047

Chapter 7

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

1. the hexose-monophosphate shunt pathway within the erythrocyte. Through this pathway, oxidizing agents are reduced by glutathione.
2. The second and more important mechanism involves two enzyme systems: diaphorase I: requires nicotinamide adenine dinucleotide (NADH) the major enzymatic system (This enzyme system is responsible for the removal of 95-99% of the methemoglobin that is produced under normal circumstances.) Cytochrome b5 reductase plays a major role in this process by transferring electrons from NADH to methemoglobin, an action that results in the reduction of methemoglobin to hemoglobin. diaphorase II: requires nicotinamide adenine dinucleotide phosphate (NADPH). plays only a minor role in the removal of methemoglobin. This enzyme system utilizes glutathione production and glucose-6phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin. Play a more important role in methemoglobin regulation in patients with cytochrome b5 reductase deficiencies. can be accelerated by exogenous cofactors such as methylene blue Effect of Methemoglobin: • does not bind oxygen, thus leading to a functional anemia. • causes a left shift of the oxygen-hemoglobin dissociation curve, resulting in decreased release of oxygen to the tissues. Normal people generate met-Hb but in very low levels in the range of 0.5% to 3%. should be suspected when the oxygen saturation as measured by pulse oximetry is significantly different (lower) from the oxygen saturation calculated from arterial blood gas analysis (saturation gap). (low SpO2 with normal PaO2 and SaO2(on ABG) • presence of anemia and cyanosis despite oxygen treatment results from both of these effects. Causes • congenital (secondary to a deficiency in methemoglobinemia reductase) • acquired Dapsone local anesthetics (topical and injectable) nitrates amyl nitrite aniline dyes The presence of methemoglobin may also be a marker and predictor of sepsis, resulting from release of excessive amounts of nitrous oxide (NO) patients with low catalase activity (inherited or acquired) treated with rasburicase for tumor lysis syndrome formation of hydrogen peroxide methemoglobinemia Some authors have suggested that catalase activity be measured before rasburicase therapy is initiated in this setting. Drugs that cause methaemoglobinaemia include: • Phenacetin • Sulphonamides • Dapsone • Primaquine • Lidocaine • Procaine • Benzocaine.

Congenital (hereditary) Methemoglobinemia • autosomal recessive • two forms of congenital cytochrome b5 reductase (b5R) deficiency exist: type Ib5R deficiency type IIb5R more common cytochrome b5 reductase is absent only in RBCs Homozygotes appear cyanotic but usually are otherwise asymptomatic. Heterozygotes may develop acute, symptomatic methemoglobinemia after exposure to certain drugs or toxins. Methemoglobin levels typically range from 10% to 35%. Life expectancy is not influenced presence of abnormal hemoglobins (hemoglobin M [Hb M]) • autosomal dominant • in most of these hemoglobins, tyrosine replaces the histidine residue, which binds heme to globin. • This replacement displaces the heme moiety and permits oxidation of the iron to the ferric state. • Hb M is more resistant to reduction by the methemoglobin reduction enzymes • Patients with Hb M appear cyanotic but are otherwise generally asymptomatic. Feature (are proportional to the methemoglobin level) : Classical presentation includes cyanosis with chocolate-colored blood • 3-15% - Slight discoloration (eg, pale, gray, blue) of the skin and blood color changes (brown or chocolate color). Discoloration of the skin and blood is the most striking physical finding. Fatigue, flu-like symptoms, and headaches may be the only manifestations in the initial phase. • 15-20% - Cyanosis, though patients may be relatively asymptomatic cyanosis is usually the first presenting symptom. • 25-50% - Headache, dyspnea, lightheadedness (even syncope), weakness, confusion, palpitations, chest pain • 50-70% - Abnormal cardiac rhythms; altered mental status, delirium, seizures, coma; profound acidosis •

> 70% - Usually, death Treatment: • Methylene blue : the first line treatment contraindicated in G6PD deficiency and ineffective with hemoglobin M. reduction of met-Hb by methylene blue is dependent upon NADPH generated by G6PD. methylene blue has an oxidant potential hemolysis in G6PD deficient. • Second line treatment: when methylene blue therapy is ineffective or contraindicated Exchange transfusion: for patients who do not respond to methylene blue or G6PD-deficient individuals who are severely symptomatic Hyperbaric oxygen treatment: another option • IV hydration and bicarbonate (for metabolic acidosis) Notes & Notes for MRCP
> By Dr. Yousif Abdallah Hamad

less common cytochrome b5 reductase is deficient in all cells, not just RBCs. associated with several other medical problems, including mental retardation, microcephaly, and other neurologic complications. Life expectancy is severely compromised, and patients usually die at a very young age.

Chapter 7

Haematology&Oncology

Cyanosis without hypoxia • Persistent cyanosis without hypoxia (a normal Pao2) suggests a diagnosis of methaemoglobinaemia or sulfhaemoglobinaemia. • In a cyanosed patient the amount of reduced haemoglobin in the blood is at least 5 g/dl • The blue colour of the skin and mucous membranes is due to hypoxia and not hypercapnia. Hypoxia should be corrected by oxygen

therapy • What is the possible cause of Desaturation on SaO2 (using an oximeter) in spite of normal PaO2? Methaemoglobinaemia accumulation of reversibly oxidised methaemoglobin causing reduced oxygen affinity of the Hb molecule with consequent cyanosis. It can occur due to: an inherited condition or as a consequence of drugs such as nitrites.

Heparin • can be given as either: unfractionated, intravenous heparin, or low molecular weight heparin (LMWH), given subcutaneously. • Heparins generally act by activating antithrombin III. • Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. • LMWH however only ↑ the action of antithrombin III on factor Xa The table below shows the differences between standard heparin and LMWH: Standard Heparin (LMWH) administration Intravenous Subcutaneous Action duration short long Mechanism of action Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, XIa and XIIa Side-effects Bleeding HIT Osteoporosis Monitoring Activated partial thromboplastin time (APTT) Notes Useful in situations where there is a↑ risk of bleeding as anticoagulation can be terminated rapidly Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Activates antithrombin III. Forms a complex that inhibits factor Xa Bleeding Lower risk of HIT and osteoporosis Anti-Factor Xa (although
routine monitoring is not required) Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Heparin-induced thrombocytopaenia (HIT) • Types

1. Type 1 HIT non-immune mediated reaction due to a direct effect of the drug on platelets. occur soon after the initial administration of heparin (within two days) self-limiting condition and the platelet count will normalise with continued heparin administration.
2. Type 2 HIT immune mediated condition mechanism: IgG antibodies against heparin bound to platelet factor 4 (PF4). Antibody-heparin-PF4 complex will be eliminated by the immune system (→ thrombocytopenia), and activates platelets → thrombosis It is a prothrombotic condition despite being associated with low platelets. typically arises 4 to 10 days after starting heparin therapy. Patients may develop both venous and arterial thromboses, low platelet counts and mild abnormalities of coagulation. The D-dimer level is raised due to widespread thrombus formation. • Features include a greater than 50% reduction in platelets, thrombosis and skin allergy • Patients with (HIT), particularly those with associated thrombosis, often have evidence of increased thrombin generation that can lead to consumption of protein C. If these patients are given warfarin without a concomitant parenteral anticoagulant to inhibit thrombin or thrombin generation, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis. To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor, or fondaparinux, until the platelet count

returns to normal levels. • Diagnosis: HIT is confirmed by: HIT antibody serotonin-release assay (SRA). • Treatment options include alternative anticoagulants such as lepirudin and danaparoid Argatroban is not cleared via the kidneys; therefore, this drug is safer than lepirudin/fondaparinux for HIT patients with renal insufficiency. Lepirudin is a direct thrombin inhibitor, which is cleared by kidneys exclusively, and is contraindicated in renal insufficiency. Fondaparinux can be used in HIT as it does not bind to platelets, but it is contraindicated in renal insufficiency. Heparin-induced hyperkalaemia • Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion. Heparin overdose • Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH. • The dose of protamine sulphate given is dependent upon the dose of LMWH administered and the time of administration. If protamine is given within eight hours of the LMWH then a maximum neutralising

dose is 1 mg protamine/100 units (or 1 mg) of LMWH given in the last dose. If more than eight hours have passed since the dose of LMWH was given, administer 0.5 mg protamine per 100 units (or 1 mg) of LMWH given. • Protamine is administered by slow IV infusion (over 10 minutes) to avoid a hypotensive reaction. • Protamine requires a high level of caution when being prescribed and administered. Heparin resistance • Heparin resistance is seen in up to 22% of patients undergoing cardiopulmonary bypass surgery. • Several mechanisms resulting in heparin resistance have been identified, including: antithrombin deficiency, increased heparin clearance, elevated heparin-binding proteins, and elevated factor VIII and fibrinogen levels. • For cardiopulmonary bypass in particular, rapid neutralisation of thrombin is required. In order for heparin to be successful in this, it requires antithrombin III which is an alpha2globulin. It is therefore thought that antitthrombin III deficiency is the underlying problem which is seen in patients resistant to heparin during cardiopulmonary bypass. • Heparin and thyroid function test Heparin is having an "in vitro" effect on thyroxine (T4) levels. IV heparin interferes with the thyroid function tests assay on occasions displacing bound thyroid hormone. Normal TSH + high T3 and T4 Heparin and delivery • Women who are anticoagulated with heparin until the onset of labor generally experience vaginal delivery with no greater blood loss than non-anticoagulated gravidas. • However, Cesarean delivery in heparinized patients is accompanied by a significantly greater blood loss than would otherwise be anticipated. • If preterm labor develops in a patient receiving heparin, only the mother is anticoagulated, and protamine sulfate can be used to reverse maternal heparinization. What is the best way to monitor rivaroxaban compliance? Prothrombin time (PT)

Novel oral anticoagulants (NOACs) The table below summaries the three NOACs: dabigatran, rivaroxaban and apixaban. Dabigatran Rivaroxaban Apixaban UK brand name Pradaxa Xarelto Eliquis Mechanism of action Direct thrombin inhibitor Direct factor Xa inhibitor Route Oral Oral Oral Excretion Majority renal Majority liver Majority faecal NICE indications Prevention of VTE following

hip/knee surgery Prevention of VTE following hip/knee surgery Treatment of DVT and PE Treatment of DVT and PE Prevention of stroke in nonvalvular AF* Prevention of stroke in nonvalvular AF* *NICE stipulate that certain other risk factors should be present. These are complicated and differ between the NOACs but generally require one of the following to be present: • prior stroke or transient ischaemic attack • age 75 years or older • hypertension • diabetes mellitus • heart failure Dabigatran Rivaroxaban Apixaban Mechanism of action Direct thrombin inhibitor Route Oral Oral Oral Excretion Majority renal Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Direct factor Xa inhibitor Prevention of VTE following hip/knee surgery Treatment of DVT and PE Prevention of stroke in non-valvular AF* Direct factor Xa inhibitor Direct factor Xa inhibitor Majority liver Majority faecal

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

Dabigatran Stop dabigatran two days before polypectomy • Mode of action: Dabigatran is a direct thrombin inhibitor with a rapid onset of action. • It is administered as a prodrug The prodrug dabigatran etexilate is rapidly converted by tissue esterases to dabigatran. • it is predominately (80%) excreted by the kidneys. • The anticoagulant effect starts within minutes of oral ingestion and peaks after 2-3 hours. • Advantage of dabigatran: due to its short half-life, a patient's coagulation status will normalize more rapidly than that of a patient treated with warfarin in almost all cases. No need for routine monitoring • Disadvantage of dabigatran Dabigatran is not recommended in patients with prosthetic heart valves because their safety and efficacy have not established. The rates of thromboembolism are higher for valves in the mitral compared with those in the aortic position. caged-ball valves are the most thrombogenic followed by tilting-disk and bi-leaflet valves. more thromboembolic events (e.g., valve thrombosis, stroke, TIA, and myocardial infarction) were observed with dabigatran than with warfarin; excessive major bleeding (predominantly postoperative pericardial effusions requiring intervention for hemodynamic compromise) was observed with dabigatran, compared with warfarin. • Monitoring of the anticoagulant effects of dabigatran In general, “routine” monitoring is not required in most cases. However, in some clinical situations a clinician may wish to determine the degree to which dabigatran is reducing the coagulant potential of the blood; e.g., if a patient taking dabigatran requires emergency surgery, has an intracranial or major systemic bleed, or is being considered for thrombolysis due to an ischemic stroke. The thrombin time (TT) and ecarin clotting time are considered the most accurate measures of dabigatran's anticoagulant effect. The aPTT and, if available, the thrombin time (TT) should be used to measure the anticoagulant effect of dabigatran, INR and PT tests are unreliable • Effect of dabigatran on procedural bleeding risk Dabigatran should be discontinued 1 to 2 days (creatinine clearance ≥ 50 mL/min) or 3 to 5 days (creatinine clearance <50 mL/min) before invasive or surgical procedures. Clinicians may want to consider “longer” periods of discontinuation for patients undergoing major surgery in which bleeding could have serious consequences (e.g.,

cardiac, neurosurgery, major abdominal or pelvic, spinal puncture, or placement of a spinal or epidural catheter or port). If surgery is urgent and cannot be delayed, there is an increased risk of bleeding; patients with a normal aPTT appear to have a low risk of serious bleeding. • conversion from warfarin to dabigatran (eg : patient had difficulty attending for regular INR) if a patient is taking warfarin with a therapeutic INR, it is recommended to : Stop warfarin, perform daily INR, start dabigatran when INR falls below 2.0 The anticoagulant effect of dabigatran starts minutes after its oral administration and peaks after 2-3 hours. • Contraindications Dabigatran is contraindicated if eGFR <30ml/min. Rivaroxaban, a direct inhibitor of activated factor X, is contraindicated if eGFR <15 and needs dose adjustment if eGFR 15–29 mL/minute. Ecarin clotting time is prolonged by direct thrombin inhibitors such as dabigatran. Treatment with aspirin, warfarin or heparins does not affect Ecarin clotting time. Idarucizumab reverses dabigatran

---

Warfarin Warfarin - clotting factors affected mnemonic - 1972 (10, 9, 7, 2) P450 inhibitors ↑ INR INR also ↑ by ABX that kill intestinal flora by ↓ Vit K absorption Warfarin action inhibition of vitamin K epoxide reductase • Warfarin is an oral anticoagulant which inhibits the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of clotting factor II, VII, IX and X (mnemonic = 1972) and protein C. (warfarin reduces protein C levels in the blood) • Warfarin inhibits epoxide reductase (specifically the VKORC1 subunit), thereby diminishing available vitamin K and vitamin K hydroquinone in the tissues which inhibits the carboxylation activity of the glutamyl carboxylase. • The half-life of warfarin is approximately 44 h Indications • venous thromboembolism: target INR = 2.5, if recurrent 3.5 • atrial fibrillation, target INR = 2.5

Haematology&Oncology • mechanical heart valves, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves. Side-effects • haemorrhage • teratogenic, although can be used in breast-feeding mothers the most common teratogenic effect is Nasal hypoplasia • skin necrosis: 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 • purple toes Contraindications • Warfarin is generally avoided in pregnancy. In the first trimester it is associated with an increased risk of miscarriage, and teratogenic side effects which include chondrodysplasia patellae, asplenia and diaphragmatic herniae. In the second and third trimester it is associated with retroplacental and intracerebral foetal haemorrhage, as well as foetal microcephaly, optic atrophy and developmental delay. Monitoring • Patients on warfarin are monitored using the INR (international normalised ration), the ratio of the prothrombin time for the patient over the normal prothrombin time. • Warfarin has a long half-life and achieving a stable INR may take several days. Factors that may potentiate warfarin • liver disease • P450 enzyme inhibitors, e.g.: amiodarone, Clarithromycin, ciprofloxacin Clarithromycin increase INR more than ciprofloxacin

 Clarithromycin is metabolised by CYP3A4 and is an inhibitor, meaning that it does affect INR to a limited extent, leading to an increase. Ciprofloxacin is a moderate inhibitor of CYP1A2; some effect is expected on INR, but not as great as that for clarithromycin. • cranberry juice • drugs which displace warfarin from plasma albumin, e.g. NSAIDs • inhibit platelet function: NSAIDs Interaction • Lipid-lowering agents Simvastatin, rosuvastatin and fibrate potentiate the anticoagulant effects of warfarin Atorvastatinand pravastatinare least likely to interfere with warfarin Cholestyramine (a cholesterol-binding resin) is known to reduce the anticoagulant action of warfarin Cholestyramine reduces absorption of a number of drugs including warfarin. • cranberry juice (↑↑warfarin effect ↑↑ INR).The cause is thought to be bioflavonoids contained in the cranberry juice, which block cytochrome-P450-related warfarin metabolism (CYP2C9) • Paracetamol given in repeated doses may lead to an enhanced response to warfarin and therefore an increased INR • Commonly used drugs that may lead to an increased INR include cephalosporins, azathioprine, cimetidine, metronidazole and testosterone derivatives • Diazepam is a p450 enzyme inducer and is therefore likely to reduce INR

• the concurrent use of clopidogrel with warfarin increases the bleeding risk. • Co-enzyme Q10 is similar to vitamin K and reduces warfarin's anticoagulant effect (warfarin exerts its anticoagulant effect though inhibition of the synthesis of vitamin K dependent clotting factors). Warfarin: management of high INR A 2005 update of the BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP in major bleeding. Situation Management Major bleeding Stop warfarin Give intravenous vitamin K 5mg Prothrombin complex concentrate - if not available then FFP INR > 8.0 Minor bleeding Stop warfarin Give intravenous vitamin K 1-3mg Repeat dose of vitamin K if INR still too high after 24 hours Restart warfarin when INR < 5.0 INR > 8.0 No bleeding Stop warfarin Give vitamin K 1-5mg by mouth, using the intravenous preparation orally Repeat dose of vitamin K if INR still too high after 24 hours Restart when INR < 5.0 INR 5.0-8.0 Minor bleeding Stop warfarin Give intravenous vitamin K 1-3mg Restart when INR < 5.0 INR 5.0-8.0 No bleeding Withhold 1 or 2 doses of warfarin Reduce subsequent maintenance dose *as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage Prothrombin concentrates are products of choice for warfarin reversal in the setting of active bleeding and a markedly raised INR. management of mother and neonate if preterm labor develops in a patient on warfarin • The management is difficult if preterm labor develops in a patient on warfarin, because both the mother and the fetus are anticoagulated. • the best management to prevent fetal/neonatal hemorrhage Give fresh frozen plasma to the neonate immediately after delivery • Vitamin K administration does not achieve immediate reversal of maternal anticoagulation (which may persist for 24 hours); more rapid reversal requires the transfusion of fresh frozen plasma. • Fetal levels of coagulation factors do not correlate with maternal levels, and infusion of fresh frozen plasma into the mother does not reliably reverse fetal anticoagulation. • A cesarean delivery may prevent hemorrhagic fetal death, and fresh frozen plasma should be administered to the neonate.

Haematology&Oncology Porphyrias Overview Acute intermittent porphyria (AIP) AIP can present with features of an acute abdomen, hypertension, psychiatric disturbance and hyponatraemia, Aetiology • autosomal dominant • caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Epidemiology • The most common acute porphyria is acute intermittent porphyria. • 20-40-year olds more likely to be affected (only rarely presents before puberty) • AIP is more common in females (5:1) Features • 90% of affected individuals remain asymptomatic throughout their lives. • typically present with abdominal symptoms, • neuropsychiatric symptoms Seizures occur in 10-20% of patients with acute intermittent porphyria (AIP). A range of psychiatric symptoms, including hypomania and delirium may be seen. • hypertension and tachycardia • urine turns deep red on standing • Photosensitivity is unusual in AIP Investigations • Patients excrete urinary porphobilinogen (PBG) between and during acute attacks. • Faecal porphyrin excretion is usually normal or slightly increased. • All attacks of porphyria increase the activity of hepatic 5-aminolevulinate (ALA) synthase. • Lab features hyponatraemia, mild leukocytosis. Diagnosis • Urinary porphobilinogen assay is the optimal way to establish the diagnosis. The best initial test • diagnosis is confirmed by measuring erythrocyte porphobilinogen deaminase activity. Factors precipitate an acute attack: • Stress, • Infection • Pregnancy • Menstruation • starvation • Drugs sulphonamides, barbiturates phenytoin. Most anti-epileptics should not be given, but gabapentin is safe and the most appropriate choice for seizures occur in (AIP). ACE inhibitors and calcium channel blockers Ibuprofen is safe for use in acute intermittent porphyria, but diclofenac should be avoided.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology Acute intermittent porphyria: drugs Drugs which may precipitate attack Safe Drugs • Alcohol • Barbiturates • Benzodiazepines • Tricyclic antidepressants • Halothane • Oral contraceptive pill • Sulphonamides • Cephalosporins • Erythromycin • Isoniazid • flucloxacillin • Anabolic steroids

• Sulphonylureas • Theophylline • Antihistamines • MAOIs • Amiodarone • Simvastatin. • Diuretics • calcium channel blockers • ACE inhibitors

• Paracetamol • Aspirin • Ibuprofen
• Codeine • Morphine • Chlorpromazine • β-blockers • Gabapentin • Penicillin • Metformin • amoxicillin
Treatment of seizures in AIP Gabapentin Treatment: • decrease the activity of delta-aminolevulinic acid synthase (ALA) glucose (carbohydrate loading) high-glucose diets or infusions have been used for mild attacks of pain without neurological symptoms intravenous haem arginate thereby decreasing heme precursor synthesis. The treatment of choice opiate analgesia. Distinguishing between lead poisoning and acute intermittent porphyria • Which one of the following features in an adult patient presenting with porphyrinuria would most suggest

lead poisoning rather than acute intermittent porphyria as a cause? Anaemia Anaemia occurs only in lead poisoning and is due to: inhibition of ferrochelatase (the activity of this enzyme is normal in acute intermittent porphyria) a decrease in red cell lifespan enzyme inhibition (pyrimidine 5'-nucleotidase) leading to the accumulation of pyrimidine nucleotides in red cells, which in turn reduces the stability of the cell membrane (and is seen on a blood film as basophilic stippling)

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Porphyria cutanea tarda (PCT) • most common hepatic porphyria mechanism • defect in uro-porphyrinogen decarboxylase Aetiology • inherited most cases are sporadic may be inherited (autosomal dominant), • acquired may be caused by hepatocyte damage e.g. alcohol, (the commonest cause), oestrogens (oral contraceptive pill) excess iron (haemochromatosis) hepatitis C Features • The most common presenting sign of PCT is fragility of sun exposed skin after mechanical trauma, leading to erosions and bullae, worst on dorsal hands, forearms, and face. • classically photosensitive rash with bullae, Bullae develop on sun-exposed areas When exposed to light, uroporphyrinogen generates free radicals that cause blistering of the skin. lesions heal slowly, leaving scars. • skin fragility on face and dorsal aspect of hands Investigations • plasma total porphyrins The best initial test Porphyrins are increased in liver, plasma, urine and stool. • Urine: elevated uroporphyrinogen (Urinary porphyrins) and pink fluorescence of urine under Wood's lamp • Porphobilinogen (PBG) is normal. • Assay of red blood cells for uroporphyrinogen decarboxylase (UROD) activity is now available • Antinuclear antibodies are frequently seen Management • withdrawal of the precipitant • phlebotomy to deplete the excess iron stores that exacerbate the porphyria. Venesection is effective (450 ml/week) until haemoglobin is 120 g/L. • Chloroquine may also be effective because it promotes porphyrin excretion. Variegate porphyria • autosomal dominant • defect in protoporphyrinogen oxidase • photosensitive blistering rash • abdominal and neurological symptoms • more common in South Africans

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

Hodgkin's lymphoma (HL) Overview • Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. • haematological malignancy arising from mature B cells. • Lymphadenopathy, typically painless and most commonly involving the cervical and/or supraclavicular nodal chain, is the most common presenting symptom of HL. Epidemiology • It has a bimodal age distributions being most common in the third and seventh decades Risk factors • history of EBV infection • family history of Hodgkin's lymphoma • young adults from higher socio-economic class • Immunodeficiency: e.g., organ or cell transplantation, immunosuppressants, HIV infection , chemotherapy • Autoimmune diseases (e.g., rheumatoid arthritis, sarcoidosis) Features • Painless lymphadenopathy Most common is cervical lymph nodes (in ~60–70% of patients) • Mediastinal mass → chest pain, dry cough, and shortness of breath • Splenomegaly or hepatomegaly may occur if the spleen or liver

are involved. • B symptoms Night sweats, weight loss > 10% in the past 6 months, fever > 38°C (100.4°F) • Can occur in a variety of diseases, such as non-Hodgkin lymphoma, other malignancies, tuberculosis, and various inflammatory diseases • Pel-Ebstein fever Intermittent fever with periods of high temperature for 1–2 weeks, followed by afebrile periods for 1–2 weeks. Relatively rare but very specific for HL. • Alcohol-induced pain • Pruritus (focal or generalized)

Histological classification Type Frequency Prognosis Notes Nodular sclerosing Most common (around 70%) Good prognosis Mixed cellularity Around 20% Good prognosis Lymphocyte predominant Around 5% Best prognosis Lymphocyte depleted Rare Worst prognosis Poor prognosis • weight loss > 10% in last 6 months • fever > 38 C • night sweats • Other factors associated with a poor prognosis identified in a 1998 NEJM paper included: age > 45 years stage IV disease haemoglobin < 10.5 g/dl lymphocyte count < 600/l or < 8% male albumin < 40 g/l white blood count > 15,000/l A mass of >10 cm in size Fatigue, pruritus, EBV infection although they are common, BUT they have no prognostic significance. Staging Ann-Arbor staging of Hodgkin's lymphoma • I: single lymph node • II: 2 or more lymph nodes/regions on same side of diaphragm • III: nodes on both sides of diaphragm Spleen is regarded as a Lymph Node region, So lymphoma with splenomegaly Stage III • IV: spread beyond lymph nodes Each stage may be subdivided into A or B • A = no systemic symptoms other than pruritus • B = weight loss > 10% in last 6 months, fever > 38c, night sweats (poor prognosis) Diagnosis • Lymph node biopsy would be more likely to be positive, RSC is evident on microscopy. • Bone marrow Hodgkin results in patchy bone marrow infiltration, an isolated bone marrow biopsy may yield non-specific results. Bone marrow biopsy is more useful for staging of advanced disease Management: • Early stage (IA or IIA): Radiotherapy and chemotherapy. Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

More common in women. Associated with lacunar cells Associated with a large number of ReedSternberg cells

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

 Secondary malignancy is the long-term complication of the radiotherapy (need long term monitoring) • Later stage (III, IVA or IVB): Chemotherapy alone. • Large mass in chest regardless of stage: Radiotherapy and chemotherapy. • Chemotherapy includes ABVD: Adriamycin (also known as Doxorubicin), Bleomycin, Vincristine, Doxorubicin, cyclophosphamide, prednisolone, Rituximab & others Bleomycin related pulmonary fibrosis is a major toxicity of the ABVD regimen A high-resolution CT scan and pulmonary function tests are required to diagnose this condition. Oxygen therapy should be used with caution in these patients as there is concern about further lung damage secondary to oxygen free radicals. Although doxorubicin (also known as adriamycin) can cause cardiotoxicity, this is unusual at the doses used in this regimen and one would expect abnormalities on the ECG. • Relapsed Hodgkin lymphoma salvage chemotherapy followed by BEAM conditioned autologous stem cell transplantation as the established gold standard. . Prognosis is good overall, but it depends on classification and staging. Hodgkin's lymphoma (HL) Non-Hodgkin's lymphoma (NHL) Younger age Older age more often restricted to lymph nodes in the

neck. Peripheral lymphadenopathy is common Reed-Sternberg cells are present. Reed-Sternberg cells are NOT present. Extra-nodal involvement un common Extra-nodal involvement is common

---

Non-Hodgkin's lymphoma (NHL) (NICE guideline 2016) • include any kind of lymphoma except Hodgkin’s lymphomas. • Most of NHL are of B cell phenotype, although T cell tumours are increasingly being recognized. • subtypes of non-Hodgkin's lymphoma (NHL): diffuse large B-cell lymphoma Burkitt lymphoma. Diagnosis • Type of biopsy: first line excision biopsy if not surgically feasible needle core biopsy procedure • in patient with histologically high-grade B-cell lymphoma: use FISH (fluorescence in situ hybridisation) to identify a MYC rearrangement If a MYC rearrangement is found, use FISH to identify the immunoglobulin partner and the presence of BCL2 and BCL6 rearrangements. • Indications of using FDG-PET-CT imaging (fluorodeoxyglucose-positron emission tomography-CT) Staging to assess response at completion of planned treatment for: diffuse large B- cell lymphoma Burkitt lymphoma. to assess response to treatment before autologous stem cell transplantation for high-grade (NHL).

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Management • follicular lymphoma Asymptomatic patients with low grade lymphoma such as follicular lymphoma (grade 1 and 2) can be observed closely (Wait and watch approach) The value of intensive chemotherapy is questionable in asymptomatic patients. No long-term survival benefit has been demonstrated with this approach. stage IIA local radiotherapy as first-line stage IIA + asymptomatic + single radiotherapy volume is not suitable 'watch and wait' (observation without therapy) stage IIA + symptomatic + single radiotherapy volume is not suitable treat as advanced-stage (stages III and IV) symptomatic advanced-stage (stages III and IV) asymptomatic rituximab advanced-stage (stages III and IV) symptomatic rituximab + combination with: cyclophosphamide, vincristine and prednisolone (CVP) cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) mitoxantrone, chlorambucil and prednisolone (MCP) cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon- α (CHVPi) or chlorambucil Relapsed or refractory advanced-stage (stages III and IV) : induction of remission Rituximab + combination with chemotherapy maintenance therapy Rituximab monotherapy in second or subsequent remission stem cell transplantation • MALT lymphoma H. pylori-positive gastric MALT lymphoma Helicobacter pylori eradication therapy H. pylori-negative gastric MALT lymphoma Helicobacter pylori eradication therapy gastric MALT lymphoma that responds clinically and endoscopically to H. pylori eradication therapy but who have residual disease shown by surveillance biopsies of the stomach, + no high-risk features. 'watch and wait' (observation without therapy) residual MALT lymphoma after H. pylori eradication therapy + high risk of progression [H. pylori- negative at initial presentation or t(11:18) translocation], chemotherapy (for example, chlorambucil or CVP) + rituximab OR gastric radiotherapy. Non-gastric MALT lymphoma localised disease sites radiotherapy if radiotherapy is not suitable or disseminated disease chemotherapy (for example, chlorambucil or CVP) + rituximab localised + asymptomatic + radiotherapy is not suitable 'watch and wait' (observation without therapy) • Mantle cell lymphoma advanced-stage , symptomatic chemotherapy + rituximab localised stage I or II radiotherapy non-progressive + asymptomatic + radiotherapy is not suitable 'watch and wait' (observation without therapy) chemosensitive mantle cell lymphoma

 autologous stem cell transplantation previously untreated + stem cell transplantation is unsuitable Bortezomib

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

Haematological malignancies: genetics Below is a brief summary of the common translocations associated with haematological malignancies t(9;22) - Philadelphia chromosome • present in > 95% of patients with CML • this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22 • the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal • poor prognostic indicator in ALL t(15;17) • seen in acute promyelocytic leukaemia (M3) • fusion of PML and RAR-alpha genes t(1:14) • This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates BCL10 t(8;14) • seen in Burkitt's lymphoma • MYC oncogene is translocated to an immunoglobulin gene t(11;14) • Mantle cell lymphoma • deregulation of the cyclin D1 (BCL-1) gene t(11; 18) • This translocation is associated with MALT (mucosa-associated lymphoid tissue) lymphoma and deregulates MALT1 t(14;18) • This translocation is associated with follicular lymphoma • results in a chimeric heavy-chain Ig (chromosome 14) and BCL2 (chromosome 18) gene. • This disease presents with painless “waxing and waning” lymphadenopathy in additional to constitutional symptoms.

Haematological malignancies: infections Viruses • EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma • HTLV-1: Adult T-cell leukaemia/lymphoma • HIV-1: High-grade B-cell lymphoma Bacteria • Helicobacter pylori: gastric lymphoma (MALT) Protozoa • malaria: Burkitt's lymphoma

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Burkitt's lymphoma • Burkitt's lymphoma is a monoclonal proliferation of B lymphocytes, which results (in approximately 90% of the cases) from chromosome translocations that involve the Myc gene. chromosome translocation means that a chromosome is broken, which allows it to associate with parts of other chromosomes. • It is a high-grade B-cell neoplasm. • There are two major forms:

1. endemic (African) form: typically involves maxilla or mandible
2. sporadic form: abdominal (e.g. ileo-caecal) tumours are the most common form. More common in patients with HIV • Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The classic chromosome translocation in Burkitt's lymphoma involves chromosome 8, the site of the MYC gene. • The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form. Microscopy findings • 'starry sky' appearance:

lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells Management • Management is with chemotherapy. This tends to produce a rapid response which may cause 'tumour lysis syndrome'. Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin*) is often given before the chemotherapy to reduce the risk of this occurring. *allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective Complications of tumour lysis syndrome include: Hyperkalaemia Hyperphosphataemia Hypocalcaemia Hyperuricaemia acute renal failure Prognosis • Localised Burkitt's is associated with around a 90% survival rate, • although the prognosis is less good in adults.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

Cancer in the UK The most common causes of cancer in the UK are as follows* •

1. Breast •
2. Lung •
3. Colorectal •
4. Prostate •
5. Bladder •
6. Non-Hodgkin's lymphoma •
7. Melanoma •
8. Stomach •
9. Oesophagus •
10. Pancreas The most common causes of death from cancer in the UK are as follows: •
11. Lung •
12. Colorectal •
13. Breast •
14. Prostate •
15. Pancreas •
16. Oesophagus •
17. Stomach •
18. Bladder •
19. Non-Hodgkin's lymphoma •
20. Ovarian • Cancer is the cause of 26% of deaths in the UK, and is a more common cause of death than cardiovascular disease. • Lung cancer is the biggest cancer killer in the UK (in both male and female), although breast cancer has the highest incidence *excludes non-melanoma skin cancer

---

Acute lymphoblastic leukaemia (ALL) Epidemiology • ALL is a disease of children. • Most common malignant disease in children • Peak incidence: 2–5 years Classification (The WHO classification) • B-cell ALL (around 80–85% of cases) • T-cell ALL (around 15–20% of cases) Risk factors • Children

with certain genetic and immunodeficiency syndromes are at increased risk. These include: Down syndrome, Neurofibromatosis type 1, Bloom syndrome, and ataxia telangiectasia. Features • The most common presenting symptoms of ALL are nonspecific: fever, infection, bleeding, bone pain, or painless lymphadenopathy. Fever and lymphadenopathy are rare in AML, but can be common first signs in ALL • Testicular enlargement (rare finding) • Airway obstruction (stridor, difficulty breathing) caused by mediastinal infiltration • Meningeal leukemia (or leukemic meningitis) → headache, neck stiffness Diagnosis • Bone marrow aspirate or biopsy: confirmatory diagnostic tests AML: > 20% myeloblasts in the bone marrow ALL: > 25% lymphoblasts in the bone marrow

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Prognostic features Good prognostic factors Poor prognostic factors • French-American-British (FAB) L1 type • common ALL • pre-B phenotype • low initial WBC • del(9p) • t(12;21) • FAB L3 type • T or B cell surface markers • Philadelphia translocation, t(9;22) • t(8:14) the worst prognosis • age < 2 years or > 10 years • male sex • CNS involvement • high initial WBC (e.g. > 100 * 109/l) • non-Caucasian • The 8:14 chromosomal translocation is associated with a particularly poor prognosis, and is found in approximately 1% of adults with ALL. The incidence of CNS involvement is very high at the point of diagnosis, and median event free survival after chemotherapy is only two months. Treatment • Before ALL treatment with chemotherapy, if blast cells count is very high (˃ 100 * 109/l) the patient needs Leukapheresis to prevent sludge in of capillary beds, this can be lifesaving. • Philadelphia positive ALL: Chemotherapy + rituximab + Tyrosine Kinase Inhibitor high dose chemotherapy (usually UKALL 14 or hyper-CVAD), together with the anti-CD20 monoclonal antibody rituximab and a tyrosine kinase inhibitor in view of the BCR-ABL positivity. • Central nervous system (CNS) therapy (intrathecal) is indicated in all patients with ALL • Lumber puncture (LP) should be delayed until chemotherapy has begun • Allogeneic stem cell transplantation

---

Chronic lymphocytic leukaemia (CLL) Overview • (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are almost always B-cells (99%) Prevalence • CLL is the most common form of leukemia found in adults in Western countries. • generally, affects older populations (The median age at diagnosis is 72 years) Features • often none CLL + anaemia with positive Coombs test autoimmune haemolytic anaemia (AHA) Prednisolone is the initial intervention of choice. rituximab is the second-line step.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

• constitutional: anorexia, weight loss • bleeding, infections • lymphadenopathy more marked than CML Complications • hypogammaglobulinaemia leading to recurrent infections Infections are the most frequent complication causing death in patients with CLL. Although intravenous immunoglobulin prevents recurrent infections it does not prolong survival. • Autoimmune complications are common with CLL: warm autoimmune haemolytic anaemia in 10-15% of

patients the combination of spherocytes with a raised bilirubin, LDH and positive direct Coombs' test is consistent with an autoimmune haemolysis. immune thrombocytopenia (ITP) the next step in management Chemotherapy and intravenous immunoglobulin In ITP, platelets would only be indicated for life threatening bleeding (or platelet count <10 ×109/L) • transformation to high-grade lymphoma (Richter's transformation) Investigations • Blood film: smudge cells (also known as smear cells) smudge cells are the artifacts produced by the lymphocytes damaged during the slide preparation. ≥5000 monoclonal B lymphocytes/µl. The clonality of the circulating B lymphocytes needs to be confirmed by flow cytometry. • Immuno-phenotyping: Peripheral blood flow cytometry is the most valuable test to confirm a diagnosis of CLL. will demonstrate the cells to be B-cells CD5, CD19 and CD23 are characteristically positive. • Although a bone marrow biopsy is not required for diagnosis, it is recommended for the diagnostic evaluation of unclear cytopaenias, or FISH or molecular genetics if peripheral blood cell lymphocytosis does not allow adequate immunophenotyping • An extended FISH analysis is recommended before the start of therapy because the detection of additional cytogenetic abnormalities [del(11q) or trisomy 12] may have therapeutic consequences Peripheral blood film showing smudge B cells

Management • observation policy is usual during the early stages of the disease. • Indications for treatment progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia Bone marrow compromise (stage C disease). Lymphocyte doubling time of less than 12 months massive (>10 cm) or progressive lymphadenopathy massive (>6 cm) or progressive splenomegaly progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months Immune complications, for example, ITP, autoimmune haemolysis systemic symptoms: (Disabling B symptoms) weight loss > 10% in previous 6 months, fever >38 C for > 2 weeks, extreme fatigue, night sweats • Drugs fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients monitoring by regular blood counts What antimicrobial prophylaxis should he receive before starting chemotherapy with fludarabine? Co-trimoxazole Fludarabine is a purine analogue that is phosphorylated intracellularly. All of the purine analogues cause myelosuppression, but there is a significantly higher risk of patients developing Pneumocystis jirovecii pneumonia while on treatment. Use of prophylactic co-trimoxazole (Septrin) has dramatically reduced the frequency of this severe opportunistic infection in these patients. Co-trimoxazole should be continued after chemotherapy until the CD4 counts exceeds 200 cells/mm3 (0.2 ×109/L). • Regular infusions of immunoglobulin to prevent infections Recurrent infections are recognised in CLL due to hypogammaglobulinaemia and immune paresis; but are not an indication for disease control. CLL prognostic factors Poor prognostic factors (median survival 3-5 years) • male sex • age > 70 years • lymphocyte count > 50 • prolymphocytes comprising more than 10% of blood lymphocytes • lymphocyte doubling time < 12 months • raised LDH • CD38 expression positive • deletions of part of the short arm of chromosome 17 (del 17p) Chromosomal changes • deletion of the long arm of chromosome 13 (del 13q) is the most common abnormality, being seen in around 50% of patients. It is associated with a good prognosis • deletions of part of the short arm of chromosome 17 (del 17p) are seen in around 5-10% of patients and are associated with a poor prognosis

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 7

Haematology&Oncology

Differential diagnosis • mantle cell lymphoma (MCL) These tumour cells express B-cell surface antigens and also expresses CD5, but usually not CD23. For cases that express CD23, staining for cyclin D1 or SOX11 and fluorescence in situ hybridisation (FISH) for detecting a translocation (11;14) are useful for establishing the diagnosis of MCL. • small lymphocytic lymphoma (SLL) In the WHO classification, small lymphocytic lymphoma (SLL) and CLL are considered to be a single entity. CLL is effectively the same disease as SLL except the disease is found mostly in the bone marrow or blood. SLL is found mostly in lymph nodes The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a number of B lymphocytes in the peripheral blood not exceeding 5 × 109/l. SLL cells show the same immunophenotype as CLL. The diagnosis of SLL should be confirmed by histopathological evaluation of a lymph node biopsy, whenever possible. • monoclonal B-lymphocytosis' (MBL) In absence of lymphadenopathy, organomegaly, cytopaenia and clinical symptoms, the presence of fewer than 5000 monoclonal B lymphocytes/µl defines 'monoclonal B-lymphocytosis' (MBL) can be detected in 5% of subjects with normal blood count. Progression to CLL occurs in 1%–2% of MBL cases per year.

Acute myeloid leukaemia (AML) • AML is the most common form of acute leukaemia in adults. • It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder. • Acute leukemia is defined as an accumulation of more than 20 percent of immature blasts at the bone marrow. Chronic myeloid leukaemia often ends in acute blastic transformation after a mean duration of approximately four years. • classically associated with Down syndrome. • Alkylating agents is a chemotherapy drug class that increases the risk of developing AML. • characterized by cells with positive cytoplasmic staining for myeloperoxidase. • The median age of onset of AML is 65 years. Presentation • Vague and non-specific (flu-like symptoms)
• Due to pancytopenia (Infection, anaemia , bleeding) • Splenomegaly may occur but typically mild and asymptomatic. • LN swelling is rare.

Revision #1
Created 2026-01-06 17:52:19 UTC by Omar Ayman
Updated 2026-01-06 17:52:19 UTC by Omar Ayman