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# Chapter 7

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

Haematology&Oncology Types • Sickle cell trait: heterozygous (HbAS)  occurs when a child inherits a sickle gene from one parent and a normal gene from the other parent. • Sickle cell disease: homozygous (HbSS)  occurs when a child inherits a sickle gene from each parent. • Other, rarer forms of sickle cell disease in which the person has only one copy of the mutation that causes Hb S and one copy of another abnormal Hb allele. Examples:  “HbSC”: (sickle –haemoglobin C disease).  “HbS/β+”: (sickle-beta-plus-thalassemia).  “HbS/β0” : (sickle-beta-zero-thalassemia) Sickling of the erythrocyte • A low partial pressure of oxygen (PO2) causes HbS to polymerise and precipitate resulting in sickling of the erythrocyte.  HbSS patients sickle at PO2 of 5-6 kPa  HbAS patients sickle at PO2 of 2.5-4 kPa.  HbSC Sickling occurs at around 4 kPa. Sickle cell disease and malaria • Sickle cell trait (HbAS) is known to protect against falciparum malaria. As a result, the frequencies of sickle cell carriers are high in malaria-endemic areas. • Patients with HbSS are at higher risk of severe malaria with complications and have a higher mortality rate. Feature • Black pigment gallstones occur in 50 % of patients with sickle cell disease  due to an increase in bilirubin excretion.  Their small size allows migration into the common bile duct causing low-grade obstruction.  Typically leading to hyperbilirubinaemia rather than bile duct dilatation.  cholecystectomy is suggested for patients with sickle cell disease if abdominal surgery is being performed for other reasons.  Due to decreased life span of the erythrocyte, average 17 days (normal 120 days), there is also a chronic circulating unconjugated hyperbilirubinaemia. • There is often an inability to concentrate urine  The inner medulla is hypoxic, hypertonic and acidotic and therefore predisposes to sickling of red blood cells, which results in vasoocclusion and reduction in renal medullary blood flow.  proximal tubule dysfunction  impairs urinary concentration  distal tubular dysfunction  impairs potassium excretion. • Functional hyposplenism in SCD also renders sufferers susceptible to infection with encapsulated bacteria (pneumococci, meningococci).  Patients with sickle cell disease have a predisposition to develop osteomyelitis due to Salmonella species.

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Sickle-cell crises: Four main types of crises are recognised: • thrombotic crises, also known as painful crises or vaso-occlusive crises  precipitated by infection, dehydration, deoxygenation ,acidosis , cold temperatures, extreme exercise and stress.  infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen

and brain • sequestration crises  sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia  acute chest syndrome: dyspnoea, chest pain, pulmonary infiltrates, low pO2 - the most common cause of death after childhood  stroke  5-10% of sickle cell patients will suffer a stroke, usually during childhood.  The risk can be predicted by transcranial Doppler measurement of middle cerebral artery (MCA) flow rate,  prompt institution of a prophylactic transfusion program to reduce the HbS % can prevent further strokes.  treatment once occurred  Exchange transfusion programme • aplastic crises  caused by infection with parvovirus  sudden fall in haemoglobin without an appropriate ↑reticulocytosis.  The condition is self-limited, with bone marrow recovery occurring in 7-10 days, followed by brisk reticulocytosis. • haemolytic crises  rare  The anaemia associated with sickle cell disease is usually only symptomatic below 70 g/L, as oxygen is released more readily from erythrocytes.  remember, patients with sickle cell tend to run with a Hb between 70-90 g/L normally  The anemia of SC is usually a chronic, reasonably well-compensated hemolytic anemia with an appropriate reticulocytosis. For example, the mean hemoglobin and hematocrit concentrations on average may be 79 g/L and 22.9% respectively, with a reticulocyte count of between 3-15%. Diagnosis of sickle cell disease requires the detection of HbS. • Sickledex test: addition of reagent to blood  turbidity confirming the presence of HbS, but it gives no information on other haemoglobins. • Haemoglobin electrophoresis is the only investigation that determines the nature of the haemoglobinopathy  predominance of HbS.  Absent HbA.  HbF 2-20% Treatment • General management  analgesia e.g. opiates  NSAIDs do not usually provide effective analgesia on their own in sickle cell painful crises.  rehydrate  oxygen



Haematology&Oncology  consider antibiotics if evidence of infection  blood transfusion  exchange transfusion: e.g. if neurological complications • Avoid  iron therapy: There is a tendency to iron overload and therefore iron therapy is not usually indicated.  Intra-articular steroids have been associated with a sickle cell crisis, the mechanism of which is not fully understood, but they should be avoided. • pharmaceutical interventions to prevent sickle cell crisis and other acute complications  Hydroxyurea  acts by inhibiting ribonucleotide reductase, which inhibits both purine and pyrimidine synthesis.  Action: ↑fetal haemoglobin (Hb F) which protects against sickling.  reduces the incidence of acute chest syndrome and the need for blood transfusion  The major side effect is severe myelosuppression.  Malaria chemoprophylaxis in endemic area • Acute chest syndrome  defines as 'an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray'.  management:  Oxygen therapy to maintain saturations > 95%  Intravenous fluids to ensure euvolaemia  Adequate pain relief  Incentive spirometry in all patients presenting with rib or chest pain  Antibiotics with cover for atypical organisms  Early consultation with the critical care team and haematology  Blood transfusion:  A senior haematologist will make a decision as to whether a simple or exchange transfusion is necessary.  guidelines suggest Hb target of 100-110g/L in either instance. • All adults who have hyposplenism, including patients with SCD, need:  Yearly influenza vaccine.  Pneumococcal C vaccine, (adults and children over 2 years) repeated every five years.  Haemophilus influenzae type b; if not already given as part of childhood immunisation.  Conjugated meningococcal C vaccine; if not already given as part of childhood immunisation.  Meningococcal ACWY vaccine; if travelling to areas with high risk of meningitis. • Patients with

sickle cell disease are prone to infections within encapsulated organisms because of their asplenic state.  These include:  Streptococcus pneumoniae,  Haemophilus influenzae and  Neisseria meningitidis.  To combat these infections, patients with homozygous sickle cell disease should be on lifelong penicillin and be vaccinated against these organisms. Salmonella osteomyelitis is seen in patients with sickle cell anaemia

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screening for sickle cell disease in a pregnant women: • She will first be screened for sickle cell carrier status. • If that test is positive, her partner will be screened, • If both are found to be carriers this is confirmed by genetic testing before offering chorionic villus sampling (CVS) (8-10 weeks) or amniocentesis (14-16 weeks). Priapism • Priapism is most often due to idiopathic thrombosis of the prostatic venous plexus. • Other causes include:  leukaemia,  sickle-cell anaemia and  carcinomatosis. • Priapism occurs fairly frequently which may lead to permanent impotence if it is not relieved.

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Sideroblastic anaemia Definition • Sideroblastic anaemia is a condition where red cells fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion. This leads to deposits of iron in the mitochondria that form a ring around the nucleus called a ring sideroblast. Causes: It may be congenital or acquired • Congenital cause: delta-aminolevulinate synthase-2 deficiency  The enzyme delta aminolevulinic acid (ALA) is essential in the biosynthesis of heme.  Delta ALA requires pyridoxine (vitamin B6) and copper as cofactors.  Hereditary sideroblastic anemia follows a X-linked genetic inheritance pattern. • Acquired causes  myelodysplasia (seen in older age groups)  alcohol  the most common reversible cause  lead  drugs: anti-TB medications, chloramphenicol.  Pyridoxine (vitamin B6) deficiency, caused by isoniazid and oral contraceptives, is a reversible cause of sideroblastic anemia. Investigations • hypochromic microcytic anaemia (more so in congenital) • Basophilic stippling:  visualization of ribosomes on the surface of red blood cells  can be seen on a peripheral blood smear of patients with sideroblastic anemia. • Ferritin levels are increased • bone marrow:  sideroblasts and increased iron stores  Sideroblasts are red cell precursors with iron-laden mitochondria and are detected via Prussian blue staining.  Ringed sideroblasts are pathognomonic for sideroblastic anemia. Management • supportive • treat any underlying cause

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Haematology&Oncology  removal of toxic agents such as zinc and lead, and drugs such as penicillamine and isoniazid. • pyridoxine may help • Deposition of iron in secondary haemochromatosis (haemosiderosis):  Oral iron chelators  First-line :  oral deferasirox  Second-line:  Deferiprone  side effect: bloody dyscrasias and liver dysfunction.  Liver function tests are imperative whilst the patient is being administered both deferiprone and deferasirox.  Desferrioxamine results in compliance issues due to the subcutaneous route and long infusion time.  Whereas phlebotomy is effective at decreasing iron overload, in a patient who is anaemic this is not a viable option. The figure illustrates sideroblasts, which are nucleated (immature)

erythrocytes with granules of iron in their cytoplasm.

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Haemolytic anaemias: by site The combination of anaemia and jaundice should always suggest haemolytic anaemia until proved otherwise • In intravascular haemolysis free haemoglobin is released which binds to haptoglobin.  The benefit of this process (Haptoglobin binds with free plasma hemoglobin):  permits degradative enzymes access to the hemoglobin,  preventing the loss of iron via the kidneys,  shielding the kidneys from damage by hemoglobin. • As haptoglobin becomes saturated haemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test). • Free haemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria Intravascular haemolysis Extravascular haemolysis • mismatched blood transfusion • G6PD deficiency* • red cell fragmentation: heart valves, TTP, DIC, HUS • paroxysmal nocturnal haemoglobinuria • cold autoimmune haemolytic anaemia • haemoglobinopathies: sickle cell, thalassaemia • hereditary spherocytosis • haemolytic disease of newborn • warm autoimmune haemolytic anaemia *strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as a intravascular cause Haemolytic anaemias: by cause Hereditary causes • can be subdivided into membrane, metabolism or haemoglobin defects  membrane: hereditary spherocytosis/elliptocytosis  metabolism: G6PD deficiency  haemoglobinopathies: sickle cell, thalassaemia Acquired causes • can be subdivided into immune and non-immune causes  Acquired: immune causes  autoimmune: warm/cold antibody type  alloimmune: transfusion reaction, haemolytic disease newborn  drug: methyldopa, penicillin  methyldopa  Anti-RBC antibodies  penicillin  reaction between penicillin-like drugs and their antibodies  Acquired: non-immune causes  microangiopathic haemolytic anaemia (MAHA): TTP/HUS, DIC, malignancy, pre-eclampsia  prosthetic cardiac valves  paroxysmal nocturnal haemoglobinuria  infections: malaria  Direct (non-immune) red cell toxicity may occur after lead exposure. laboratory tests • Hemoglobin: decreased • MCV: normocytic • Reticulocyte count and reticulocyte production index: increased • Unconjugated bilirubin: increased • LDH: increased (esp. in intravascular hemolysis) • Haptoglobin: reduced

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Microangiopathic anemia • The patient’s newly diagnosed heart murmur along with new anemia and schistocytes indicate aortic stenosis as the underlying cause. • Aortic stenosis  mechanical destruction of RBCs (as they travel through the narrowed aortic opening)  microangiopathic anemia • Schistocytes are fragmented RBCs. Also called helmet cells, they are pathognomic of microagiopathic hemolytic anemias. Zieve syndrome • triad of jaundice, hemolytic anemia, and hyperlipidemia. • Hepatic dysfunction is usually evident in all cases. • Hemolytic anemia is reversible. • Hyperlipidemia due to excess alcohol intake causes metabolic and osmotic abnormalities in (RBCs), making them very susceptible to hemolysis. • Peripheral blood smear reveals:  normocytic normochromic anemia  acanthocytes  Acanthocytes are also called spur cells.  They have multiple projections on their surface caused by hyperlipidemia. • Definitive

treatment  alcohol cessation. Zieve's syndrome should be suspected whenever there is anemia and elevation of unconjugated bilirubin in the setting of acute alcohol intake with no obvious sign of gastrointestinal bleeding.

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Autoimmune haemolytic anaemia (AIHA) • Autoimmune haemolytic anaemia (AIHA) may be divided in to 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis. • It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs. • AIHA is characterised by a positive direct antiglobulin test (Coombs' test) Warm AIHA • In warm AIHA the antibody (usually IgG) causes haemolysis best at body temperature and haemolysis tends to occur in extravascular sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy. • Causes of warm AIHA  autoimmune disease: e.g. systemic lupus erythematosus*  SLE can rarely be associated with a mixed-type AIHA  neoplasia: e.g. lymphoma, CLL  drugs: e.g. methyldopa, Penicillins, Cephalosporins, levodopa, NSAIDs and Quinidine  treated by  stopping the drug ± short course of oral prednisolone. • The bone marrow respond by increasing RBCs production, which will be evident in peripheral blood by increase in the reticulocytes, immature RBCs, which will have high MCV.
• Management options include steroids, immunosuppression and splenectomy.

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• Blood transfusion can be life-saving until immunosuppression can take effect. • All patients with active haemolysis are at risk of acquiring folate deficiency due to increased metabolic demands and all should receive folic acid replacement therapy. Cold AIHA • The antibody in cold AIHA is usually IgM and causes haemolysis best at 4 deg C. • Haemolysis is mediated by complement and is more commonly intravascular. • Causes of cold AIHA  neoplasia: e.g. lymphoma  infections: e.g. mycoplasma, EBV  Secondary cold agglutinin disease typically presents with anaemia and haemoglobinuria due to intravascular haemolysis two to three weeks following infection such as with:  Mycoplasma pneumoniae  Viruses (EBV, CMV, etc)  Legionnaires' disease  Malaria  The best diagnostic test  Cold agglutinin titre  Cold agglutinins occur normally but at very low titres. • Features may include symptoms of Raynaud's and acrocyanosis • Patients respond less well to steroids Warm AIHA Cold AIHA Definition haemolysis best at body temperature haemolysis best at 4 deg C Antibody IgG IgM Site of haemolysis extravascular (e.g :spleen) intravascular Causes • autoimmune disease: e.g. systemic lupus erythematosus • neoplasia: e.g. lymphoma, CLL • drugs: e.g. methyldopa • neoplasia: e.g. lymphoma • infections: e.g. mycoplasma, EBV Treatment steroids, immunosuppression and splenectomy. respond less well to steroids Paroxysmal cold haemoglobinuria (PCH) • a rare type of autoimmune haemolytic anaemia (AIHA) occurring primarily in children/adolescent. • The classic symptom is a sudden onset of haemoglobinuria following exposure to cold, even for a few minutes.
• Symptoms may occur minutes to hours following exposure to cold. • Haemoglobinuria is not always present because in some persons with PCH the autoantibody level is not high enough to cause intravascular haemolysis. • The direct agglutination test (DAT) (Coomb’s test) is usually negative.

Haematology&Oncology Cold agglutinin disease • caused by autoantibodies that react at temperatures < 37 °C, • typical causes are:  lymphoproliferative disorders,  infections such as mycoplasma or Epstein–Barr virus.  Around 50% of cases are idiopathic.  Non-Hodgkin's lymphoma is more typically associated with cold agglutinins than Hodgkin's. Hook effect • Also called or the prozone effect • In agglutination test, a person's serum (which contains antibodies) is added to a test tube, which contains a particular antigen. • If the antibodies agglutinate with the antigen to form immune complexes, then the test is interpreted as positive. • However, if too many antibodies are present that can bind to the antigen, then the antigenic sites are coated by antibodies, and few or no antibodies directed toward the pathogen are able to bind more than one antigenic particle. Since the antibodies do not bridge between antigens, no agglutination occurs. Because no agglutination occurs, the test is interpreted as negative. In this case, the result is a false negative. • The range of relatively high antibody concentrations within which no reaction occurs is called the prozone. • The effect can also occur because of antigen excess, when both the capture and detection antibodies become saturated by the high analyte concentration. In this case, no sandwich can be formed by the capturing antibody, the antigen and the detection antibody. In this case, free antigen is in competition with captured antigen for detection antibody binding. • Examples include: • high levels of syphilis antibodies in HIV patients or high levels of cryptococcal antigen leading to false negative tests in undiluted samples. • This phenomenon is also seen in serological tests for Brucellosis. • when the serum is diluted, the blocking antibody is as well and its concentration decreases enough for the proper precipitation reaction to occur.

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Hereditary spherocytosis Epidemiology • most common hereditary haemolytic anaemia in people of northern European descent Aetiology • autosomal dominant defect of red blood cell cytoskeleton • the most frequent cause is a mutation in the spectrin gene;  spectrin is a component of the red cell membrane. • The most common mutation in a Northern European population is a combined spectrin and ankyrin mutation, which is found in 40–65% of patients. • the normal biconcave disc shape is replaced by a sphere-shaped red blood cell • red blood cell survival reduced as destroyed by the spleen Pathophysiology • Genetic mutation → Defects in RBC membrane proteins (especially spectrin and/or ankyrin) responsible for tying the inner membrane skeleton with the outer lipid bilayer → Continuous loss of lipid bilayer components → Decreased surface area of RBCs in relation to volume → Sphere-shaped RBCs with decreased membrane stability → Inability to change form while going through narrowed vessels:



→ Entrapment within splenic vasculature → Splenomegaly → Destruction via splenic macrophages → Extravascular hemolysis Features Patient with hereditary spherocytosis + acute abdomen  think of: Biliary colic or rupture spleen. normocytic anaemia, gallstones and family history  hereditary spherocytosis • failure to thrive • Congenital skeletal abnormalities (eg, tower-shaped skull, polydactylism) occasionally occur. • Anemia and pallor • jaundice (↑unconjugated bilirubin) • gallstones (pigment stones)  common and may be the presenting symptom  (made of calcium

bilirubinate)  may lead to cholecystitis • Splenomegaly with left upper quadrant pain • aplastic crisis precipitated by parvovirus infection Complications • Aplastic crisis  can be triggered by parvovirus B19 infection. Investigations • Normocytic anemia (normal MCV) • increase in both RDW and MCHC ( the high MCHC, indicating hyperdense cells) • Findings of hemolytic anemia  ↑ Unconjugated bilirubin  ↑ LDH  ↓ Haptoglobin  Reticulocytosis • Direct antiglobulin (direct Coombs) test  to exclude autoimmune hemolytic anemia (positive Coombs test), since spherocytosis is seen in both clinical presentations  Direct Coombs' test is negative in Hereditary spherocytosis, as it is not an immune haemolysis • Eosin-5-maleimide binding test (EMA): test of choice, as results are readily available (within two hours) • Osmotic fragility test (Rupture of Spherocytes in mildly hypotonic solution),  unreliable and is no longer recommended in routine clinical practice.  this has now been replaced by the eosin-5-maleimide binding to red cells and then being detected by flow cytometry. • Osmotic gradient ektacytometry  used to differentiate hereditary spherocytosis from hereditary stomatocytosis, but is only available in specialised laboratories. • If the diagnosis is equivocal, the cryohaemolysis test and EMA binding can be used. • In atypical cases, gel electrophoresis analysis of erythrocyte membranes is the test of choice. • Blood smear  Characteristic spherocytes (absent central pallor)  Potentially anisocytosis • Ultrasound:  to evaluate gallbladder complications

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Haematology&Oncology Diagnosis

1. The first step in analysis of a spherocytic hemolytic anaemia is  direct antiglobulin test (to determine whether the process is hemolytic or not).
2. If negative  confirm HS with other tests.
3. The osmotic fragility test is unreliable and is no longer recommended in routine clinical practice.
4. Osmotic gradient ektacytometry is used to differentiate hereditary spherocytosis from hereditary stomatocytosis Management • supportive for most patients: folate replacement • splenectomy  best avoided until at least 6 years of age to reduce the risk of post-splenectomy sepsis.  It is important to rule out stomatocytosis where splenectomy is contraindicated because of the thrombotic risk.

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Hereditary elliptocytosis (HE) • autosomal dominant condition. • Elliptocytosis is usually caused by spectrin and spectrin-protein 4.1 defects. • Horizontal membrane protein defects (for example, spectrin ankyrin interaction defect) results in HE whereas vertical defects result in hereditary spherocytosis. • Features  Clinical manifestations range from an asymptomatic carriage to severe haemolytic anaemia.  Most patients with HE or its variants lead healthy lives.  The degree of haemolysis does not correlate with the percentage of elliptocytes seen in the blood.  presence of cigar-shaped elliptocytes on the peripheral blood smear (The hallmark of HE)  Elliptocytes are normochromic and normocytic and range from few to 100% of erythrocytes. • Complication  Aplastic crisis • Treatment  Heterozygotes are asymptomatic but show elliptocytes on blood film; they do not have haemolysis and do not require any particular treatment  The treatment for symptomatic hereditary elliptocytosis is splenectomy. Hereditary elliptocytosis

Glucose-6-phosphate dehydrogenase (G6PD) deficiency Basics • (G6PD) plays a vital role in the hexose monophosphate pathway • It is involved in the oxidation of glucose 6-phosphate to 6-phosphoglycerate.This oxidation reaction is needed in RBCs as it provides the only source of NADPH • NADPH  maintains the level of glutathione  protect the RBCs against oxidative damage from compounds like hydrogen peroxide Prevalence • G6PD deficiency is the commonest red blood cell enzyme defect. • It is more common in people from the Mediterranean, Africa and Chinese Aetiology • inherited in a X-linked recessive fashion. • Homozygotes and heterozygotes can be symptomatic, although the disease typically is more severe in persons who are homozygous for the deficiency. Factors which Precipitates crisis: • infections (the most common cause) • drugs • broad (fava) beans  Favism is most common in persons with G6PD class II variants, but rarely it can occur in patients with the G6PD A–variant (Class III  African descent). • henna Pathophysiology • ↓ G6PD → ↓ glutathione → increased red cell susceptibility to oxidative stress • The haemolytic anaemia is non-immune (direct antiglobulin test [DAT] negative). Features • usually asymptomatic • neonatal jaundice is often seen • intravascular haemolysis  Decreased haptoglobin levels, hematuria, and presence of urinary hemosiderin indicate severe intravascular hemolysis. • acute hemolysis can cause back or abdominal pain and jaundice secondary to a rise in unconjugated bilirubin  Jaundice, in the setting of normal liver function, typically does not occur until > 50% of the erythrocytes have been hemolyzed. • gallstones are common • splenomegaly may be present • Heinz bodies (denatured hemoglobin) on blood films Diagnosis: • made by using a G6PD enzyme assay • usually done by fluorescent spot test detecting the generation of NADPH from NADP.  The test is positive if the blood spot fails to fluoresce under ultraviolet light. • In patients with acute hemolysis, testing for G6PD deficiency may be falsely negative because older erythrocytes with a higher enzyme deficiency have been hemolyzed. Young erythrocytes and reticulocytes have normal or near-normal enzyme activity. • Female heterozygotes may be hard to diagnose because of X-chromosome mosaicism leading to a partial deficiency that will not be detected reliably with screening tests. • Acute haemolytic reaction  Blood count is normal between attacks of haemolysis  During an attack the blood film may show:  irregularly contracted cells  bite cells



Haematology&Oncology  blister cells  Heinz bodies  Reticulocytosis • Peripheral blood smear  Heinz bodies (rarely seen in clinical practice) • Reticulocyte count: Increases four to seven days after hemolysis • Haptoglobin  Decreased Treatment • avoidance exposure to an oxidative stressor in the form of an infection, oxidative drug, or fava beans • Acute hemolysis is self-limited, but in rare instances it can be severe enough to warrant a blood transfusion  Hemolysis typically occurs 24 to 72 hours after ingestion, with resolution within 4 to 7 days. • Methaemoglobinaemia in G6PD-deficient patients is best treated with exchange transfusion. Some drugs causing haemolysis • anti-malarials: primaquine • Quinine/quinidine. • Ciprofloxacin • Nitrofurantoin • chloramphenicol • sulph- group drugs: sulphonamides, sulphasalazine, sulfonylureas • vitamin K, probenecid • aspirin and (NSAIDs) Some drugs thought to be safe • penicillins • cephalosporins • macrolides • tetracyclines • trimethoprim  In “Co-trimoxazole”: the sulfamethoxazole causes haemolysis in

G6PD, not the trimethoprim. Comparing G6PD deficiency to hereditary spherocytosis: G6PD deficiency Hereditary spherocytosis Gender Male (X-linked recessive) Male + female (autosomal dominant) Ethnicity African + Mediterranean descent Northern European descent Typical history • Neonatal jaundice • Infection/drugs precipitate haemolysis • Gallstones • Neonatal jaundice • Chronic symptoms although haemolytic crises may be precipitated by infection • Gallstones • Splenomegaly is common Blood film Heinz bodies Spherocytes (round, lack of central pallor) Diagnostic test Measure enzyme activity of G6PD Osmotic fragility test



Other notes • G6PD deficiency confers partial protection against malaria • Hemolysis begins 24 to 72 hours after exposure to oxidant stress. • Hemolysis due to oxidant stresses are usually self-limiting within 8 to 14 days due to the compensatory production of young red blood cells with high levels of G6PD. • Young RBCs are not vulnerable to oxidative damage and hence limit the duration of hemolysis. • G6PD deficiency is an X-linked inherited disease that primarily affects men. • Women may be affected if:  they are homozygous, which occurs in populations in which the frequency of G6PD deficiency is quite high.  Heterozygous women (carriers) can experience clinical disease as a result of:

1. X chromosome inactivation,
2. gene mosaicism, or
3. hemizygosity • Severe hemolysis due to G6PD deficiency may manifest as methemoglobinemia

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_Paroxysmal nocturnal haemoglobinuria (PNH) The triad of hemolytic anemia, pancytopenia, and thrombosis  PNH • (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. • Caused by increased sensitivity of cell membranes to complement due to a lack of glycoprotein glycosyl-phosphatidyl-inositol (GPI). • Patients are more prone to venous thrombosis • 50% of PNH affected individuals are died due to thrombotic complications Pathophysiology • GPI can be thought of as an anchor which attaches surface proteins to the cell membrane • complement-regulating surface proteins, e.g. decay-accelerating factor CD 55 (DAF) and Membrane Inhibitor of Reactive Lysis CD 59 (MIRL)., are not properly bound to the cell membrane due a lack of GPI • Hemolysis occurs when patients develop a mild acidosis at night, due to a relative hypoventilation, resulting in the passage of dark urine in the early morning. • thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation • Intrinsic hemolytic anemia with intravascular hemolysis Features • symptoms of anemia (Pallor, fatigue, weakness) • Intermittent jaundice • haemoglobinuria  classically dark-coloured urine in the morning (although has been shown to occur throughout the day) • Abdominal pain  may be due to small mesenteric vein thrombi. Complications • thrombosis e.g. Budd-Chiari syndrome • Vasoconstriction: headache, pulmonary hypertension • aplastic anaemia may develop in some patients • ↑ Risk of acute leukemias Investigations • CBC  haemolytic anaemia  pancytopaenia • Dipstick analysis of the urine:

Haematology&Oncology  will be positive for 'blood', but the microscopy will show no red blood cells.  This because there is intravascular haemolysis, with intravascular release of haemoglobin. This then passes through the renal tubules, ending up in the urine, and turning the dipstick analysis positive. However, because there are no actual red blood cells in the urine, the microscopy will be negative. • Flow cytometry (immunophenotyping) of blood  absence of CD55 and CD59 on the surface of RBCs  now replaced Ham's test as the gold standard investigation in PNH • Ham's test:  acid-induced haemolysis (normal red cells would not)  acidified serum (pH 6.2) is added to blood: PNH cells, but not normal cells, will be lysed. • Coombs test: negative Management • blood product replacement • anticoagulation • eculizumab, a monoclonal antibody directed against terminal protein C5 (C5 inhibitor), is reducing intravascular haemolysis • stem cell transplantation  The gold standard curative treatment

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Splenectomy • Following a splenectomy patients are particularly at risk of infections from:  pneumococcus,  Haemophilus,  meningococcus and  Capnocytophaga canimorsus*(*usually from dog bites) • Vaccination  if elective, should be done 2 weeks prior to operation  Hib, meningitis A & C  annual influenza vaccination  pneumococcal vaccine every 5 years • Antibiotic prophylaxis  penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life



Blood products Whole blood fractions Fraction Key points Packed red cells • Used for transfusion in chronic anaemia and cases where infusion of large volumes of fluid may result in cardiovascular compromise. • Product obtained by centrifugation of whole blood. • In a stable patient, red cell packs may be transfused over 90-120 minutes  Rapid infusion of red cells or fresh frozen plasma may be required in an acutely bleeding patient but not in patient who is stable. Platelet rich plasma • Usually administered to patients who are thrombocytopaenic and are bleeding or require surgery. • It is obtained by low speed centrifugation. Platelet concentrate • Prepared by high speed centrifugation • administered to patients with thrombocytopaenia. • the life span of transfused platelets is only 3-7 days. • platelet transfusion should not take more than 20-30 minutes. • Patients who are refractory to platelet transfusions:  should be first investigated to check for adequate platelet rises. This is best done on a one or two-hour post platelet transfusion sample.  Further test would include checking for HLA antibodies Fresh frozen plasma • Prepared from single units of blood. • Contains clotting factors, albumin and immunoglobulin. • Unit is usually 200 to 250ml. • Usually used in correcting clotting deficiencies in patients with hepatic synthetic failure who are due to undergo surgery. • Usual dose is 12-15ml/Kg-1. • It should not be used as first line therapy for hypovolaemia. Cryoprecipitate • Formed from supernatant of FFP. • Rich source of Factor VIII and fibrinogen. • Allows large concentration of factor VIII to be administered in small volume. SAG-Mannitol Blood Removal of all plasma from a blood unit and substitution with: •

Sodium chloride • Adenine • Anhydrous glucose • Mannitol Up to 4 units of SAG M Blood may be administered. Thereafter whole blood is preferred. After 8 units, clotting factors and platelets should be considered. Plasma derivatives • plasma derivatives (such as factor VIII) are prepared from several thousand plasma donations, typically 20,000, or 5,000 kg of plasma at a time. • Pooled plasma has been sourced from outside the UK since 1999 to avoid vCJD risks.

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 The process involves several chemical steps including:  ethanol extraction,  chromatography, and  viral inactivation steps which results in a freeze-dried product. • These products have a long shelf life of several months to years. Cell saver devices These collect patients own blood lost during surgery and then re-infuse it. There are two main types: • Those which wash the blood cells prior to re-infusion. These are more expensive to purchase and more complicated to operate. However, they reduce the risk of re-infusing contaminated blood back into the patient. • Those which do not wash the blood prior to re-infusion. Their main advantage is that they avoid the use of infusion of blood from donors into patients and this may reduce risk of blood borne infection. It may be acceptable to Jehovah's witnesses. It is contraindicated in malignant disease for risk of facilitating disease dissemination. Blood products used in warfarin reversal Immediate or urgent surgery in patients taking warfarin:

1. Stop warfarin
2. Vitamin K (reversal within 4-24 hours)  IV takes 4-6h to work (at least 5mg)  Oral can take 24 hours to be clinically effective
3. Fresh frozen plasma  Used less commonly now as 1st line warfarin reversal  30ml/kg-1  Need to give at least 1L fluid in 70kg person (therefore not appropriate in fluid overload)  Need blood group  Only use if human prothrombin complex is not available
4. Human Prothrombin Complex (reversal within 1 hour)  Bereplex 50 u/kg  Rapid action but factor 6 short half life, therefore give with vitamin K Neonatal exchange transfusion • An exchange transfusion requires blood which is plasma reduced whole blood in CPD (citrate phosphate dextrose/anticoagulant), irradiated and less than five days old. • The Rh group should either be Rh negative or identical to the neonate, to avoid haemolytic transfusion reaction in the neonate. Blood Transfusion Thresholds ■ Sepsis: 7 g/dL ■ Upper or lower GI bleeds: 7 g/dL ■ Acute neurologic injury or TBI : 7 g/dL ■ Stable CV disease: 8 g/dL ■ ACS: 10 g/dL

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Blood product transfusion complications Complications • haemolytic: immediate or delayed • febrile reactions • transmission of viruses, bacteria, parasites, vCJD • hyperkalaemia • iron overload • ARDS • clotting abnormalities Immediate haemolytic reaction • occur during the transfusion. • e.g. ABO mismatch • massive intravascular haemolysis Delayed haemolytic transfusion reaction • occurs 24 hours after the transfusion. • This happens in a patient who has

been previously immunised by transfusions or pregnancy. The antibodies are not detectable initially but become obvious as a secondary immune response to the antigen exposure during the transfusion occurs. Febrile reactions • due to anti HLA antibodies in recipient serum or granulocyte specific antibodies (for example, sensitisation during previous pregnancy or previous blood transfusion). • Febrile non-haemolytic reactions are very common and are due to the presence of pyrogenic cytokines released from leucocytes during storage of the blood units.  apart from a mild fever, the patient is very well.  rapid rise in temperature may be due to ABO incompatibility, but With ABO incompatibility patients become shocked very quickly. Rhesus D mismatch • It is very often necessary to give D positive platelets to D negative people due to platelet shortage. • If the recipient of this mismatch is a female of child bearing age, then prophylactic anti- D should be administered with the platelets to prevent production of immune anti- D. • If anti-D does not administered, the immune anti-D she has made can cross the placenta when she become pregnant in the future and cause haemolytic disease of the fetus/newborn, if the baby is D positive, and this can be life threatening to the baby.  Advise patient that this is only likely to be of consequence should she become pregnant in the future. Causes a degree of immunosuppression • e.g. patients with colorectal cancer who have blood transfusions have a worse outcome than those who do not The risk of viral transmission • A broad knowledge of the risks may be required while consenting a patient for blood transfusion. • in the United Kingdom, the risks;  For hepatitis B are 1 per 1.3 million donations  For HIV are 1 in 6.5 million and  For hepatitis C 1 in 28 million donations. Transmission of vCJD • although the absolute risk is very small, vCJD may be transmitted via blood transfusion • a number of steps have been taken to minimise this risk, including: • → from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present



Haematology&Oncology • →from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported • → from 2004 onward, recipients of blood components have been excluded from donating blood iron overload • secondary to chronic blood transfusion (eg : in myelodysplastic syndrome) • early signs:  grey skin  early hear failure  diabetes • treatment:  iron chelation with desferrioxamine subcutaneously  bind iron  needs to be given for 8 – 12 hours a day for 5 – 7 days per week  common side effects of desferrioxamine:  high frequency deafness  retinopathy  Yersinia infection irradiated blood products • the advantage of irradiated red cells  Inactivates donor lymphocytes • Indications for irradiated blood products  Those at risk of transfusion associated with graft versus host disease such as neonates  Those receiving purine analogues-based chemotherapy  Hodgkin's lymphoma  Immunodeficiency states  Post bone marrow transplants Pre-operative request for the blood bank for elective surgeries • Group and save only  A 'group and save' is adequate for elective surgeries and is standard practice in most modern blood banks. This will involve blood grouping and its confirmation as well as an antibody screen.  Other options include cross match and a direct Coombs' test are not routinely done for elective surgery Transfusion errors • Mislabelling of samples, requests, or wrongly identifying recipients are the commonest transfusion errors. January 2016 exam: What is the risk of variant Creutzfeldt-Jakob Disease (vCJD) transmission via blood transfusion?  Measures are taken to reduce the risk of vCJD transmission but there remains a very

small risk of transmission



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Transfusion Related Acute Lung Injury (TRALI) Definition • (TRALI) is a rare but serious syndrome characterized by sudden acute respiratory distress within six hours after blood product administration Risk factors • Caused by anti-HLA, Human Neutrophil Antigens (HNA) or anti-granulocytes antibody in donor blood. • Donor's blood sensitization occurs in:  Multiparous ♀ develop these antibodies through exposure to fetal blood  Previous transfusion  Transplantation patient • When blood is obtained from above mentioned donors, it carries higher risk for recipient to develop TRALI; those who have lung pathology are more susceptible. TRALI symptoms resemble ARDS. Pathophysiology • transfused human leukocyte or neutrophil antigen (HLA or HNA) antibodies  activation of donor neutrophils  Neutrophils adhere to pulmonary endothelium to increase permeability and cause pulmonary edema. • Patients with certain clinical conditions (eg, infection, inflammation, surgery) have primed neutrophils that are susceptible to activation by transfused bioactive substances. • TRALI has two proposed pathophysiologic mechanisms:

1. the antibody hypothesis. (antigen-antibody interactions)  The human leukocyte antigen (HLA class I, HLA class II) or human neutrophil antigen (HNA) antibody in the transfused component reacts with neutrophil antigens in the recipient The recipient's neutrophils lodge in the pulmonary capillaries and release mediators that cause pulmonary capillary leakage.  As a consequence, many patients with TRALI will develop transient leukopenia.  However, transfusions of blood components containing neutrophil antibodies may cause leukopenia, that do not meet the definition of TRALI.
2. The neutrophil priming hypothesis:  does not require antigen-antibody interactions  occurs in patients with clinical conditions that predispose to neutrophil priming and endothelial activation such as infection, surgery, or inflammation.  Bioactive substances in the transfused component activate the primed, sequestered neutrophils, and pulmonary endothelial damage occurs. • Both mechanisms lead to pulmonary edema in the absence of circulatory overload. Feature • Occurring within 1 to 6 hours of transfusion of plasma-containing blood components. • Patients present with the rapid onset of dyspnea and tachypnea. • There may be associated fever, cyanosis, and hypotension. • Clinical examination reveals hypoxic respiratory distress, and pulmonary crackles may be present without signs of congestive heart failure or volume overload. • Chest x-ray (CXR) shows evidence of bilateral pulmonary edema unassociated with heart failure (non-cardiogenic pulmonary edema), with bilateral patchy infiltrates, which may rapidly progress to complete "white out" indistinguishable from acute respiratory distress syndrome (ARDS). • Physiologic findings include acute hypoxemia with PaO2/FiO2 less than 300 mmHg and normal cardiac function on echocardiogram.

Haematology&Oncology Diagnosis: • confirmed by finding of anti-HLA or anti-Neutrophil antibody in donors’ or recipient blood. Treatment • Early and intensive pulmonary support reduces the risk of a fatal outcome. • Since the pulmonary edema in TRALI is not related to fluid overload or cardiac dysfunction, but to altered vascular permeability in the lungs with exudation of fluid and protein into the alveoli, it is logical that:  maintenance of adequate circulating volume is the most beneficial and appropriate therapy.  Corticosteroids,  epinephrine  and also ventilatory support are treatment options. How to distinguish TRALI and ARDS from Pulmonary oedema? • In the exam take into account the clinical findings and scenario to distinguish. • The hallmark of ARDS is refractory hypoxia with non-cardiogenic pulmonary edema • Normal pulmonary capillary wedge pressure is between 5 - 15 mmHg. A PCWP exceeding 15 mmHg suggests mitral stenosis, mitral insufficiency, severe aortic stenosis, aortic regurgitation, ventricular failure, or other cardiac defects or pathologies. • When the PCWP exceeds 20 mmHg, the transmission of this pressure back into the pulmonary vasculature increases pulmonary capillary hydrostatic pressure which can lead to pulmonary oedema.

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Graft versus host disease (GVHD) See transplant topic in renal system

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Plasma exchange Indications for plasma exchange (also known as plasmapheresis) • Guillain-Barre syndrome • myasthenia gravis • Goodpasture's syndrome • ANCA positive vasculitis e.g. Wegener's, Churg-Strauss • TTP/HUS • cryoglobulinaemia • hyperviscosity syndrome e.g. secondary to myeloma

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Deep vein thrombosis (DVT) DVT Risk Factors: • Hematological  Thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency  Polycythemia  Paroxysmal nocturnal hemoglobinuria  Hyperviscosity syndrome • Autoimmune  Antiphospholipid syndrome  Behcet's

• Drugs  Combined oral contraceptive pill: 3rd generation more than 2nd generation  Antipsychotics (especially olanzapine) have recently been shown to be a risk factor • Other conditions  Homocystinuria Diagnosis If a patient is suspected of having a DVT a two-level DVT Wells score should be performed: Two-level DVT Wells score Clinical feature Points Active cancer (treatment ongoing, within 6 months, or palliative)

Paralysis, paresis or recent plaster immobilisation of the lower extremities Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia Localised tenderness along the distribution of the deep venous system Entire leg swollen

Calf swelling at least 3 cm larger than asymptomatic side

Pitting oedema confined to the symptomatic leg

Collateral superficial veins (non-varicose)

Previously documented DVT

An alternative diagnosis is at least as likely as DVT -2 Clinical probability simplified score • DVT likely: 2 points or more • DVT unlikely: 1 point or less If a DVT is 'likely' (2 points or more) • a proximal leg vein ultrasound scan should be carried out within 4 hours and, if the result is negative, a D-dimer test • if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and low-molecular weight heparin administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours) If a DVT is 'unlikely' (1 point or less) • perform a D-dimer test and if it is positive arrange: • a proximal leg vein ultrasound scan within 4 hours • if a proximal leg vein ultrasound scan cannot be carried out within 4 hours low-molecular weight heparin should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours) Management Low molecular weight heparin (LMWH) or fondaparinux should be given initially after a DVT is diagnosed. • a vitamin K antagonist (i.e. warfarin) should be given within 24 hours of the diagnosis Notes & Notes for MRCP
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Haematology&Oncology • the LMWH or fondaparinux should be continued for at least 5 days or until the international normalised ratio (INR) is 2.0 or above for at least 24 hours, whichever is longer, i.e. LMWH or fondaparinux is given at the same time as warfarin until the INR is in the therapeutic range • warfarin should be continued for at least 3 months. At 3 months, NICE advise that clinicians should 'assess the risks and benefits of extending treatment' • NICE add 'consider extending warfarin beyond 3 months for patients withunprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding'. This essentially means that if there was no obvious cause or provoking factor (surgery, trauma, significant immobility) it may imply the patient has a tendency to thrombosis and should be given treatment longer than the norm of 3 months. In practice most clinicians give 6 months of warfarin for patients with an unprovoked DVT/PE • for patients with active cancer NICE recommend using LMWH for 6 months • for patients with active ulcerative colitis who developed DVT :  may require Emergency colectomy, as such warfarinisation would be inappropriate.  should be heparinised as this would be easily reversible if it needs to be discontinued prior to surgery or if severe worsening of bleeding occurs. Time of starting prophylaxis in elective knee replacement surgery: • LMWH or fondaparinux (s/c factor X inhibitor)  should be started 6 – 12 hours after surgery • Dabigatran (oral factor X inhibitor)  1 – 4 hours after surgery Unprovoked VTE  (Malignancy investigations and thrombophilia screening) • As both malignancy and thrombophilia are obvious risk factors for deep vein thrombosis NICE make recommendations on how to investigate patients with unprovoked clots. Malignancy investigations • Offer all patients diagnosed with unprovoked DVT or PE who are not already known to have cancer the following investigations for cancer:  a physical examination (guided by the patient's full history) and  a chest X-ray and  blood tests (full blood count, serum calcium and liver function tests) and urinalysis. • Consider further investigations for cancer with an abdomino-pelvic CT scan (and a mammogram for women) in all patients aged over 40 years with a first unprovoked DVT or PE Thrombophilia screening • not offered if patients will be on lifelong warfarin (i.e. won't alter management) • consider testing for antiphospholipid antibodies if unprovoked DVT or PE • consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE The next most

important investigation: • Unprovoked VTE  chest X-ray, blood tests and urinalysis • Unprovoked VTE + family history of VTE  Thrombophilia screening

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Pregnancy: DVT/PE Coagulation elements in pregnancy: • Increased  factors VII, VIII, IX, X, and XII ,fibrinogen, plasminogen, and D-dimer. • Decreased  factor XI and protein S. • Not changed  Factor II, protein C, and anti-thrombin III. Overview • pregnancy is a hypercoagulable state • majority occur in last trimester Pathophysiology • increase in factors VII, VIII, X and fibrinogen • decrease in protein S • uterus presses on IVC causing venous stasis in legs Management • warfarin contraindicated • S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)

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Post-thrombotic syndrome • It is increasingly recognised that patients may develop complications following a DVT. • Venous outflow obstruction and venous insufficiency result in chronic venous hypertension. • The resulting clinical syndrome is known as post thrombotic syndrome. Features • painful, heavy calves • pruritus • swelling • varicose veins • venous ulceration Management • Compression stockings should be offered to all patients with deep vein thrombosis to help reduce the risk of post-thrombotic syndrome. • NICE state the following:  Offer below-knee graduated compression stockings with an ankle pressure greater than 23 mmHg to patients with proximal DVT a week after diagnosis or when swelling is reduced sufficiently and if there are no contraindications, and:  advise patients to continue wearing the stockings for at least 2 years  ensure that the stockings are replaced two or three times per year or according to the manufacturer's instructions  advise patients that the stockings need to be worn only on the affected leg or legs.

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Venous thromboembolism: prophylaxis in patients admitted to hospital Venous thromboembolism (VTE) still accounts for a significant proportion of avoidable hospital deaths. In an effort to tackle this problem NICE produced guidelines in 2010. Before admission • advise women to consider stopping oestrogen-containing oral contraception or HRT 4 weeks before surgery.

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Haematology&Oncology • assess the risks and benefits of stopping antiplatelet therapy 1 week before surgery. The following patients are deemed at risk of VTE Medical patients • if mobility significantly reduced for >= 3 days or • if expected to have ongoing reduced mobility relative to normal state plus any VTE risk factor (see below) Surgical patients and patients with trauma • if total anaesthetic + surgical time > 90 minutes or • if surgery involves pelvis or lower limb and total anaesthetic + surgical time > 60 minutes or • if acute surgical admission with inflammatory or intra-abdominal condition or • if expected to have significant reduction in mobility or • if any VTE risk factor present (see below) VTE risk factors • active cancer or cancer treatment • age > 60 years • critical care admission • dehydration • known thrombophilias • obesity (BMI > 30 kg/m2) • one or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or

respiratory pathologies; acute infectious diseases; inflammatory conditions) • personal history or first-degree relative with a history of VTE • use of HRT • use of oestrogen-containing contraceptive therapy • varicose veins with phlebitis In-patient VTE prophylaxis As a general rule pharmacological VTE prophylaxis is used for medical patients unless there is a contraindication. For surgical patients mechanical VTE prophylaxis is offered for patients at risk. Pharmacological VTE prophylaxis is also given for if the risk of major bleeding is low. Pharmacological VTE prophylaxis options: • fondaparinux sodium • low molecular weight heparin (LMWH) • unfractionated heparin (UFH) (for patients with renal failure) Mechanical VTE prophylaxis options: • anti-embolism stockings (thigh or knee length) • foot impulse devices • intermittent pneumatic compression devices (thigh or knee length) Post-procedure VTE prophylaxis For certain procedures pharmacological VTE prophylaxis is recommended for all patients, using one of the following: • dabigatran, started 14 hours after surgery • fondaparinux, started 6 hours after surgery • LMWH, started 6-12 hours after surgery • rivaroxaban, started 6-10 hours after surgery. • Apixaban Procedure Length of prophylaxis Elective hip 28-35 days Elective knee 10-14 days Hip fracture 28-35 days