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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Superficial thrombophlebitis • Superficial thrombophlebitis, as the name suggests describes the inflammation associated with thrombosis of one of the superficial veins, usually the long saphenous vein of the leg. • This process is usually non-infective in nature but secondary bacterial infection may rarely occur resulting in septic thrombophlebitis. • Around 20% with superficial thrombophlebitis will have an underlying deep vein thrombosis (DVT) at presentation and 3-4% of patients will progress to a DVT if untreated. • The risk of DVT is partly linked to the length of vein affected - an inflammed vein > 5 cm is more likely to have an associated DVT. Management • Traditionally NSAIDs have been used, with topical NSAIDs for limited and mild disease and oral NSAIDs for more severe disease. • Topical heparinoids have also be used in the management of superficial thrombophlebitis. • A Cochrane review however found topical NSAIDs and heparinoids have no significant benefit in terms of reducing extension or progression to DVT. • Oral NSAIDs were however shown to reduce the risk of extension by 67%. • Compression stockings are also used. • Remember that the ankle-brachial pressure index (ABPI) should be measured before prescribing compression stockings, particularly if using class 2 or above stockings. • One of the major changes to the management of superficial thrombophlebitis is the increased use of low-molecular weight heparin. This has been shown to reduce extension and transformation to DVT. • SIGN produced guidelines in 2010: Patients with clinical signs of superficial thrombophlebitis affecting the proximal long saphenous vein should have an ultrasound scan to exclude concurrent DVT. Patients with superficial thrombophlebitis should have anti-embolism stockings and can be considered for treatment with prophylactic doses of LMWH for up to 30 days or fondaparinux for 45 days. If LMWH is contraindicated, 8-12 days of oral NSAIDS should be offered. Patients with superficial thrombophlebitis at, or extending towards, the sapheno-femoral junction can be considered for therapeutic anticoagulation for 6-12 weeks. • This may be a significant departure from our current practice - the majority of patients with superficial thrombophlebitis (i.e. those affecting the long saphenous vein) should be referred for an ultrasound scan.

Thrombophilia: causes inherited thrombophilias: • the most common Factor V Leiden • the higher risk of VTE Anti-thrombin III deficiency Inherited thrombophilias • Gain of function polymorphisms factor V Leiden (activated protein C resistance): most common cause of thrombophilia prothrombin gene mutation: second most common cause • Deficiencies of naturally occurring anticoagulants antithrombin III deficiency protein C deficiency Reduced degradation of

factors Va and Villa

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Haematology&Oncology protein S deficiency The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias: Condition Prevalence Relative risk of VTE Factor V Leiden (heterozygous) 5%

Prothrombin gene mutation (heterozygous) 1.5%

Protein C deficiency 0.3%

Protein S deficiency 0.1% 5-10 Antithrombin III deficiency 0.02 10-20 Acquired thrombophilias: • Antiphospholipid syndrome • Drugs the combined oral contraceptive pill NICE recommend testing for thrombophilia in case of unprovoked venous thromboembolism and family history. Indications of thrombophilia testing: Thrombophilia testing is considered useful in patients presenting with: • A first episode of venous thromboembolism (VTE) at a young age (usually considered less than 45 years of age) • Idiopathic venous thrombosis • A family history of thrombosis, particularly in a first degree relative • VTE in an unusual vascular territory • Neonatal purpura fulminans • Warfarin induced skin necrosis

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Factor V Leiden Epidemiology • Factor V Leiden (activated protein C resistance) is the most common inherited thrombophilia, being present in around 5% of the UK population. • present in 5-9% of the European population but is rare in people of Asian and African descent. Aetiology • It is due to a mutation in the Factor V Leiden mutation. • mostly inherited in an autosomal dominant fashion

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• caused by an amino acid substitution results in replacement of arginine with glutamine in the amino acid chain, that impairs the ability of activated protein C and S to inactivate factor Va. Pathophysiology • Normally, activated protein C inactivates factor V in the clotting cascade → decreases the activation of thrombin. • However, in patients with these defects, factor V remains active → activates prothrombin → increases thrombotic events. Features • results in a 30% lifetime risk of VTE for homozygotes and 5-10% for heterozygotes. • Heterozygotes have a 4-5 fold risk of venous thrombosis. Diagnosis • The gold standard for the diagnosis of factor V Leiden is genetic testing for the mutation. Management • prophylaxis against thromboembolism. • Contraceptive medications and devices that contain the hormone estrogen should not be used Non-hormonal and progesterone-only methods are safe for use in these patients • patients with no history of VTE are not indicated for prolonged anticoagulation prophylaxis.

Protein C deficiency • Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis • Protein C is synthesized in the liver. • It is a relatively common

thrombophilia disorder, affecting 1 in 500 individuals. Function of protein C • inactivation of factors Va and VIIIa. Features • venous thromboembolism • skin necrosis following the commencement of warfarin: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis The best initial step for the management of warfarin-induced skin necrosis is stopping warfarin. Diagnosis • Copperhead snake venom assay the best test to detect protein-C deficiency Management • Patients with a history of a thrombotic event should receive prophylactic anticoagulation for life. What pathological process is most likely to be responsible for increased propensity to clot in a patient diagnosed with protein C deficiency? Reduced degradation of factors Va and VIIIa

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Antithrombin III deficiency • Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:3,000 of the population. • Inheritance is autosomal dominant Function of Antithrombin III • Antithrombin III inhibits several clotting factors, primarily thrombin, factors II, IX, and X. the affinity of Antithrombin III for Factor II and X is much greater, and it thus has a much stronger inactivation effect on these factors. • It mediates the effects of heparin Features • recurrent venous thromboses • arterial thromboses do occur but are uncommon Diagnosis • The best initial test for diagnosing antithrombin III deficiency is thrombin-heparin cofactor level. Management • thromboembolic events are treated with lifelong warfarinisation • heparinisation during pregnancy* *as patients with antithrombin III deficiency have a degree of resistance to heparin, anti-Xa levels should be monitored carefully to ensure adequate anticoagulation • antithrombin III concentrates (often using during surgery or childbirth)

Hereditary haemorrhagic telangiectasia (HHT) • Also known as Osler-Weber-Rendu syndrome • characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Genetic • autosomal dominant • Two genes: ENG (endoglin) and ALK-1 (activin receptor like kinase-1) encode proteins expressed on vascular endothelial cells. Mutations in these genes cause an imbalance in angiogenesis. Epidemiology • occurs in approximately 1 in 5000 of the population. • 20 % of cases occur spontaneously without prior family history. • commonly presents in teenagers. 62% are diagnosed by age 16. Features and complications • over 90% present with nosebleeds (the most common initial mode of presentation) • GI telangiectasias and arteriovenous malformations (AVMS) may cause chronic slow bleeding leading to iron deficiency anemia • AVMS in the respiratory system may cause dyspnoea and cyanosis and paradoxical cerebral emboli. • GI telangiectasias and arteriovenous malformations may cause acute haemorrhage • In the brain AVMS, angiomas and aneurysms may lead to stroke Diagnosis • There are 4 main diagnostic criteria (Curacao criteria).

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1. epistaxis: spontaneous, recurrent nosebleeds
2. telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
3. visceral lesions: for example, gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
4. family history: a first-degree relative with HHT • The diagnosis is definite if 3 criteria are present, suspected with 2 criteria and unlikely if fewer than 2 criteria are present. The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations Mucocutaneous telangiectasias involve the lips (HHT)

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Haematology&Oncology The slide shows the typical appearance of hereditary haemorrhagic telangiectasia (also known as Osler-Weber-Rendu disease)

Idiopathic thrombocytopenic purpura (ITP) • ITP is an immune mediated reduction in the platelet count. • Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex. • Most often the stimulus is unknown, but it can be secondary to other autoimmune disorders (e.g. SLE), viral infections (e.g. CMV, VZV, hepatitis C, HIV), Helicobacter pylori, medication and lymphoproliferative disorders. • It results in isolated thrombocytopenia, with the most common presenting sign being a purpuric rash. • ITP can be divided into acute and chronic forms: Acute ITP • more commonly seen in children • equal sex incidence • may follow an infection or vaccination • usually runs a self-limiting course over 1-2 weeks Chronic ITP • more common in young/middle-aged women • tends to run a relapsing-remitting course Evan's syndrome • ITP in association with autoimmune haemolytic anaemia (AIHA) Investigations • antiplatelet autoantibodies (usually IgG) • bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia Management • No treatment is an option if asymptomatic. • oral prednisolone (80% of patients respond) • splenectomy if platelets < 30 after 3 months of steroid therapy • IV immunoglobulins • immunosuppressive drugs e.g. cyclophosphamide Prognosis • The principal cause of death in patients with ITP is intracranial haemorrhage

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Langerhans cell histiocytosis .Also called (Eosinophilic granuloma, Histiocytosis X) Definition • Abnormal proliferation of pathogenic Langerhans cells (dendritic cells found in the skin) in single or multiple organs. This leads to inflammation and tissue destruction in different organs of the body • It is the most common type of histiocytosis (i.e., syndrome characterised by the abnormal proliferation of histiocytes). Pathophysiology • Exact aetiology and pathogenesis is unknown; • thought to be either a malignant process or due to immune dysregulation Features • more frequent in children (< 15 year) □ typically presents in childhood with bony lesions • bone pain, (present in 80% of patients, and are commonly seen on scalp) typically in the skull or proximal femur • skin rash , cutaneous nodules • Cranial involvement: Diabetes insipidus □ polyurea and polydipsia

(common in patients with multi-system disease) • recurrent otitis media/mastoiditis • GIT involvement : hepatosplenomegaly Young girl with multiple well defined 'punched out' osteolytic lesions with scalloped edges (geographic skull) are seen in the bilateral parietal regions. The lesions have a characteristic bevelled edge. Diagnostics • X-ray: osteolytic lesions • Tissue biopsy of lesion (confirmatory test): on electromicroscopy tennis racket-shaped Birbeck granules proliferation of Langerhans cells; polygonal cells with coffee-bean shaped nuclei, eosinophilic cytoplasm, and Birbeck granules presence of CD1a and langerin (CD207) or Birbeck granules is definitive for diagnosis. Treatment • Multi-system disease is treated with systemic, multi-agent chemotherapy.

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Myelofibrosis Overview • a myeloproliferative disorder • thought to be caused by hyperplasia of abnormal megakaryocytes • the resultant release of platelet derived growth factor is thought to stimulate fibroblasts • haematopoiesis develops in the liver and spleen • commonly associated with the JAK2 kinase mutation. Features • e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom) • massive splenomegaly (due to extramedullary hematopoiesis) • hypermetabolic symptoms: weight loss, night sweats etc Complications • Myelofibrosis can change to acute myeloid leukaemia. Laboratory findings • anaemia • high WBC and platelet count early in the disease • 'tear-drop' poikilocytes on blood film • unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed bone marrow biopsy is characterized by excessive proliferation of megakaryocytes. • high urate and LDH (reflect increased cell turnover) Blood film showing the typical 'tear-drop' poikilocytes of myelofibrosis Treatment • Bone marrow transplant is the only curative treatment

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Myelodysplastic syndrome (MDS) Overview • premalignant condition. • primarily affects elderly people (> 60). • more common in males than in females Pathophysiology • clonal mutation predominates in the bone marrow, suppressing healthy stem cells. • the main cause of cytopenias In the early stages of MDS increased apoptosis (programmed cell death). As the disease progresses and converts into leukemia, proliferation of leukemic cells overwhelms the healthy marrow.

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Causes • primary or idiopathic MDS (80%) • genetic predisposition • hematopoietic stem cell injury caused by exposure to any of the following: Cytotoxic chemotherapy Radiation Viral infection Genotoxic chemicals (eg, benzene) Features macrocytic anaemia, thrombocytopenia and neutropenia with a small number of circulating blasts suggests a diagnosis of myelodysplastic syndrome • 80% of patients present because of symptoms of anaemia (fatigue and malaise) • Petechiae, ecchymoses, and nose and gum bleeding are common manifestations of a low platelet count. • neutropenia may leads to fever and infections • blood film: dimorphic picture (some red

cells are hypochromic and microcytic, while others appear macrocytic) neutrophils are hypogranular and hyposegmented (Pelger-Huet cells). The peripheral blood count may show; single cytopenia (anemia, thrombocytopenia, or neutropenia) in the early phase or bicytopenia (2 deficient cell lines) or pancytopenia (3 deficient cell lines) in later stages. unexplained macrocytic anemia with no evidence of megaloblastic anemia • Bone marrow aspirate stained with Perls' stain showed ring sideroblasts Ring sideroblasts contain an abnormally high concentration of iron, usually stored in perinuclear mitochondria. Perls' stain (which stains for iron) shows this iron deposition as a dark ring around the margin of the nucleus. Cytogenetic studies of the bone marrow cells: Chromosomal abnormalities are clonal and include 5q-, monosomy 7 (-7) or 7q-, trisomy 8 (+8), Multiple combinations indicates a very poor prognosis. A single abnormality, except those involving chromosome 7, indicates good prognosis. Classification • The (French-American-British (FAB) system classifies MDS into the following five subgroups : Refractory anemia (RA) RA with ringed sideroblasts (RARS) RA and RARS are characterized by ≤5% myeloblasts in bone marrow. RARS is defined morphologically as having 15% erythroid cells with abnormal ringed sideroblasts, Both RA and RARS have a prolonged clinical course and a low prevalence of progression to acute leukemia. progression to acute leukemia occurred in 5% of RARS cases, compared with 25% of RAEB cases RA with excess blasts (RAEB; 6-20% myeloblasts) RAEB in transition to AML (RAEB-T; 21-30% myeloblasts)

 acute myeloid leukemia (AML; >30%). Chronic myelomonocytic leukemia (CMML) manifests as monocytosis of ≥1000/µL, total white blood cell (WBC) count of < 13,000/µL, and trilineage dysplasia. CMML must be differentiated from classic chronic myelocytic leukemia, which is characterized by a negative Ph chromosome. • WHO classification 2008: Refractory anaemia with unilineage dysplasia- ie anaemia, neutropaenia or thrombocytopaenia (<5% blasts) Refractory anaemia with ring sideroblasts (<5% blasts; >15% sideroblasts) Refractory anaemia with multilineage dysplasia (based on bone marrow dysplasia in 2 or more myeloid lineages) Refractory anaemia with excess blasts-1(5-9% blasts) and refractory anaemia with excess blasts -2 (10-19%) Blasts > 20% is now classified as acute myeloid leukaemia. Myelodysplasia unclassified Myelodysplasia with isolated 5qdel(cytogenetic abnormality with prognostic significance) Prognosis • Median survival is two years. • Patients are more likely to have serious infections or life-threatening bleeds than blastic transformation. • MDS who progress to acute leukemia have a poor prognosis than that of de novo acute myeloid leukemia (response to chemotherapy is worse) • International Prognostic Scoring System (IPPS) The revised I (IPSS-R) score is calculated on the basis of five variables:

1. Hemoglobin level
2. Absolute neutrophil count
3. Platelet count
4. Percentage of bone marrow blasts
5. Cytogenetic category Management • Supportive therapy, including transfusions of the cells that are deficient (ie, red blood cells [RBCs], platelets), and treatment of infections

are the main components of care. As the vast majority are elderly patients with other medical conditions, excessive intervention is unwarranted (لا يزيد ها). Granulocyte-colony stimulating factor (G-CSF) and recombinant erythropoietin (rEpo) can improve blood counts. National Comprehensive Cancer Network (NCCN) guidelines recommend the use of erythropoiesis-stimulating agents (ESAs) for treatment of symptomatic anemia in patients in the R-IPSS very low risk, low risk, or intermediate risk category whose tumor lacks the 5q31 deletion and whose level of endogenous EPO is ≤500 mU/mL. In cases of the presence of ringed sideroblasts or an absence of response, the addition of granulocyte colony-stimulating factor (G-CSF; filgrastim), 1–2 μg/kg 1–3 times per week should be considered. • hypomethylating agent azacytidine, which has been shown to improve survival compared with either supportive or aggressive therapy and is approved for use in MDS by (FDA). • Aggressive cytotoxic chemotherapy is generally reserved for treatment of transformation to acute myelogenous leukaemia (AML) in younger patients.

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Leuco-erythroblastic anaemia • leuco-erythroblastic anaemia (left-shifted granulocytic series and nucleated red blood cells) • This can be seen with: high bone marrow turnover, e.g. in severe haemolytic anaemia (the reticulocyte count will be high), myelofibrosis and chronic myeloid leukaemia (where there will be splenomegaly and the white cell and platelet count will usually be raised) bone marrow invasion. Often in bone marrow invasion the invading malignancy will already have been diagnosed previously. The diagnosis requires a bone marrow trephine, which will usually show replacement of haematopoietic tissue with malignant cells.

Polycythaemia Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary Types and causes • Relative causes dehydration stress: Gaisbock syndrome • Primary causes polycythaemia rubra vera • Secondary causes Erythropoietin-secreting tumours: Renal cell carcinoma Hepatocellular carcinoma Haemangioblastoma Uterine fibroids. Chronic hypoxia: COPD Right-to-left cardiac shunts Sleep apnoea High altitude Chronic carbon monoxide poisoning (including heavy smoking). Features • Symptoms of hyperviscosity syndrome, including: dizziness tinnitus headaches blurred vision, and pruritus. • Signs include: Various ophthalmological changes (for example, dilated retinal veins) Neurological findings, Facial plethora ('ruddy' appearance).

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Haematology&Oncology Differential diagnosis Secondary erythrocytosis EPO Expected Relative (apparent) polycythemia (↑RBC mass due to ↓in plasma volume) ↔ ↓ ↔ • Severe dehydration • Stress erythrocytosis Appropriate absolute polycythemia ↑ ↔ ↓ • High-altitude exposure • Hypoxia: chronic pulmonary and cardiac disease (physiological ↑in RBC mass, secondary to conditions associated with increased stimulation of erythropoiesis due to reduced oxygen saturation) Inappropriate absolute polycythemia (non-physiological ↑in RBC mass, secondary to conditions associated with autonomous production of EPO, renal diseases that affect the EPO secreting cells, and neoplasms). ↑↑ ↔ ↔ • Paraneoplastic syndrome, especially with: • Absolute

erythrocytosis, as opposed to apparent, is defined as an HCT greater than 0.60 in males and HCT greater than 0.56 in females. • To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia: JAK2 mutation JAK2 is a crucial tyrosine kinase which transmits the EPO signal to increase red cells production. Red cell mass studies The discovery of the JAK2 mutation has made red cell mass a second-line investigation for patients with suspected JAK2-negative PRV. In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg Management • Venesection of patients who are symptomatic is the first line management of polycythaemia. • The diagnostic workup and exclusion of secondary causes usually follows after initial treatment patient with symptoms of hyperviscosity needs to be venesected urgently and an agreed work-up can be performed later. Notes & Notes for MRCP
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Oxygen saturation Underlying conditions plasma volume Renal cell carcinoma (RCC) Hepatocellular carcinoma (HCC) • Polycystic kidney disease (PKD)

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Polycythaemia rubra vera (PRV) Definition • Polycythaemia rubra vera (PRV) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. Aetiology • a mutation in JAK2 is present in approximately 95% of patients with PRV and this has resulted in significant changes to the diagnostic criteria. • occurs due to abnormal negative feedback of hematopoietic growth factor signaling. Epidemiology • peak incidence in the sixth decade Pathophysiology • mutation in the JAK2 gene →↑tyrosine kinase activity → uncontrolled, EPOindependent proliferation of the myeloid cell lines → ↑ blood cell mass (erythrocytosis, thrombocytosis, and granulocytosis) → hyperviscosity + slow blood flow →↑ risk of thrombosis and poor oxygenation. Features • hyperviscosity • pruritus, typically after a hot bath • splenomegaly • haemorrhage (secondary to abnormal platelet function NOT NUMBER) • plethoric appearance • hypertension in a third of patients • low ESR • Low EPO levels the strongest pointer towards primary polycythaemia myeloproliferative increased red blood cell production by the marrow turns off endogenous EPO production low EPO level. • raised leukocyte alkaline phosphatase (ALP) • Mild prolonged PT & PTT: this is related to the ratio of plasma and citrate. In the blue tubes that are used for coagulation tests the ratio is normally 1 citrate to 9 of whole blood. If there is less plasma due to the polycythaemia there will be excess citrate and this will prolong coagulation tests such as the APTT and prothrombin time. • Others: hyperuricaemia, peptic ulceration. Investigations • full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients) • JAK2 mutation • serum ferritin • renal and liver function tests • If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

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Haematology&Oncology red cell mass arterial oxygen saturation abdominal ultrasound serum erythropoietin level bone marrow aspirate and trephine cytogenetic analysis erythroid burst-forming unit (BFU-E) culture Diagnostic criteria JAK2-positive PRV - diagnosis requires both

criteria to be present Criteria Notes A1 High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted) A2 Mutation in JAK2 JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria Criteria Notes A1 Raised red cell mass (>25% above predicted) OR haematocrit

> 0.60 in men, >0.56 in women A2 Absence of mutation in JAK2 A3 No cause of secondary erythrocytosis A4 Palpable splenomegaly A5 Presence of an acquired genetic abnormality (excluding BCRABL) in the haematopoietic cells B1 Thrombocytosis (platelet count >450 * 109/l) B2 Neutrophil leucocytosis (neutrophil count > 10 * 109/l in nonsmokers; > 12.5*109/l in smokers) B3 Radiological evidence of splenomegaly B4 Endogenous erythroid colonies or low serum erythropoietin Management • aspirin • venesection: first line treatment the target hematocrit value after performing phlebotomy is less than 45 %. • Hydroxyurea: the preferred cytoreductive agent used in high-risk patients. slight increased risk of secondary leukaemia • phosphorus-32 therapy

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• H2-receptor antagonists may be useful in relieving itching this is somewhat surprising. Conventionally it is the H1 antagonists that tend to be used for pruritus in other settings. Prognosis • thrombotic events are a significant cause of morbidity and mortality • 5-15% of patients progress to myelofibrosis Pastest note Transition from primary polycythaemia to myelofibrosis occurs in about 30%of patients, therefore, the probability of developing myelofibrosis is higher and thus more likely than acute leukaemia • 5-15% of patients progress to acute leukaemia (risk increased with chemotherapy treatment) particularly if patients have been exposed to radioactive phosphorous treatment or busulfan therapy. Progression to acute myeloid leukaemia is seen in around 5% of patients.

Myelofibrosis • Primary myelofibrosis is a disorder in which normal bone marrow tissue is gradually replaced with a fibrous scar-like material. • Over time this leads to progressive bone marrow failure. • Most commonly seen in older adults (5th/6th decade) • It is almost always accompanied by significant splenomegaly and is JAK2 mutation-positive in about 50% of cases. • fatigue, splenomegaly and teardrop cells Complications • Portal hypertension occurs in 7% of patients with primary myelofibrosis may be related to increased portal flow resulting from marked splenomegaly and to intrahepatic obstruction resulting from thrombotic obliteration of small portal veins. This may result in variceal bleeding or ascites. Hepatic or portal vein thrombosis may occur. Symptomatic portal hypertension is managed by splenectomy, with or without the creation of a portosystemic shunt. • Peripheral blood smear tear-drop RBC membrane is disrupted when RBC passed through fibrosis to leave bone marrow nucleated RBCs band granulocytes Treatment • It is generally incurable, • although bone marrow transplantation and JAK2 inhibitors have a role in younger patients.

Disseminated intravascular coagulation (DIC) Pathophysiology • (DIC) is characterized by: systemic activation of blood coagulation deposition of fibrin microvascular thrombi in various organs multiple organ dysfunction syndrome (MODS). ongoing activation of coagulation consumption of coagulation proteins and platelets may induce severe bleeding

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Haematology&Oncology Pathogenesis of DIC (2020 UpToDate) NET: neutrophil extracellular trap; PT: prothrombin time; aPTT: activated partial thromboplastin time; FDPs: fibrin degradation products; dsDNA: double-stranded DNA; MAHA: microangiopathic hemolytic anemia. Epidemiology • present in 1% of hospitalized patients. Common Causes • Sepsis and severe infection (most commonly) • Trauma (neurotrauma) • Organ destruction (eg, pancreatitis) • Malignancy (solid and lymphoproliferative/myeloproliferative malignancies) • acute hemolytic transfusion reaction. • Obstetric complications: Amniotic fluid embolism abruptio placentae (HELLP) syndrome : triad of:

1. Hemolysis,
2. Elevated Liver enzymes,
3. Low Platelets eclampsia

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Diagnosis • CBC Thrombocytopenia (low Platelet count) • Coagulation profile prolonged PT and aPTT low plasma fibrinogen • D-dimers produced by the action of plasmin on cross-linked fibrin These tests reflect the microangiopathy of DIC sensitive, specific, and efficient in the diagnosis of DIC • Fibrin degradation products (FDP) Increased levels of FDP occur in a variety of conditions in which clot formation and lysis occur. sensitive, specific, and efficient in the diagnosis of DIC • Peripheral smear microangiopathic changes on peripheral blood smear The presence of schistocytes, or red cell fragments, is a frequent but nonspecific Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes Treatment • Fibrinogen replacement infusion (cryoprecipitate) is the appropriate first choice • Platelet transfusion is recommended if the count is less than 50 ×109/L. • When bleeding is the major problem, the aim is to: maintain the prothrombin and activated thromboplastin time at a ratio of 1.5 times of the control maintain the fibrinogen level above 1 g/L. the combination of the D-dimer and the FDP assay provides the most rapid and specific diagnosis of DIC.

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Thrombocytopenia Causes of thrombocytopenia: ↓production (bone marrow infiltration, suppression, or fibrosis), ↑ destruction (DIC, ITP, and TTP/HUS), dilution sequestration due to splenomegaly. Causes of severe thrombocytopenia • ITP • DIC • TTP • haematological malignancy

Causes of moderate thrombocytopenia • heparin induced thrombocytopenia (HIT) • drug-induced (e.g. quinine, diuretics, sulphonamides, aspirin, thiazides) • alcohol • liver disease • hypersplenism • viral infection (EBV, HIV, hepatitis) • pregnancy • SLE/antiphospholipid syndrome • vitamin B12 deficiency Gestational thrombocytopaenia • very common. • Most importantly, the patient should be closely monitored from the present time until she delivers • The platelet count is very mildly reduced • no specific intervention • Steroids may only need to be considered if the platelet count is persistently less than 30 within the last 2 weeks of pregnancy. • Steroids may be considered in the last couple of weeks of pregnancy to raise the platelet count temporarily so that a caesarean section or epidural anaesthesia may be undertaken safely. This may well be combined with intravenous immunoglobulin immune thrombocytopenia • the patient is well. • There is post viral illness with quite marked thrombocytopenia but other full blood count (FBC) parameters are normal. • The diagnosis is one of exclusion, • The most important investigation is a blood film. Although not diagnostic, this will confirm the FBC findings and also exclude more sinister pathology such as leukaemia. • in the absence of major bleeding, management would be observation, as it can resolve spontaneously. Safety for different procedures when thrombocytopenic: • In general, a platelet count of 10-20 ×109 /L is safe for most procedures. The exceptions to this are major surgery and procedures involving the CNS and eyes. In the latter cases, the platelet count should be above 50 ×109/L.

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Thrombocytosis Definition • Thrombocytosis is an abnormally high platelet count, usually ≥450 × 109/L • Thrombopoietin is the key hormone in the regulation of megakaryocyte differentiation. Causes • reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection or surgery The most common cause of thrombocytosis is a reactive thrombocytosis. May occur as a response to exercise Secondary thrombocytosis does not place the patient at risk for haemostatic or cardiovascular events. • iron deficiency • Malignancy secondary cause for thrombocytosis is crucial to exclude before considering a diagnosis of a myeloproliferative disorder. • essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera adequate iron stores are requisite diagnostic criteria (WHO) for essential thrombocytosis. • hyposplenism

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Essential thrombocytosis (ET): Definition • Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis. • Megakaryocyte proliferation results in an overproduction of platelets, in the absence of any identifiable cause. Epidemiology • usually affects older people between the ages of 50 and 70 years • occurs equally in both males and females. Features • asymptomatic (25-33%) • tingling or burning in the hands and feet, headache, visual problems, weakness and dizziness. burning sensation in the hands is a characteristic symptom Erythromelalgia burning pain, warmth, and redness of the extremities The pain increases with exposure to heat and improves with cold These symptoms result from excessive numbers of platelets causing blockages in small or large blood vessels in different parts of the body. • Other symptoms include sweating, low-grade

fever, and pruritus. • Splenomegaly (40-50%) • Hepatomegaly (20%) • both thrombosis and haemorrhage can be seen Investigations • Complete blood cell count (CBC) platelet count > 600 * 109/l Around 30% will also have a mildly raised RBC and / or WBC. A red blood cell (RBC) mass study helps to exclude polycythemia vera. The RBC mass is elevated in polycythemia vera, but is normal in essential thrombocytosis.

Haematology&Oncology • Genetic studies The majority of patients have mutations in one of three genes:

1. Janus kinase 2 (JAK2), 50-60% of patients.
2. calreticulin (CALR), found in 25%
3. myeloproliferative leukemia virus oncogene (MPL). about 3-5% of cases. MPL codes for the thrombopoietin receptor protein, which promotes the growth and proliferation of megakaryocytes. The mutations result in constitutive activation of the thrombopoietin receptor protein. Rare cases involve mutations in the thrombopoietin gene (THPO), associated with autosomal dominant hereditary thrombocytosis • Bone marrow examination ↑ bone marrow cellularity (found in 90%) Megakaryocytic hyperplasia is common Bone marrow reticulin is usually increased, but collagen fibrosis is uncommon • Elevation of C-reactive protein (CRP), fibrinogen, and interleukin 6 levels suggests secondary thrombocytosis, because those are acute-phase reactants • Vitamin B-12 levels are increased in 25% of patients • Uric acid levels are elevated in 25% of patients Diagnosis • British guidelines propose the following five criteria for diagnosis of essential thrombocytosis :
4. Sustained platelet count ≥450 × 109/L
5. Presence of an acquired pathogenetic mutation (eg, in the JAK2, CALR or MPL genes)
6. No other myeloid malignancy, especially polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome
7. No reactive cause for thrombocytosis and normal iron stores
8. Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm; reticulin is generally not increased (grades 0–2/4 or grade 0/3) Diagnosis requires the presence of criteria 1–3 or criterion 1 plus criteria 3–5. Adverse prognostic markers for essential thrombocythaemia (ET): • Age above 60 • Symptomatology - particularly thrombosis and • Platelet count above 1500. • Previous thrombosis • Obesity • Cardiovascular risk factors such as smoking, hypertension, and hypercholesterolemia • Markers of hypercoagulability such as factor V Leiden and antiphospholipid antibodies [4] • JAK2 mutation Management Essential thrombocythaemia + high-risk of thrombosis Aspirin + hydroxycarbamide

• low risk observation only • high-risk of thrombosis (eg, age >60, history of thrombosis, or platelet counts >1500). hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count first-line treatment interferon-α is also used in younger patients Interferon alfa is a biologic response modifier. used as second line in older patient Interferon alfa is not known to be teratogenic and does not cross the placenta, perhaps making it safe for use during pregnancy. Italian guidelines recommend interferon alfa as a first-line platelet-lowering therapy for patients younger than 40 years low-dose aspirin may be used to reduce the thrombotic risk low-dose aspirin may be useful in treating patients with symptoms of microvascular occlusion (eg, erythromelalgia). Patients with the JAK2 mutation or cardiovascular risk factors can be treated with daily low-dose aspirin Extreme thrombocytosis may promote the abnormal adsorption of large von Willebrand factor (VWF) multimers. These patients should be screened for the presence of acquired von Willebrand disease (VWD). if ristocetin cofactor level (Functional von Willebrand Factor) is at least 30% in absence of other high-risk factors; Low-dose aspirin therapy (eg, ≤100 mg/day) is acceptable if it is less than 30%, all aspirin should be avoided. • Plateletpheresis If platelet is very high with symptoms of clotting or bleeding Prognosis • extremely good in ET with survival of over two decades expected. • The risk of transforming to acute myeloid leukaemia is relatively low (<1%).

Thrombotic thrombocytopenic purpura (TTP) (TTP) is classically characterised as a pentad of: thrombocytopenia, microvascular haemolysis, fluctuating neurological signs, renal impairment and fever. Pathogenesis of thrombotic thrombocytopenic purpura (TTP) • abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels • in TTP there is a deficiency of ADAMTS13 (a metalloprotease enzyme) which breakdowns large multimers of von Willebrand's factor • The primary event that occurs appears to be endothelial damage, which then leads to thrombus formation, end organ damage (eg brain and kidneys) and platelet consumption • overlaps with haemolytic uraemic syndrome (HUS) Causes • post-infection e.g. urinary, gastrointestinal (Escherichia coli 0157 subtype) • pregnancy

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Haematology&Oncology • drugs: ciclosporin, oral contraceptive pill, penicillin, metronidazole antiplatelets: clopidogrel or ticlodipine (< 1%), acyclovir, FK506, Penicillamine sulphonamides • tumours • SLE • HIV Features • rare, typically adult females • fever • fluctuating neuro signs (microemboli) • microangiopathic haemolytic anaemia • renal failure • thrombocytopenia • Which investigation will be most useful to establish the diagnosis? Peripheral blood film The peripheral blood film reveals fragmented RBCs (schistocytes, eg, spherocytes, segmented RBCs, burr cells, or helmet cells). Management • no antibiotics - may worsen outcome • plasma exchange is the treatment of choice TTP has an untreated mortality of up to 90% and therefore rapid plasma exchange (PEX) may be a life saving intervention. • steroids, immunosuppressants Intravenous methylprednisolone is indicated after treatment with PEX has been completed. • Vincristine • Platelet transfusion in TTP is only indicated if there is an on-going life-threatening bleed. • There is no current role for intravenous immunoglobulin in the routine management of TTP, however there have been reports of its successful use in PEX- and steroid-refractory cases. Prognosis • In adults, the mortality rate 20-50% January 2013 exam: H/O

confusion + fever + ↓Platelets 65 , ↑Urea 23, ↑Creatinine 366.What is the most likely diagnosis?
 Thrombotic thrombocytopenic purpura

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Von Willebrand's disease The combination of a petechial skin rash combined with a slightly elevated APTT and reduced factor VIII activity make Von Willebrand's disease the most likely diagnosis Overview • Von Willebrand's disease is the most common inherited bleeding disorder. • The majority of cases are inherited in an autosomal dominant fashion if both parents have the disease, then three-quarters of their offspring will have the disease, assuming they are both heterozygotes. In an autosomal dominant condition, there is no carrier state. • characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemoarthroses and muscle haematomas are rare • Symptoms are exacerbated by medications that inhibit platelet function, such as aspirin and other NSAIDs. Role of von Willebrand factor • large glycoprotein which forms massive multimers • Von Willebrand factor is a coagulation protein that binds to collagen and to the GpIb platelet receptor during platelet adhesion. promotes platelet adhesion to damaged endothelium • carrier molecule for factor VIII • Factor VIII circulates bound to von Willebrand factor (vWF), which protects factor VIII from degradation. Decreased vWF (in part) prolongs the PTT by leading to decreased factor VIII. In people with hemophilia, strategies to increase circulating levels of factor VIII include maximizing vWF levels. increases vWF secretion (leading to increased functional levels of factor VIII). Even in hemophilia A, there is still a small amount of normal factor VIII (<5%). • The intrinsic coagulation pathway is defective in von Willebrand disease. Types • type 1: partial reduction in vWF (80% of patients) the most common form patients have up to a 50% reduction in von Willebrand factor (vWF). Autosomal dominant with variable penetrance Many are asymptomatic and are only diagnosed following an episode of bleeding associated with a dental extraction or minor surgery. • type 2: abnormal form of vWF • type 3: total lack of vWF (autosomal recessive) (most severe form) Investigation • prolonged bleeding time (due to impaired platelet adhesion and aggregation) The bleeding time would be a good screening test but it will not give a quantitative measurement of bleeding tendency in type I vWBD neither sensitive nor specific platelet function analyser (PFA100), have better testing characteristics than the bleeding time • APTT may be prolonged (due to reduced circulating factor VIII). • factor VIII levels may be moderately reduced

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 the most useful test to assess bleeding tendency in Von Willebrand's disease ? Plasma factor VIII activity • vWB antigen and activity (Ristocetin cofactor assay) (RICOF) The most useful test in practice is to do the vWB antigen and activity (RICOF), but you would also do FVIIIc as this is also low in vWD. • In type I vWD the prothrombin time (PT) and Platelet count will be normal. • defective platelet aggregation with ristocetin Management • tranexamic acid for mild bleeding • desmopressin (DDAVP): raises levels of vWF by inducing release of vWF from Weibel-Palade

bodies in endothelial cells DDAVP is the initial treatment of choice for patients with VWD type 1. Other therapies such as factor VIII concentrates containing VWF are not usually required. • factor VIII concentrate • In minor trauma, desmopressin (DDAVP) can be used to increase the concentration of VWF. The choice of treatment for a mild vWB facing a more invasive procedure would be DDAVP, providing there is no contraindication. vWB factor concentrate would be reserved as second line treatment to DDAVP. • for major surgery, factor VIII concentrate is used to increase the concentration of vWF. The most commonly used is Humate-P. Purified or recombinant preparations are avoided since they contain only small concentrations of vWF. In cases of severe vWD or prior to major surgery, the product of choice is intermediate purity (vWF rich) factor VIII, which contains the highest concentration of von Willebrand factor. • for Women with menorrhagia: Oral contraceptives (the Pill) raise the level of von Willebrand factor in the blood for women with Type 1 VWD.

Haemophilia Definitions • Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX Hemophilia A (factor VIII): ~80% of cases Hemophilia B (factor IX): ~20% of cases Etiology • X-linked recessive disorder Occurs almost exclusively in males due to an X-linked pattern of inheritance. typically skips generations A carrier mother has a 50% chance of passing down the disease to her sons and a 50% chance of passing down the carrier gene to her daughters. • Up to 30% of patients have no family history of the condition. Pathophysiology • The pathological problem in both haemophilia A and haemophilia B is the inability to form a functional tenase complex to activate factor X to factor Xa • The intrinsic coagulation pathway is defective in hemophilia. Features • typically present initially with easy bruising secondary to minimal trauma, • haemoarthroses, haematomas

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 Musculoskeletal bleeding is the most common type of haemorrhage. • prolonged bleeding after surgery or trauma, Severity Clinical signs Factor VIII or IX activity Physiologic condition None ≥ 50% Mild hemophilia Hematomas following severe trauma > 5% to < 50% Moderate hemophilia Hematomas following mild trauma ≥ 1% to 5% Severe hemophilia Spontaneous hematomas < 1% Petechial bleeding is a common sign of platelet disorders, NOT coagulation disorders such as hemophilia Blood tests • prolonged APTT • mixing study requested if the aPTT is prolonged. The patient's plasma is mixed with normal plasma and the aPTT repeated. Correction of aPTT with mixing study suggests coagulation factor deficiency. • plasma factor VIII and IX assay • bleeding time, thrombin time, prothrombin time normal Although female carriers of the haemophilia gene do not normally suffer from increased bleeding risk, APTT may be prolonged. Treatment • factor VIII or IX replacement. • Side effects: Up to 10-15% of patients with haemophilia A develop antibodies to factor VIII treatment

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Methemoglobinemia Methemoglobin • hemoglobin is oxidized to the ferric (Fe3+) • ↓ affinity for O2 • ↑ affinity for cyanide (CN-) CN- poisoning treated with methemoglobin • Methemoglobin (met-Hb) results from the presence of iron in the ferric form (Fe3+) instead of the usual ferrous form (Fe2+). • met-Hb cannot carry oxygen • met-Hb is a naturally occurring oxidized metabolite of hemoglobin, and physiologic levels (< 1%) are normal. • Methemoglobinemia (congenital or

acquired) occurs when (RBCs) contain methemoglobin at levels higher than 1%. • Acquired methemoglobinemia is considerably more common than congenital forms. • The low level of methemoglobin is maintained through 2 important mechanisms.