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Notes & Notes for MRCP

By Dr. Yousif Abdallah Hamad

Catheter-Associated UTI Overview • Once catheter is in place, the • risk of bacteriuria Once catheter is in place: □ short-term catheterization (ie, 2-4 days) □ 10% - 30% □ long-term catheterization □ 90% -100% • the most common source of gram-negative bacteremia in hospitalized patients Causes • Enteric pathogens (eg, Escherichia coli) are most commonly responsible • Proteus and Pseudomonas species are the organisms most commonly associated with biofilm growth on catheters. • Candida, especially Candida albicans, is the second-most-common organism that can cause catheter-associated urinary tract infection or asymptomatic colonization Diagnosis • diagnosis of catheter-associated urinary tract infection can be made when the urine culture shows 100 or more CFU per mL of urine from a catheterized patient. Treatment • Symptomatic bacteriuria □ mild to moderate infections: oral quinolones, usually for 10 to 14 days. □ The recommended duration of therapy for severe infections is 14 to 21 days. • Asymptomatic bacteriuria □ not recommended, with the following exceptions: □ patients who are immunosuppressed after organ transplantation, □ patients at risk for bacterial endocarditis and □ patients who are about to undergo urinary tract instrumentation

Urinary tract obstruction in children (posterior urethral valves) Overview • A poor urinary stream suggests a urinary tract obstruction (usually infravesical) • The most common cause in a male child is posterior urethral valves • posterior urethral valves: symmetrical folds of urothelium extending distally from the prostatic urethra to the external urinary sphincter • Renal dysplasia is usually associated with posterior urethral valves Diagnosis • The best diagnostic method is a micturating cystourethrography • The other option is endoscopy . Complications • 30% of patients experience end-stage renal disease • Vesicoureteric reflux occurs in half the patients

Third edition Notes & Notes For MRCP part 1 & 2 Dr. Yousif Abdallah Hamad Haematology Oncology Updated

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Haematology&Oncology Haematological changes during pregnancy • Platelet $\square$ Isolated thrombocytopenia $\square$ occur in 8% $\square$ Usually mild with platelet above 70 $\square$ Occur due to presence IgG antibodies, which are reactive to platelet $\square$ No intervention - recover after delivery • Hypercoagulable state $\square$ $\uparrow$ clotting factors $\square$ result of venous stasis secondary to uterine pressure on great veins of lower extremity • Anemia $\square$ $\uparrow$ plasma volume by 50% $\square$ RBC mass only $\uparrow$ by 30% $\square$ Result is a dilutional gap of 15-20% • Leukocytosis $\square$ result of granulocyte demargination $\square$ no absolute increase in WBC number

Hyposplenism Causes • splenectomy • sickle-cell • coeliac disease, dermatitis herpetiformis • Graves' disease • systemic lupus erythematosus • amyloid Features • Howell-Jolly bodies • siderocytes

Eosinophilia Causes • Pulmonary causes $\square$ asthma $\square$ allergic bronchopulmonary aspergillosis $\square$ Churg-Strauss syndrome $\square$ Löffler's syndrome $\square$ tropical pulmonary eosinophilia $\square$ eosinophilic pneumonia $\square$ hypereosinophilic syndrome • Infective causes $\square$ schistosomiasis $\square$ nematodes: Toxocara, Ascaris, Strongyloides $\square$ cestodes: Echinococcus • Other causes $\square$ drugs: sulfasalazine, nitrofurantoin $\square$ psoriasis/eczema $\square$ eosinophilic leukaemia (very rare)

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Eosinopenia (Decrease eosinophils) Causes • Cushing syndrome would result in a decrease in eosinophils. • Corticosteroids can cause eosinopenia through sequestration of eosinophils in lymph nodes.

Hyper-eosinophilic syndrome (HES) Definition • peripheral blood eosinophil count of >1.5 for more than 6 months. • In hypereosinophilic syndrome, the eosinophils represent more than 20 percent of the cell population in the bone marrow. • HES are defined as the association of Hypereosinophilia (as defined above), with eosinophil-mediated organ damage, in which other causes for the damage have been excluded. Features • Hypereosinophilic syndrome most commonly causes manifestations involving the skin. • pruritus. • fatigue, myalgia, • fever, night sweats, • diarrhoea • The most common neurological manifestation of hypereosinophilic syndrome is stroke. • Other symptoms depend on the organ involved: $\square$ cardiac disease causes chest pain and dyspnoea, $\square$ respiratory disease presents with a dry cough. Treatment • The first line of treatment of patients with non-myeloid hypereosinophilic syndrome is glucocorticoids. • The best initial therapy for patients with hypereosinophilic syndrome associated with Fc γ RI-like1-platelet-derived growth factor receptor alpha mutation is imatinib.

Lymphopenia Causes • common finding in elderly patients. $\square$ If greater than $0.5 \times 10^9/l$ no action is normally needed • immunosuppressive drugs e.g. methotrexate • viral infections e.g. HIV • non-viral infections e.g. tuberculosis, malaria • autoimmune disorders e.g. rheumatoid • lymphoproliferative disorders

Haematology&Oncology

Blood films: pathological cell forms Pathological red cell forms Abnormality Associated condition(s) Appearance Target cells Sickle-cell/thalassaemia Iron-deficiency anaemia Hyposplenism Liver disease 'Tear-drop' (Dacrocyte) poikilocytes Myelofibrosis (The morphology results because RBCs are mechanically squeezed out of the bone marrow.) Spherocytes Hereditary spherocytosis Autoimmune hemolytic anaemia Basophilic stippling Lead poisoning Thalassaemia Sideroblastic anemia Myelodysplasia

Abnormality Associated condition(s) Appearance Howell-Jolly bodies Hyposplenism (Howell-Jolly bodies are the basophilic remnants of the RBC nucleus.) Heinz bodies G6PD deficiency Alpha-thalassaemia Schistocytes ('helmet cells') Intravascular haemolysis Mechanical heart valve Disseminated intravascular coagulation 'Pencil' poikilocytes Iron deficiency anaemia

Haematology&Oncology Abnormality Associated condition(s) Appearance Burr cells (echinocytes) Uraemia Pyruvate kinase deficiency liver disease Acanthocytes Abetalipoproteinemia (irregularly distributed spicule in red blood cells). Bite cell (Degmacyte) G6PD (when spleen removes heinz bodies from RBCs)

Blood films: typical pictures Hyposplenism e.g. post-splenectomy • target cells • Howell-Jolly bodies
□ These are spherical bluish inclusions within erythrocytes □ They are nuclear fragments of condensed DNA which are normally removed by the spleen. □ They are seen in severe haemolytic anaemias or in hyposplenic/asplenic patients. • Pappenheimer bodies • siderotic granules • acanthocytes Iron-deficiency anaemia • target cells • 'pencil' poikilocytes

• if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells Myelofibrosis • 'tear-drop' poikilocytes Intravascular haemolysis • schistocytes Megaloblastic anaemia • hypersegmented neutrophils Congenital Pelger-Huet anomaly • is a laminopathy associated with mutations in the lamin B receptor. • This leads to bilobed nuclei in neutrophils and in homozygotes, • can also be associated with: □ skeletal abnormalities which include shortened limbs. □ Like this patient, heterozygotes usually suffer no symptoms and the neutrophil anomaly is picked up as an incidental finding. MRCP part-1 – jan 2017 A 23-year-old man with tiredness and was noted to have a neutrophil abnormality on his blood film with bilobed

nuclei. His father has a skeletal anomaly with a short right arm, Examination reveals no lymphadenopathy, and abdominal examination is entirely normal. What is the most likely diagnosis? □ Congenital Pelger-Huet anomaly

Leucocyte alkaline phosphatase Raised in • myelofibrosis • leukaemoid reactions • polycythaemia rubra vera • infections • steroids, Cushing's syndrome • pregnancy, oral contraceptive pill • chronic myeloid leukaemia • pernicious anaemia • paroxysmal nocturnal haemoglobinuria • infectious mononucleosis Leukaemoid reaction Definition • Presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood. Mechanism • This may be due to: □ infiltration of the bone marrow causing the immature cells to be 'pushed out' or □ sudden demand for new cells Causes • severe infection • severe haemolysis • massive haemorrhage • metastatic cancer with bone marrow infiltration

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Differentiating chronic myeloid leukaemia from a leukaemoid reaction: Chronic myeloid leukaemia Leukaemoid reaction low leucocyte alkaline phosphatase score • high leucocyte alkaline phosphatase score • toxic granulation (Dohle bodies) in the white cells • 'left shift' of neutrophils i.e. three or less segments of the nucleus Coagulation study Prothrombin time (PT) • Prothrombin time (PT) is a measure of the time it takes for the extrinsic pathway to create a fibrin clot. • tests function of factors (I, II, V, VII, X) □ defect in any of these → ↑ PT □ e.g. vitamin K deficiency • best test to follow warfarin therapy □ normalized as an INR (international normalized ratio) □ note also increases PTT time • also used to measure hepatic function as most of the factors are synthesized in the liver Used to monitor the extrinsic pathway • Factors make up the extrinsic pathway: □ Damaged endothelium → tissue factor release → Factor VII activation → common pathway activation • In patients with vitamin K deficiency, the PT is typically prolonged while the partial thromboplastin time (PTT) is usually normal. • Long-term use of antibiotics □ changes in the gut flora □ vitamin K deficiency □ ↑ PT □ Long-term use of antibiotics (particularly cephalosporins like cefepime) would cause changes in the gut flora that result in vitamin K deficiency (due to decreased populations of the bacteria that synthesize it). □ vitamin K deficiency would impair the gamma-carboxylation of factors II, VII, IX, and proteins C and S. □ As a result, the PT, which measures the clotting time of the extrinsic pathway (starting with tissue factor and factor VII), would increase, just as it would in a patient on warfarin. Partial Thromboplastin Time (PTT) (sometimes also called Activated Partial Thromboplastin Time) • tests function of all factors EXCEPT (VII, XIII) □ defect in any of these → ↑ PTT • when prolonged indicating hemophilia or (sometimes) von Willebrand's Disease. • best test to follow heparin therapy □ note also increases PT time • Used to monitor the intrinsic pathway • Factors make up the intrinsic pathway: □ Factors XII, XI, IX, VIII. • elevated APTT could be due to: □ treatment with heparin □ haemophilia □ von Willebrand's disease, or □ antiphospholipid syndrome.

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The commonest cause of reduced APTT is $\square$ in-vitro clotting cascade activation, but tests should be repeated to exclude pathological causes of hypercoagulability. DIC vs TTP • DIC is distinguished from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) based on coagulation studies. • Although TTP and HUS are also microangiopathic hemolytic anemias, patients with these conditions do not have derangement or consumption of clotting factors. $\square$ DIC $\square$ Increased PT, PTT, decreased platelets $\square$ TTP & HUS $\square$ normal PT, normal PTT, and decreased platelets. Isolated factor deficiency • Normal PT, increased PTT, and normal platelets suggests an isolated factor deficiency such as hemophilia A and B, in which there is a deficiency of factors VIII and IX, respectively. • An isolated elevated PTT may also suggest von Willebrand's disease. Giant platelet syndrome (Bernard-Soulier syndrome; BSS) • is a defect in platelet adhesion. • The genetic defect is in glycoprotein 1b (GP1b). • characterized by increased megakaryocytes and abnormally large platelets on peripheral smear, hence its name. • thrombocytopenia and an elevated bleeding time but a normal prothrombin time (PT) and partial thromboplastin time (PTT). • BSS can be distinguished from a deficiency in von Willebrand factor (vWF) by a ristocetin test. $\square$ Ristocetin is an antibiotic that causes vWF to bind to GP1b, causing agglutination in normal blood. $\square$ In patients with either defective vWF or GP1b (BSS), platelets do not aggregate in the presence of ristocetin. $\square$ The addition of normal plasma corrects this defect in von Willebrand's disease, but not in BSS (because the platelet receptor remains defective).

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Haematology&Oncology Assessment of anaemia From BMJ best practice Causes of normocytic anaemia: • anaemia of chronic disease • chronic kidney disease • aplastic anaemia • haemolytic anaemia Causes of macrocytic anaemia: • can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow Megaloblastic causes Normoblastic causes • vitamin B12 deficiency • folate deficiency • alcohol • liver disease • hypothyroidism • pregnancy • reticulocytosis • myelodysplasia • drugs: cytotoxics Causes of microcytic anaemia: • iron-deficiency anaemia • thalassaemia* $\square$ *in beta-thalassaemia minor the microcytosis is often disproportionate to the anaemia

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$\square$ A question sometimes seen in exams gives a history of a normal haemoglobin level associated with a microcytosis. In patients not at risk of thalassaemia, this should raise the possibility of polycythaemia rubra vera which may cause an iron-deficiency secondary to bleeding. • congenital sideroblastic anaemia • anaemia of chronic disease (more commonly a normocytic, normochromic picture) • lead poisoning Iron metabolism Absorption: • Upper small intestine. • About 10% of dietary iron absorbed. • Fe^{2+} (ferrous iron) much better absorbed than Fe^{3+} (ferric iron). • Absorption is regulated according to body's need. • Increased by vitamin C (ascorbic acid) and gastric acid. $\square$ vitamin C aids iron absorption by reducing iron from the ferric to the ferrous form, and by chelating it into a complex which enhances absorption. • Decreased by PPIs, tetracycline, gastric achlorhydia, tannin (in tea). • From an intake of approximately 6 mg/1000 kcal of dietary iron only 15% is bioavailable. Distribution in body • Total body iron = 4g (2500 mg in the RBCs, 500 mg in liver, 500 mg in macrophages and about 500 mg in muscle). • Haemoglobin = 70% •

Ferritin and hemosiderin = 25% • Myoglobin = 4% • Plasma iron = 0.1%

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□ Approximately 4 mg of iron circulate within the plasma. So approximately 0.1% of body iron circulates in the plasma. Transport • Carried in plasma as Fe^{3+} bound to transferrin. Storage • Stored as ferritin in tissues. □ It is the plasma protein responsible for binding iron, □ is an acute phase reactant protein which is increased in inflammatory conditions. Excretion • The majority of iron contained within the RBCs is metabolised and re-utilised but 1 mg per day is lost through the gut. Transferrin serum transferrin is the bus that carry absorbed iron to storage places & stored as ferritin. transferrin saturation is the % of people [iron] carried by that bus [transferrin]. TIBC is the no. of empty chairs in that bus. • Transferrin is a glycoprotein responsible for internal iron exchange □ Iron (Fe^{3+}) is carried in the blood bound to transferrin. □ Fe^{2+} (ferrous iron) is oxidised to Fe^{3+} (ferric iron) by caeruloplasmin to bind to transferrin • Transferrin is the binding protein of iron. So when the levels of ferritin are low, the body signals the liver to synthesize more of Transferrin to maintain the levels of iron • Pregnancy and oral contraceptive pill (OCP) both increase transferrin. • Transferrin saturation % □ The transferrin saturation % ($\text{plasma iron} / \text{TIBC} \times 100$) is used as a measure of iron stores. □ In absence of anaemia, transferrin is about 33% saturated with iron (about one third saturated with iron). □ A value below 16% is indicative of iron deficiency. • iron deficiency □ low serum Fe, rise TIBC, rise the transferrin level. • iron overload □ fall in both TIBC and transferrin • haemochromatosis □ increased in Transferrin saturation% □ the content within mucosal cells is naturally high in haemochromatosis with high iron store saturation. □ in haemochromatosis TIBC is low because transferrin is FULL of iron and no more empty space, hence LOW TIBC and for the same reason transferrin saturation is high [FULL] Iron studies • Serum iron • Total iron binding capacity (TIBC) • Transferrin □ raised in iron deficiency anaemia (IDA) □ raised in pregnancy and by oestrogen • Transferrin saturation □ calculated by serum iron / TIBC • Ferritin □ raised in inflammatory disorders □ low in IDA • Rarer tests □ transferrin receptors □ increased in IDA • Anaemia of chronic disease

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□ normochromic/hypochromic, normocytic anaemia □ reduced serum and TIBC □ normal or raised ferritin

Iron deficiency anaemia (IDA) • iron deficiency is the most common cause of anemia worldwide. Causes • the commonest cause of iron-deficiency anaemia worldwide being hookworm infection (*Necator americanus* and *Ancylostoma duodenale*), which affects 25% of the global population. • microcytic anaemia in a female should raise the possibility of either gastrointestinal blood loss or menorrhagia. Features • Koilonychia (spoon-shaped nails) • atrophic glossitis • post-cricoid webs □ Plummer-Vinson syndrome (dysphagia, esophageal webs and iron deficiency) • other cutaneous manifestations of iron deficiency include: □ pruritus, □ dry and brittle hair □ the hair, skin, nail and

mucous membrane changes are often visible before the patient is clinically anemic. • angular stomatitis Investigations • Blood film □ target cells □ 'pencil' poikilocytes □ if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells • Serum ferritin □ Hypoferritinaemia confirms IDA and is the preferred screening test. □ the most sensitive marker for iron deficiency □ Ferritin is an acute phase reactant and may be grossly elevated in the context of acute inflammation (when it does not accurately reflect iron stores) and to a lesser degree in chronic inflammation. □ British Society Guidelines on the diagnosis and management of iron deficiency anaemia suggest that: a cut-off of 12-15 mg/L reflects iron deficiency in the absence of inflammation. Where inflammation is present a ferritin of 50 mg/L or more may still be compatible with iron deficiency. Treatment of IDA Iron tablet preparations • Among the tablet preparations, there are:

1. non-enteric coated pills □ most commonly used as initial treatment due to their lower cost.
2. enteric-coated
3. prolonged-release formulations. □ Delayed release and enteric-coated iron are better tolerated than the nonenteric coated tablets. □ less effective since they may contain less iron and their iron may not be released in the duodenum, where iron is absorbed.

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Haematology&Oncology □ patients who have been treated unsuccessfully with enteric-coated and prolonged-release iron preparations may respond well to the administration of nonenteric-coated ferrous salts • Ferrous sulphate has more elemental iron by mass than the same dose of ferrous gluconate • Sustained release preparations may improve tolerance of oral iron but do not aid absorption. Iron prescription • Ideally, patients should not take iron supplements within 1-2 hours of antacids □ alkaline environment reduces absorption (acidity required for iron solubility) • Iron tablets are recommended between meals or at bedtime to avoid the alkalinizing effect of food and to take advantage of the peak gastric acid production late at night. • calcium, phosphorus and magnesium salts contained in iron-containing multivitamin pills impair absorption of elemental iron. For this reason, multivitamin preparations should never be recommended as a sole therapy for iron deficient anemia. • Iron absorption is also delayed with tetracyclines, milk, and phosphate-containing, carbonated beverages such as soft drinks. • Iron replacement in chronic renal failure □ In chronic renal failure, Erythropoietin (EPO) therapy is only considered in patients where the ferritin is >100 mg/L. □ If ferritin < 100 □ iron replacement is the initial intervention of choice. • IV iron □ Parenteral iron acts no faster than oral iron. It is indicated when oral iron cannot be tolerated or is not absorbed. □ Indications for IV iron include: □ unable to tolerate orally, □ Patients who fail to comply with prescriptions for oral iron supplementation. □ A history of exertional angina with anaemia □ strongest indication for transfusion □ GIT disorders, such as IBD (ulcerative colitis and Crohn's disease), in which symptoms may be aggravated by oral iron therapy □ Iron is poorly absorbed from the GI tract in patients with renal failure, as such IV replacement is the modality of choice. □ It is considered best practice to administer 1000 mg of low molecular weight iron dextran in 250 mL of normal saline in 1 hour without premedication; □ a test dose of 10 to 25 mg is infused over 3 to 5 minutes prior to the first infusion.

□ If no acute reaction is observed, the remaining solution is infused over the balance of 1 hour.

□ For those with a history of drug allergies or hypersensitivity, 125 mg of methylprednisolone is infused prior to the test dose. British society of gastroenterology (BSG) guidelines 2011: • correct anaemia and replenish body stores achieved most simply and cheaply with ferrous sulphate 200 mg twice daily. • Lower doses may be as effective and better tolerated and should be considered in patients not tolerating traditional doses. • Other iron compounds (eg, ferrous fumarate, ferrous gluconate) or formulations (iron suspensions) may also be tolerated better than ferrous sulphate. • Oral iron should be continued for 3 months after the iron deficiency has been corrected so that stores are replenished. • Ascorbic acid (250e500 mg twice daily with the iron preparation) may enhance iron absorption • Iron treatment should follow transfusion to replenish stores.

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Anemia of Chronic Disease Definition • decreased RBC production due to any longstanding inflammatory, infectious, or malignant disease (includes rheumatoid arthritis, severe trauma, heart disease, diabetes mellitus, and inflammatory bowel disease) Mechanism of Anemia of Chronic Disease • there is primarily a decreased availability of iron, relatively decreased levels of erythropoietin, and a mild decrease in the lifespan of RBCs to 70-80 days (normally 120 days) □ in anemia of chronic kidney disease, ↓ erythropoietin production by the interstitial fibroblasts, (also known as type I interstitial cells), □ anemia. □ The kidneys are responsible for approximately 90% of erythropoietin production. • Increase in hepcidin level in the course of inflammatory disease □ ↓ release of iron from macrophages + ↓ dietary iron absorption. □ hepcidin is an acute-phase reactant that is increased in states of inflammation • cytokines, such as interleukins (IL-1 and IL-6), and tumor necrosis factor (TNF-alpha), □ destruction of RBC precursors and decrease the number of erythropoietin receptors on progenitor cells. Investigations • RBCs morphology □ normochromic, normocytic anemia. • Reticulocyte count □ ↓ reticulocyte count points to ↓ RBC production as the primary mechanism responsible for anemia, • ↑ ferritin • ↓ serum iron • ↓ TIBC, transferrin saturation, and MCV Treatment • treatment of the underlying disease. • If underlying disease is unknown or treatment of underlying disease does not improve symptomatic anemia □ measure EPO □ if low, administer EPO or erythropoiesis-stimulating agents (ESAs) □ make sure iron stores are sufficient □ if insufficient, patients may be resistant to EPO □ if normal, give packed RBCs

Hepcidin • Hepcidin, a peptide hormone synthesized in the liver. • reduces extracellular iron in the body by several mechanisms:

1. lowers dietary iron absorption by reducing iron transport across gut mucosal cells (enterocytes);
2. reduces iron exit from macrophages, the main site of iron storage;
3. reduces iron exit from the liver. In all three instances this is accomplished by reducing the transmembrane iron transporter ferroportin. • inflammation □ ↑ hepcidin □ ↓ serum iron due to: □ iron trapping within macrophages and liver cells

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Haematology&Oncology □ decreased gut iron absorption. □ inadequate amount of serum iron being available for developing red cells □ anemia • hemochromatosis □ ↓ hepcidin level □ iron overload due to: □ increased ferroportin mediated iron efflux from storage and increased gut iron absorption. • Hepcidin inhibits iron transport by binding to the iron export channel ferroportin which is located on the basolateral surface of gut enterocytes and the plasma membrane of macrophages. □ Inhibiting ferroportin leads to: □ ↓ iron release from macrophages □ ↓ dietary iron absorption.

Thalassaemias Alpha is located on 16, beta on 11 chromosome . Definition • The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains. • It is a haemoglobinopathy resulting from defective synthesis of globin chains required for Hb synthesis. • Each copy of chromosome 16 has two genes for the alpha globin subunit (four in total). • And each copy of chromosome 11 has one genes for the beta globin subunit (two in total). Types of haemoglobin Haemoglobin Chains % Hb in normal adult Hb A $\alpha_2\beta_2$ (two alpha and two beta chains) 97% Hb A2 $\alpha_2\delta_2$ (two alpha and two delta chains) < 3.5% Hb F $\alpha_2\gamma_2$ (two alpha and two gamma chains) <1% Alpha-thalassaemia • Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin • Alpha-thalassaemia is found in malarial regions of the world (Mediterranean, South-east Asia, Indian sub-continent, Middle East, Sub-Saharan Africa) and should be suspected in patients with these ethnic backgrounds and with microcytosis and/or anaemia. • Acquired Hb H disease is rare and occurs most commonly in male patients with myelodysplastic syndrome. Overview • 2 separate alpha-globulin genes (four in total) are located on each chromosome 16 • There are 4 different alpha-thalassaemias:

1. silent carrier (1 affected alpha-globin gene),
2. alpha-thalassaemia trait (2 affected alpha-globin genes),
3. Hb H disease (typically 3 affected alpha-globin genes)
4. Hb Bart hydrops fetalis syndrome (typically deletion of all 4 alpha-globin genes). • Clinical severity depends on the number of alpha chains present □ If 1 or 2 alpha chains are absent then the blood picture would be hypochromic and microcytic, but the Hb level would be typically normal □ Loss of 3 alpha chains results in a hypochromic microcytic anaemia with splenomegaly and HbH in red cells. This is known as Hb H disease

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□ If all 4 alpha chains absent (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops) • Persistence of HbF has survival advantages in severely affected subjects. • Co-inheritance of alpha-gene mutations, and persistence of fetal haemoglobin production, may restore the globin balance and result in a milder syndrome. • Features □ most are asymptomatic. □ Many patients with Hb H are also clinically well, but are at risk for: □ acute haemolytic episodes □ aplastic crises □ iron overload, even in the absence of chronic transfusions □ hypersplenism; and □ endocrine disease. □ Hemoglobin gel-electrophoresis □ α -thalassemia trait □ normal □ 3 gene deletion α -thalassemia □ HbH (β,β,β,β) □ 4 gene deletion α -thalassemia □ Hb Barts ($\gamma,\gamma,\gamma,\gamma$)

Beta-thalassaemia If a person has $MCV > 80$ and $MCH > 27$, in the absence of symptoms, thalassemia can be reasonably excluded. Overview • The most common cause of β -Thalassemia is the defect in mRNA splicing of the beta globin gene on chromosome 11 . • autosomal recessive • common in Mediterranean populations • β thalassaemia minor / trait □ protects against malaria □ $\uparrow$ (Hb F) □ inhibits the development of the malarial parasite. Types • β thalassaemia major (β^0): □ prevent any formation of β chains, □ the most severe form of β thalassemia. □ 2 gene depletion ($\beta^0\beta^0$) ($\alpha,\alpha,\alpha,\alpha$ hemoglobin present) □ aggregation of alpha-globin tetramers □ damage erythrocytes □ extravascular hemolysis. □ HbF tries to convert to HbA during first year of life, □ Fetal hemoglobin is protective in an infant with beta-thalassemia major, hence the disease will only present after six months of age, as its levels decrease. □ extramedullary haemopoiesis with hepatosplenomegaly and bone marrow expansion, “hair on end” appearance of bone. □ Diagnosis □ Hemoglobin electrophoresis is the best test for diagnosis □ Features □ anaemia □ splenomegaly □ occurs secondary to extramedullary hematopoiesis. □ bone deformities

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Haematology&Oncology □ bone marrow expansion can cause "chipmunk facies" or "crew cut sign" on a skull X-ray. □ Target cells on a peripheral blood smear □ early death if not treated appropriately. □ Treatment: □ lifelong regular blood transfusions, (usually every two to five weeks, to maintain the pretransfusion haemoglobin level above 9–10.5 g/dl). □ transfusion programme with iron chelation is the best initial approach. □ Indications for transfusion: □ $Hb < 7g/dl$ on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections) or □ $Hb > 7g/dl$ with: Facial changes, Poor growth, Fractures, and Extramedullary haematopoiesis □ The transfusional iron overload can be managed with iron chelation, both IV/SC (desferrioxamine) and/or oral (deferasirox). □ Desferrioxamine binds iron but needs to be given for 8-12 hours a day for 5-7 days per week, so is a major undertaking for the patient. □ SE: high frequency deafness, retinopathy and Yersinia infection. □ Stem cell transplantation options offer cure. □ parents and other siblings should be screened by genetic testing. • β thalassaemia intermedia (β^+): □ caused by a mutation in the Kozak consensus sequence of the Beta globin gene on chromosome 11. □ they allow some β chain formation to occur. □ In either case there is relative excess of α chains, but these don't form tetramers. • β thalassaemia minor / trait: □ 1 gene deletion □ Features □ usually asymptomatic □ mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia (marked microcytosis (very low MCV) (i.e. the Microcytosis is disproportionately with very low MCV for the near normal Hb level >9). □ HbA_2 ($\alpha_2\delta_2$) raised (> 3.5%) on gel electrophoresis. □ HbA_2 levels above 3.5% are screening criteria for the β thalassemia carrier state. □ Note that in cases of severe iron deficiency anaemia the HbA_2 may be normal in thalassemia minor. • Thalassemia can co-exist with other haemoglobinopathies. The most common of these are: □ HbE /thalassaemia: □ common in Cambodia, Thailand, and parts of India □ clinically similar to β thalassaemia major or thalassaemia intermedia. □ HbS /thalassaemia: □ common in African and Mediterranean populations □ clinically similar to sickle cell anaemia with additional feature of splenomegaly. □ HbC /thalassaemia: common in African and Mediterranean populations: □ HbC/β^0 thalassaemia: causes moderate to severe haemolytic anaemia with splenomegaly. □ HbC/β^+ thalassaemia: produce a milder disease.

Delta thalassaemia • about 3% of adult Hb is made of alpha and delta chains. • mutations can occur which affect the ability of this gene to produce delta chains.

Aplastic anaemia • Characterised by pancytopenia and a hypoplastic bone marrow • Peak incidence of acquired = 30 years old Features • Assessment of bone marrow cellularity is best made on trephine biopsy, which often shows replacement of the normal cellular marrow by fatty marrow. • normochromic, normocytic anaemia • leukopenia, with lymphocytes relatively spared • thrombocytopenia • may be the presenting feature acute lymphoblastic or myeloid leukaemia • a minority of patients later develop paroxysmal nocturnal haemoglobinuria or myelodysplasia • In patients with aplastic anemia, the bone marrow is markedly hypocellular. Causes • idiopathic • congenital: Fanconi anaemia, dyskeratosis congenita • drugs: cytotoxics, chloramphenicol, sulphonamides, phenytoin, gold • toxins: benzene • infections: parvovirus, hepatitis • radiation management Supportive • blood products • prevention and treatment of infection Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG) • prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes

Haematology&Oncology • is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given • immunosuppression using agents such as ciclosporin may also be given Stem cell transplantation • allogeneic transplants have a success rate of up to 80%

Pure Red Cell Aplasia (PRCA) Overview • uncommon disorder • maturation arrest occurs in the formation of erythrocytes. Erythroblasts are virtually absent in bone marrow; however, white blood cell and platelet production are normal. • The anemia due to PRCA is usually normocytic but can be macrocytic. Diagnosis • characteristics of PRCA include

1. Severe unexplained anemia
2. ↓ Reticulocyte count <1%
3. The presence of less than 0.5% mature erythroblasts in the bone marrow
4. Normocellular bone marrow in most cases Causes • most cases of chronic PRCA are idiopathic (acquired primary). • Secondary PRCA associated with: □ Autoimmune disorders (eg, type 1 diabetes, thyroiditis, rheumatoid arthritis, Sjögren syndrome) □ Thymomas □ Systemic lupus erythematosus □ Hematologic malignancies □ Solid tumors □ Erythropoietin-induced pure red cell aplasia in treatment of CKD anaemia Treatment • can be transient and reversible (PRCA due to medications and infections are often reversible.) • symptomatic anaemia □ transfusion • Treatment of underlying conditions □ parvovirus B19 infections □ High-dose intravenous immunoglobulin □ PRCA due to drugs □ disappear when the drug is stopped. □ thymoma □ thymectomy or gamma irradiation of the thymus • Immunosuppressive: □ Corticosteroids are the mainstay of therapy (45% respond) □ the

first choice □ cyclosporine, azathioprine, Cyclophosphamide and rituximab are used

Fanconi's Anaemia • Autosomal recessive • Aplastic anaemia • ↑ risk of AML • Neurological manifestation • Skeletal abnormalities • Skin pigmentation (café; au lait spots)

Notes & Notes for MRCP

By Dr. Yousif Abdallah Hamad

Macrocytic anaemia Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow Megaloblastic causes Non-megaloblastic causes • vitamin B12 deficiency • folate deficiency • alcohol • liver disease • hypothyroidism • pregnancy • reticulocytosis • myelodysplasia • drugs: cytotoxics • If serum folate levels are low, serum vitamin B12 and methylmalonic acid levels should be measured to exclude concurrent vitamin B12 deficiency before folate levels are corrected. • Normal serum homocysteine levels make folate deficiency unlikely. • RBC folate is a more accurate indicator of folate deficiency than serum folate level.

_Vitamin B12 (cobalamin) deficiency Function of vitamin B12 deficiency • Red blood cell development • Maintenance of the nervous system. • B12 is necessary for normal folate metabolism, and therefore when there is a primary B12 deficiency, one can see a low red cell folate as a consequence. Sources • Vit B12 is only found in foods of animal origin e.g. meat, fish and eggs. Metabolism • It is absorbed after binding to intrinsic factor (IF) (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. • A small amount of Vit. B12 is passively absorbed without being bound to IF. • Hepatic stores of vitamin B12 can last for up to 5 years, so it is not uncommon for vegans to display vitamin B12 deficiency years after starting their diet Causes • Dietary deficiency of Vit B12: like vegetarians □ An MCV of >115 fL is typically seen in nutritional deficiency. □ very rare □ Folate deficiency due to dietary problems is common, particularly in the elderly, but it does take many years to become B12 deficient as a result of dietary deficiency. • Pernicious anaemia • Post gastrectomy □ A patient with combined iron deficiency and B12 deficiency, Which operation is he most likely to have had? □ Partial gastrectomy • Disorders of terminal ileum (site of absorption): Crohn's, blind-loop, Malabsorption of vitamin B-12 secondary to small bowel bacterial overgrowth, tapeworm, etc. • Bacterial overgrowth syndrome □ characterized by diarrhea, steatorrhea, and macrocytic anemia. □ The common feature is proliferation of colonic bacteria in the small bowel. In normal individuals, the small bowel is relatively sterile. □ Common bacteria involved are E.coli or bacteroides. □ Macrocytic anemia results from increased utilization of vitamin B12 by the colonized bacteria.

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Haematology&Oncology □ Steatorrhea is caused by reduced concentration of conjugated bile acids. Bacteroides can convert conjugated bile acids to unconjugated bile acids, which result in impaired micelle formation. □ Diarrhea is due to steatorrhea. Features of vitamin B12 deficiency • Macrocytic anaemia • mild jaundice is typical of megaloblastic anaemia (vitamin B12 or folate

deficiency) because of increased destruction of red cell precursors in the bone marrow. • Sore tongue and mouth • Neuropsychiatric symptoms: e.g. Ataxia, Mood disturbances □ Neurological involvement can be present in B12 deficiency even in the absence of anaemia, especially in patients over the age of 60. □ The peripheral nerves are most commonly involved, followed by subacute degeneration of the spinal cord. □ Early signs are loss of peripheral vibration and joint position sense, which is usually followed by loss of reflexes and weakness. □ The legs and feet are usually more involved than the hands. □ In the late stages there may be spasticity, upgoing plantars and ataxia but thankfully this is rare in the UK. • Serum methylmalonic acid levels are elevated in vitamin B12 deficiency. □ more sensitive Serum vitamin B12 levels, and should be used to definitively exclude vitamin B12 deficiency. □ elevated homocysteine and methylmalonic acid levels. • Blood smear will show hypersegmented neutrophils. Treatment • even in case of profound anaemia, if the patient is not haemodynamically compromised □ no need for blood transfusion. • intramuscular vitamin B12 and oral folic acid. • Patient need to continue on treatment with ferrous sulphate as iron stores are likely to be depleted rapidly once the marrow starts functioning. • Giving oral folic acid without vitamin B12 would be hazardous and could precipitate subacute combined degeneration of the spinal cord.

Pernicious anaemia Epidemiology • more common in females (F:M = 1.6:1) • typically develops in middle to old age • more common if blood group A Pathophysiology • autoimmune disease caused by antibodies to gastric parietal cells or intrinsic factor • results in vitamin B12 deficiency • associated with thyroid disease, □ diabetes □ Addison's □ rheumatoid □ vitiligo • predisposes to gastric carcinoma Features • lethargy, weakness • dyspnoea • paraesthesia • mild jaundice • diarrhoea • sore tongue

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• possible signs: □ retinal haemorrhages, □ mild splenomegaly, □ retrobulbar neuritis Investigation Normal serum gastrin excludes pernicious anaemia • anti-gastric parietal cell antibodies in 90% (most common, but low specificity) • anti-intrinsic factor antibodies in 50% (specific for pernicious anaemia) • macrocytic anaemia • pancytopenia (with low WCC and platelets) • LDH may be raised due to ineffective erythropoiesis • also low serum B12, • hypersegmented polymorphs on film, megaloblasts in marrow • Schilling test □ radiolabelled B12 given on two occasions □ first on its own □ second with oral IF □ urine B12 levels measured macrocytic anaemia and isolated B12 deficiency (folate is normal) suggest an isolated problem with B12 absorption □ pernicious anaemia Management • If no neurological involvement: 1 mg of IM Hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months. • If a patient has deficient in both vitamin B12 and folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration (SCD) of the cord.

Sickle cell disease (SCD) Overview • autosomal recessive • Sickle cell disease is a haemoglobinopathy caused by the substitution of glutamic acid by valine at position 6 (from the N-terminal) of the beta chain. (In sickle cell anaemia, valine replaces glutamic acid at the sixth amino acid of the beta globin) • HbS is caused by a single base mutation on the beta-chain • The β globin gene is found on the short arm of chromosome 11. HbS has the following properties: • contains two

α -like globins and two β -like globins and four haem molecules. • less negatively charged, due to the loss of glutamate for valine. • has a life span of only 30 days compared to the normal 120 days. • less soluble than HbA. • has lower affinity for oxygen than HbA (right-shift of the oxygendissociation curve), which increases the risk of desaturation, but improves the yield of oxygen to the tissues.

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