSAIDS, intra-articular steroids • sulfasalazine and methotrexate are sometimes used for persistent disease Prevention • Antibiotics given at the time of the non-gonococcal venereal infection will reduce the likelihood of that person developing reactive arthritis. Appropriate treatment during the acute stage would be doxycycline 100 mg bd if Chlamydia infection is confirmed. Prognosis • Prognosis with respect to long-term complications is better when dysenteric infection is the precipitant factor rather than Chlamydial infection. • arthritis usually resolves in 3 months • In general, symptoms last from a few weeks to around 6 months in total. symptoms rarely last more than 12 months •

Around 25% of patients have recurrent episodes • 10% of patients develop chronic disease • In HLA-B27-positive patients, ankylosing spondylitis may develop in up to 50% of patients who have suffered an episode of reactive arthritis. • HIV infection is associated with a higher risk of reactive arthritis HLA-B27 is found in 80–90 % of Caucasians with HIV-associated reactive arthritis, while studies of Africans with HIV-associated reactive arthritis have found nearly all to be HLA-B27-negative • Rarer long-term complications include: urethral stricture, cataracts, and aortic root necrosis. Keratoderma blenorrhagica

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Amyloidosis Amyloidosis should always be considered in a patient with a long-standing inflammatory and/or infectious disease who presents with kidney, liver, or GI involvement. Overview • amyloidosis is describes the extracellular deposition of an insoluble fibrillar protein termed amyloid • amyloid also contains a non-fibrillary protein called: amyloid-P component, derived from the acute phase protein serum amyloid P apolipoprotein E heparan sulphate proteoglycans • the accumulation of amyloid fibrils leads to tissue/organ dysfunction Causes • Amyloidosis may be inherited or acquired; acquired form is associated with long standing chronic illnesses (DM, Rheumatoid Arthritis). Feature • unexplained weight loss, • fatigue, • oedema resistant to diuretic therapy. • joint pains and stiffness, usually upper limbs more than lower limbs. Types • Light-chain amyloidosis (AL-amyloidosis) Most common form of amyloidosis in developed nations Aetiology: primary disease caused by plasma cell dyscrasias e.g., : multiple myeloma, Waldenström's macroglobulinemia, non-Hodgkin lymphoma Pathophysiology: increased production of the light chains of immunoglobulins → deposition of AL (amyloid light chain) protein in various organs Features: rapidly progressive clinical course Heart: restrictive cardiomyopathy, atrioventricular block An ECG is required in all patients to look for conduction abnormalities. Kidney: nephrotic syndrome, type II renal tubular acidosis, nephrogenic diabetes insipidus Tongue: macroglossia → obstructive sleep apnea Nervous system: Amyloid peripheral neuropathy carpal tunnel syndrome only seen in AL, never seen in AA autonomic neuropathy Gastrointestinal tract: malabsorption periorbital ecchymoses Enlargement of the submandibular salivary glands

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 shoulder pad sign due to periarticular infiltration with amyloid and pseudohypertrophy is specific for AL Bleeding disorders • Reactive amyloidosis (AA-amyloidosis) Etiology: secondary disease Chronic inflammatory conditions (e.g., IBD, rheumatoid arthritis, SLE, vasculitis) Chronic infectious diseases (e.g., tuberculosis, bronchiectasis, leprosy, osteomyelitis) Certain tumors (e.g., renal cell carcinoma, lymphomas) Pathophysiology: chronic inflammatory process → increased production of acute phase reactant SAA (serum amyloid-associated protein) → deposition of AA (amyloidassociated) protein in various organs Clinical features Kidney: most common feature renal involvement

 nephrotic syndrome, type II renal tubular acidosis, nephrogenic diabetes insipidus Adrenal glands: primary adrenal insufficiency Liver and spleen: hepatomegaly, splenomegaly Gastrointestinal tract: malabsorption • β-2 microglobulin amyloidosis Precursor protein is β-2 microglobulin, part of the major histocompatibility complex Associated with patients on renal dialysis neurological impairment in patients on longstanding dialysis. Diagnosis • Biopsy Biopsy of abdominal wall fat, the rectum or a salivary gland can be examined The tissue is treated with Congo red stain the amyloid proteins appear applegreen birefringence on Light microscopy. • Tests to diagnose the underlying disease Light chain amyloidosis Serum electrophoresis: monoclonal gammopathy Urine test for Bence-Jones proteins multiple myeloma Reactive amyloidosis: ESR, CRP, chest x-ray Renal amyloid with congo red staining - apple-green birefringence

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Rheumatology Renal amyloid with congo red staining - apple-green birefringence Congo red staining. Amyloid deposits are seen in both the arteries/arterioles and within the glomerulus. The deposit of amyloid within the mesangium is not dissimilar to the nodular lesions seen in diabetic nephropathy Pathological feature of amyloidosis

1. Electron micrography - fibrillar appearance
2. x Ray diffraction pattern - beta pleated sheet structure
3. Haematoxylin and eosin staining - amorphous eosinophilic appearance
4. Congo red histological staining - apple-green birefringence
5. Solubility in water and buffers of low ionic strength. Treatment • The only treatment is renal transplantation. • It can be reduced by using high flux dialysis membranes in patients who are likely to be on dialysis for a prolonged period.

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Amyloidosis: cardiac • Cardiac amyloidosis most commonly presents as restrictive cardiomyopathy, associated with AL Amyloidosis • Presentation: Typical presentation of right heart failure: Jugular venous distension Peripheral oedema Orthopnoea and paroxysmal nocturnal dyspnea are typically absent • Diagnosis Combination of low-voltage ECG and thickened ventricular walls is one of the characteristic features of cardiac amyloidosis. Echocardiographic abnormalities include: dilatation of atria, thickened interatrial septum, diastolic dysfunction and smallvolume ventricles. The most distinctive feature of cardiac amyloidosis is a sparkling, granular appearance of myocardium, but this is a relatively insensitive feature occurring only in about 25% of cases. Cardiac amyloidosis is associated with a 'global speckled' pattern on echo. The ECG typically shows low-voltage complexes with poor R wave progression in the chest leads (a pseudoinfarction pattern). Management of AL • The most effective treatment is autologous bone marrow transplants with stem cell rescues. However, many patients are too weak to tolerate this approach • Other treatments can involve application of chemotherapy similar to that used in multiple myeloma. A combination of bortezomib and dexamethasone has been proposed, as has melphalan and dexamethasone. • Digoxin is contraindicated in cardiac amyloidosis (restrictive

cardiomyopathy)

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

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 it is poorly virulent, symptoms of PA infection may occur many years after original arthropathy, it is sensitive to penicillins, clindamycin and carbapenems. Feature • Fifty percent of cases will have an associated bacteraemia. • Early x-rays are almost always normal. Management • synovial fluid should be obtained before starting treatment • intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends flucloxacillin or clindamycin if penicillin allergic • antibiotic treatment is normally be given for several weeks (BNF states 6-12 weeks) ideally these should be intravenous for 2 weeks and then oral for 4 weeks. • needle aspiration should be used to decompress the joint • surgical drainage may be needed if frequent needle aspiration is required • if patient on warfarin, what is the most appropriate management of anticoagulation before joint aspiration and injection? If INR is within the therapeutic range no need to stop the warfarin or change the dose. The risk of a thrombotic episode if anticoagulation is changed outweighs any risk associated with injecting joint while taking anticoagulation.

Sjogren's syndrome • Sjogren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces. • It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around 10 years after the initial onset. • primary Sjögren's syndrome occurs alone and more likely to have positive anti Ro SSA antibodies than secondary Sjögren's). • Hypergammaglobulinaemia is present in 80% of individuals. • Typically secondary Sjögren's has pre-existent rheumatoid or systemic lupus erythematosus before the development of Sjögren's symptoms. • more common in females (ratio 9:1). • There is a marked increased risk of lymphoid malignancy (40-60 fold) Features • dry eyes: keratoconjunctivitis sicca • dry mouth • vaginal dryness • arthralgia • Raynaud's, • myalgia • sensory polyneuropathy • renal tubular acidosis (usually subclinical) • Plasma cell infiltration of salivary and lacrimal glands: Parotid swelling.

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Complication • higher risk of developing lymphoma These lymphomas are primarily of B cell origin. High risk factors for lymphoma development in Sjogren's syndrome patients include: persistent unilateral or bilateral parotid gland enlargement, splenomegaly and lymphadenopathy, low C4 complement levels, type 2 mixed cryoglobulinaemia Investigation •

rheumatoid factor (RF) positive in nearly 100% of patients • ANA positive in 70% • anti-Ro (SSA) antibodies in 70% of patients with PSS Anti-Ro antibody is associated with: congenital complete heart block neonatal lupus The mother is usually positive for anti-Ro or anti-La antibodies but may not have overt lupus erythematosus. • anti-La (SSB) antibodies in 30% of patients with PSS • Hypergammaglobulinaemia (↑ IgG) in 80% • low C4 • Schirmer's test: filter paper near conjunctival sac to measure tear formation placement of a standard strip of filter paper on the inside of the lower eyelid. Wetting of less than 5 mm in 5 min indicates defective tear production. • Rose Bengal staining of the eyes commonly shows punctuate or filamentary keratitis. • histology: focal lymphocytic infiltration • the most definitive test for Sjögren's syndrome Labial gland biopsy Management • artificial saliva and tears • pilocarpine may stimulate saliva production Other causes of dry eyes, and/or dry mouth include: • past head and neck radiation • hepatitis C infection • acquired immunodeficiency disease • pre-existing lymphoma • sarcoidosis • graft versus host disease, or • the use of an anticholinergic drugs.

Systemic lupus erythematosus (SLE) • Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder. Epidemiology • much more common in females (F:M = 9:1) • more common in Afro-Caribbeans* and Asian communities

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 *It is said the incidence in black Africans is much lower than in black Americans - the reasons for this are unclear • onset is usually 20-40 years Pathophysiology • autoimmune disease • associated with HLA B8, DR2, DR3 • thought to be caused by immune system dysregulation leading to immune complex formation • the most likely immunopathological process: Activation of the classical complement pathway complement consumption is common in active SLE (indicated by the low C3 and C4). Activation of the classical complement pathway occurs in (SLE) owing to the large number of double-stranded DNA (dsDNA) and other immune complexes that form and fix complement. These immune complexes deposit in the kidneys and other organs, where they attract other components of the immune system that cause tissue damage. • immune complex deposition can affect any organ including the skin, joints, kidneys and brain • SLE can also be described as a type III hypersensitivity reaction Features The triad of fever, arthralgia and rash in a woman of childbearing age should suggest the diagnosis of systemic lupus erythematosus (SLE). General features The multisystem presentation of fever, arthralgia, pericarditis and nephritis associated with the epidemiological clues (a young black female) suggest a diagnosis of (SLE). • fatigue • fever
• mouth ulcers • lymphadenopathy Skin • malar (butterfly) rash: spares nasolabial folds • discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic • photosensitivity • Raynaud's phenomenon • livedo reticularis • non-scarring alopecia Musculoskeletal • arthralgia typically affecting the small joints of the hands, wrists and knees. • non-erosive arthritis

• Jaccoud's arthropathy gross deformities of the hands without joint damage or erosions • caused by recurrent episodes of synovitis that damage tendon sheaths and slings resulting in joint deformity • seen in: SLE Rheumatic fever Parkinson's disease, and Hypocomplementaemic urticarial vasculitis. Cardiovascular • myocarditis Respiratory • pleurisy • fibrosing alveolitis • Direct pulmonary involvement in (SLE) occurs in 30% (pleuropericarditis, atelectasis, pneumonitis, raised hemidiaphragms and pulmonary fibrosis). Renal • proteinuria • glomerulonephritis (diffuse proliferative glomerulonephritis is the most common type) Neuropsychiatric • anxiety and depression • psychosis • seizures Investigations Immunology SLE - antibodies associated with congenital heart block = anti-Ro • 99% are ANA positive (the best screening test for SLE) Almost all patients with SLE have a positive ANA test result. ANA test is sensitive but not specific for SLE. A negative result argues strongly against a diagnosis of active SLE, but does not exclude the possibility of other autoimmune diseases. Negative ANA has the highest negative predicted value (The highest negative predicted value implies the test with the greatest sensitivity.) • 20% are rheumatoid factor positive • anti-dsDNA: highly specific (> 99%), but less sensitive (70%) • anti-Smith: most specific (> 99%), sensitivity (30%) Therefore, absence of anti-DNA or anti-Sm antibodies should not exclude SLE as a diagnosis • also: anti-U1 RNP, SS-A (anti-Ro) and SS-B (anti-La) Anti-Rho and -La antibodies are associated with the development of neonatal lupus. Anti-Ro/SS-A antibodies are found in 30% of patients with SLE. Anti-Ro antibodies can cross the placenta to cause transient cutaneous lupus in the neonate (5-25% of babies) or permanent congenital heart block (1-3% of babies).

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Markers of SLE disease activity • Early markers of SLE disease activity include: falling C4 levels, although congenital C4 deficiency is itself a predisposing factor for SLE development, so these tests must be interpreted with caution. rising immunoglobulins, falling haemoglobin (Hb), white cell count (WCC), platelets and albumin. Monitoring • ESR: during active disease the CRP is characteristically normal - a raised CRP may indicate underlying infection • complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement) • anti-dsDNA titres can be used for disease monitoring (but note not present in all patients) Management • Basics NSAIDs sun-block • Hydroxychloroquine useful for skin disease • If internal organ involvement e.g. renal, neuro, eye then consider prednisolone, cyclophosphamide Complication • Lupus patients are more prone to infection. Up to two-thirds of lupus patients will have some lung involvement during the course of their disease. The most common manifestations are pleuritis and pleural effusions. SLE: pregnancy Overview • Unlike many autoimmune diseases (SLE) often becomes worse during pregnancy and the puerperium • risk of maternal autoantibodies crossing placenta • leads to condition termed neonatal lupus erythematous • neonatal complications include congenital heart block • strongly associated with anti-Ro (SSA) antibodies Treatment • azathioprine A large body of evidence from the use of azathioprine in pregnancy for the treatment of both rheumatological conditions and inflammatory bowel disease, supports it's

use. Although it is less effective in the management of SLE with renal disease versus other options, balance of benefit risk makes it the preferred intervention. • Ciclosporin appears to be associated with premature delivery and low birth weight, although it does not seem to be associated with malformations, this drives it's use as an alternative to azathioprine in patients who fail to gain control of their disease. • Cyclophosphamide, methotrexate and mycophenolate are all contraindicated for use in pregnancy.

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Drug-induced lupus erythematosus Overview • The pathogenesis of drug-induced lupus is unclear. • Factors that influence drug metabolism, such as acetylator status, have been implicated. • In addition, lupus-inducing drugs have been shown to generate a variety of cytotoxic products on exposure to MPO released from activated neutrophils. Epidemiology • Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbeans, whereas the inverse is true of idiopathic SLE. • affect the 50-70-year age group most commonly, • has a male: female ratio of 1:1 Causes The most commonly associated drugs • procainamide • hydralazine 2, • quinidine. • Isoniazid (INH) - low risk • Sulfasalazine - low risk. • Carbamazepine • Phenytoin • Lamotrigine • anti-TNF alpha agents, • Interferons • Statins • minocycline. Minocycline associated with the development of long term immunological memory, and therefore exacerbation of symptoms within 12-24 hours of rechallenge. Risk factors • strongly positive ANA • HLA-DR4 phenotype (hydralazine-induced disease) • slow acetylator status Slow acetylators have increased risk of isoniazid-induced peripheral neuropathy, and hydralazine or procainamide-induced systemic lupus erythematosus (SLE). • large total daily doses of precipitating drugs Features • symptoms are said to appear some 3 weeks to 2 years after the onset of therapy • In drug-induced lupus not all the typical features of SLE are seen, with renal and nervous system involvement being unusual. • Lack of cutaneous involvement presents with purpuric, erythematous, papular rash. They do not have a malar or discoid rash. skin (e.g. malar rash) (seen in 25%)

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Rheumatology However, drug induced lupus due to interferon and due to anti-TNF α agents, may present with malar or discoid rash, and may be anti-dsDNA antibody positive. • joint pains, myalgia and malaise are more common • pulmonary involvement (e.g. pleurisy) are common • Raynaud’s is seen in around 25% Laboratory features • ESR and C reactive protein (CRP) are both markedly elevated, • ANA is strongly positive (in 100%,) • hypergammaglobulinaemia. • Anti-dsDNA antibodies are usually negative; positive for anti-ssDNA antibody and typically negative for anti-dsDNA antibody. • antihistone antibodies are positive in 95% of drug-induced lupus (but also 50-80% of idiopathic SLE3). • anti-Ro, anti-Smith positive in around 5% • C3/C4 levels are usually normal. There are several features which distinguish drug-induced lupus from idiopathic SLE: • Males and females are equally affected in drug-induced lupus, whereas idiopathic SLE affects females nine times more frequently. • Caucasians are affected by drug-induced lupus more commonly than AfroCaribbeans, whereas the inverse is true of idiopathic SLE. • the age of onset is typically older in drug-induced lupus, but this depends on the age at drug exposure. • Fever,

arthralgia, serositis and ANA occur at least as frequently in drug-induced lupus as idiopathic SLE. • Haematological, renal and central nervous system (CNS) involvement, and double-stranded DNA autoantibodies are rare. Treatment • Typically, no further treatment is required after Withdrawal of the precipitating drug • However, there are situations where corticosteroids or disease modifying antirheumatic drugs (DMARDs) are required to aid resolution. • The time taken for symptoms to resolve after stopping minocycline is highly variable, from a few days to two years. Prognosis • Spontaneous recovery usually occurs promptly

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A woman with drug-induced lupus

drugs that induce lupus do not need to be avoided in the idiopathic type of lupus. MRCPUK-part-2-march-2018: A female diagnosed with epilepsy, suffering from an erythematous rash over sun-exposed areas of her skin. Antihistone antibodies are positive. Which medication is the most likely cause of her rash? Phenytoin, carbamazepine and lamotrigine are associated with drug-induced lupus erythematosus Antiphospholipid syndrome • Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. • It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE) • A key point for the exam is to appreciate that antiphospholipid syndrome causes a paradoxical rise in the APTT. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade Features • venous/arterial thrombosis • recurrent fetal loss • livedo reticularis • thrombocytopenia • prolonged APTT (raised aPTT which fails to correct after the addition of normal human plasma). • other features: pre-eclampsia, pulmonary hypertension False positive VDRL testing Associations other than SLE • other autoimmune disorders • lymphoproliferative disorders • phenothiazines (rare) Risk factor for thrombosis • Lupus anticoagulant is the greatest predictor of future thrombosis in patients with anti-phospholipid syndrome Diagnosis • antiphospholipid antibody syndrome (APAS) can be diagnosed if:

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 the patient has anticardiolipin antibodies, or lupus anticoagulant on two occasions, over a period of 12 weeks, and either: has had a thrombus, or a history of recurrent < 10-week pregnancy loss, or one pregnancy loss > 10 weeks in gestation when other causes of pregnancy loss have been excluded. • Antibodies • the most clinically important autoantibodies directed against phospholipid binding plasma proteins are:

1. The lupus anticoagulant
2. Anti-beta-2 glycoproetin I antibodies, and
3. The anticardiolipin antibodies. Management - based on BCSH guidelines • initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of

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

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

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

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• Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. • It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE) In pregnancy the following complications may occur: • recurrent miscarriage • IUGR • pre-eclampsia • placental abruption • pre-term delivery • venous thromboembolism Management • low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing • low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation • these interventions increase the live birth rate seven-fold

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Juvenile idiopathic arthritis (JIA) (Still’s disease) Definition • The ACR criteria define juvenile rheumatoid arthritis (JRA) by age limit (< 16 y) and the duration of disease (> 6 weeks). Epidemiology • the most common form of arthritis in children and adolescents. • Prevalence: 1/1000 children • Sex: ♀ > ♂ Types • Oligoarticular JIA Most common form (accounts for 50% of all JIA cases) affects four joints or fewer during the first 6 months, has the highest risk of developing Chronic anterior uveitis (up to 25%) Bilateral eye involvement is common RF negative ANA positive (~70% of cases) Treatment NSAIDs Possibly intra-articular steroid injections Possibly methotrexate • Polyarticular JIA 40% of cases characterised by inflammatory arthritis affecting five or more joints during the first 6 months of the disease. RF negative ANA positive (~40% of cases) Treatment: Standard therapy with methotrexate and NSAID • Systemic-onset JIA (Still's disease) < 10% of cases presents with fever, arthritis and at least one of the following: erythematous rash, generalised lymphadenopathy,

Hepatosplenomegaly serositis (including pleural and pericardial effusions)

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 RF negative ↑ Acute phase reactants (e.g., CRP, ferritin) Treatment: Poor response to methotrexate and TNF inhibitors (etanercept, adalimumab) Risk factors • Exposure to antibiotics during childhood may increase the risk of JIA. Features Joint pain, daily spiking fevers, and a 'salmon-pink' rash are classic symptoms. • persistent non-tender joint swelling (The cardinal feature) The first manifestation of JIA is often limping, especially in young children. The persistent swelling most often occurs in the large joints. Damage to joints is associated with a TH1 response. • Up to 25% of patients have a positive anti-nuclear antibody. • microcytic anaemia which tends to be resistant to iron replacement • pericarditis is often found. • hepatosplenomegaly, • JIA can decrease bone mass and increase the risk of osteoporosis. • ↑ESR (usually seen with all forms of JIA). • Rheumatoid nodules and rheumatoid factor are usually absent Rheumatoid factor (RF) is absent in most cases of JIA except seropositive polyarticular JIA. • anterior uveitis What eye condition is most commonly associated with this presentation? anterior uveitis. about 30–50% of children with JIA have uveitis at diagnosis, especially those who are antinuclear antibody (ANA) positive. The uveitis is typically asymptomatic at onset and must be screened for with an ophthalmologic slit lamp examination. Untreated uveitis can be associated with cataracts, glaucoma and macular oedema about 50–70% of people with severe uveitis develop visual impairment. If a patient with (JIA) developed new-onset anterior uveitis despite treatment with subcutaneous methotrexate adalimumab (as adalimumab is more effective in treating uveitis than etanercept) Treatment • Options for pharmacotherapy include NSAIDs, corticosteroids, methotrexate, and anti-TNF biologicals. • Treatment with IL-6 receptor antibody has proved to be successful. • As per NICE guidance, if patient had not responded to methotrexate and should be considered for biologic therapy with either adalimumab, etanercept or tocilizumab. Prognosis • Anti-CCP antibodies indicate a poor prognosis. • Early disease onset is associated with a greater degree of growth impairment and deformity.

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Adult onset Still's disease (AOSD) (Adult Still's disease) Adult-onset Still's disease →triad of persistent high spiking fevers, joint pain, and a distinctive salmon-colored bumpy rash. • typically affects 16-35-year olds Features • arthralgia • rash: salmon-pink, maculopapular (most prominent with fever) occurs in approximately 90% of patients often seen only when the patient is febrile and is easily missed. • pyrexia (> 39oC) especially in the afternoon and evening described as quotidian or diquotidian returning to 37°C or below between episodes. • lymphadenopathy • Hepatosplenomegaly, • There is often an accompanying sore throat and myalgia. Rarely there may be: • Aseptic meningitis • Cranial nerve palsies • Iritis, and • Peripheral neuropathy. Investigation • neutrophilic leukocytosis, thrombocytosis, • ↑ serum ferritin High serum ferritin, with low glycosylated fraction, are characteristic and can be used as disease activity markers. • ↑ESR and

C-reactive protein. • Interleukin (IL)-1, IL-6, IL-18, macrophage colony stimulating factor, interferon gamma and TNF-alpha are all elevated. • rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative Diagnosis • Diagnosis is clinical, and should include exclusion of infectious disease, neoplasms and other autoimmune disease. Treatment • non-steroidal anti-inflammatory drugs (NSAIDs), • corticosteroids, • disease-modifying anti-rheumatic drugs • biological agents. • Intravenous immunoglobulin may have a role. Prognosis • tends to be better when systemic symptoms predominate. Adult onset Still's disease is typically rheumatoid factor negative

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

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 presence of autoantibodies features which may suggest rheumatoid arthritis or SLE, for example arthritis or recurrent miscarriages digital ulcers, calcinosis very rarely: chilblains Investigations Which investigation would be most useful in determining whether the Raynaud’s is related to vasculitis? Nail fold capillaroscopy • The most useful initial assessment must include nail fold capillary loop examination, ideally by capillaroscope or, if not available, by ophthalmoscope using magnification. method Nailfold capillaroscopy is performed by applying a drop of oil onto the periungual region of the nail and using an ophthalmoscope set to 40 diopter to examine. interpretation Patients with connective tissue disorder such as systemic sclerosis

most often will show dilated, distorted, paucity or missed nail fold capillary loops. Management • For primary Raynaud phenomenon: First line lifestyle measures. The best initial line Advise on lifestyle changes to reduce the frequency of the attacks, such as heated gloves, stopping smoking and avoiding the cold environments Second line pharmacologic treatment. First pharmacologic line: calcium channel blockers e.g. nifedipine IV prostacyclin infusions: effects may last several weeks/months indications if the patient does not respond to nifedipine Retard or

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

Systemic sclerosis (SSc) • Systemic sclerosis is a chronic autoimmune disease characterised by increased fibroblast activity and fibrosis in a number of different organ systems. • characterised by hardened, sclerotic skin and other connective tissues. Epidemiology • It is four times more common in females (♀> ♂) • Higher incidence in African Americans • Peak incidence: 30–50 years Types: There are three patterns of disease:

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

 small bowel is also involved in 20-60% of patients, due to reduced or absent migrating motor complexes predisposing to bacterial overgrowth. initial attempts at eradication of bacterial overgrowth with metronidazole, ciprofloxacin or co-amoxiclav is appropriate. The contributes to malabsorption, as does associated pancreatic insufficiency. In the colon there is often development of diverticuli involving all layers of the intestinal wall, or constipation due to reduced motility. 2. Diffuse cutaneous systemic sclerosis • less common. • scleroderma affects trunk and proximal limbs predominately (although face may be involved in either type) Skin areas involved include also the upper arms, thighs or trunk. • associated with scl-70 antibodies • hypertension, lung fibrosis and renal involvement seen Pulmonary involvement is the second commonest organ involvement after oesophageal disease and is the leading cause of death. Pulmonary fibrosis is associated with anti-Scl-70 antibodies in up to 70% of cases. scl-70 antibodies associated with a higher risk of severe interstitial lung disease Reduced DLCO is the earliest sign of pulmonary disease in systemic sclerosis, often before fibrotic changes manifest clinically. • Diffuse cutaneous systemic sclerosis may lead to scleroderma renal crisis (SRC) in up to 10% cases. The underlying pathology of SRC is vasospasm, Features SRC may present with rapid onset renal failure, malignant hypertension, micro-angiopathic haemolytic anaemia with schistocytes. Patients may develop symptoms of fluid overload. Other risk factors for SRC include: corticosteroid use (prednisolone more than 15 mg/day), recent onset scleroderma (less than three years), and involvement of other systems. Treatment involves starting ACE inhibitors. • poor prognosis

Rheumatology

3. Scleroderma (without internal organ involvement) • tightening and fibrosis of skin • may be manifest as plaques (morphoea) or linear

Antibodies • ANA positive in 90% therefore, in a negative test consider an alternative diagnosis • RF positive in 30% • Anti-centromere antibodies associated with limited cutaneous systemic sclerosis • Anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis (anti-Scl-70) also known as Anti-topoisomerase I antibodies associated with a higher risk of severe interstitial lung disease • Anti-RNA polymerase III antibodies found in patients with diffuse disease associated with: rapidly progressive skin involvement increased risk for scleroderma renal crisis. increased risk for cancer Other investigations • Serum protein electrophoresis: ↑ γ-globulins Treatment • Immunosuppressive therapy: e.g., methotrexate • Organ-specific therapy: gastroesophageal reflux disease PPIs Renal crisis ACE inhibitors Renal crises result from an acute renal vasculopathy with associated hyperreninaemia, not glomerulonephritis. ACE inhibitors in the acute setting improves long term survival, end organ damage due to hypertension, and can lead to an improvement in renal function even up to 2 years

after crisis. Interstitial lung disease secondary to underlying diffuse systemic sclerosis: The most appropriate treatment is cyclophosphamide Azathioprine is normally used as maintenance therapy following cyclophosphamide. Prognosis • U&Es have a crucial role with respect to determining prognosis and appropriate therapeutic intervention.

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

Morphea (localised scleroderma) Definition • idiopathic inflammatory skin condition which causes excessive collagen deposition and fibrosis. Types • Morphea is classified into subtypes according to the clinical presentation and depth of tissue involvement: circumscribed morphea, the commonest form, "circumscribed/plaque" morphea.