Thrombosis

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Haemostasis

- Blood must be maintained in a fluid state in order to function as a transport system, but must be able to solidify to form a clot following vascular injury in order to prevent excessive bleeding, a process known as haemostasis.
- Successful haemostasis is localised to the area of tissue damage and is followed by removal of the clot and tissue repair.
- This is achieved by complex interactions between the vascular endothelium, platelets, coagulation factors, natural anticoagulants and fibrinolytic enzymes .
- Dysfunction of any of these components may result in haemorrhage or thrombosis

Platelets

- Platelets are formed in the bone marrow from megakaryocytes.
- Megakaryocytic stem cells
- The formation and maturation of megakaryocytes are stimulated by Thrombopoietin produced in the liver.
- Platelets circulate for 8–10 days before they are destroyed in the reticulo-endothelial system.
- Some 30% of peripheral platelets are normally pooled in the spleen and do not circulate
- Drugs which inhibit platelet function and thrombosis include aspirin (cyclo-oxygenase inhibitor), clopidogrel (adenosine diphosphate (ADP)-mediated activation inhibitor),dipyridamole (phosphodiesterase inhibitor), and the

IIb/IIIa inhibitors abciximab, tirofiban and eptifibatide(which prevent fibrinogen binding)

Clotting factors

- Clotting factors are synthesised by the liver, although factor V is also produced by platelets and endothelialcells.
- Factors II, VII, IX and X in the liver is vitamin K-dependent. Vitamin K must be reduced to its active form by a reductase enzyme. This reductase is inhibited by warfarin, and this is the basis of the anticoagulant effect of coumarins .
- Congenital (e.g.haemophilia) and acquired (e.g. liver failure) causes of coagulation factor deficiency are associated with bleeding

Investigation of coagulation

- The tissue factor ('extrinsic') pathway is assessed by the prothrombin time (PT), and the 'intrinsic' pathway by the activated partial thromboplastin time (APTT),
- Coagulation is delayed by deficiencies of coagulation factors and by the presence of inhibitors of coagulation, such as heparin .
- If both the PT and APTT are prolonged, this indicates either deficiency or inhibition of the final common pathway (which includes factors X, V, prothrombin and fibrinogen) or global coagulation factor deficiency involving more than one factor, as occurs in disseminated intravascular coagulation .
- A mixing test with normal plasma allows differentiation between a coagulation factor deficiency(the prolonged time corrects) and the presence of an inhibitor of coagulation (the prolonged time does not correct);
- the latter may be chemical (heparins) or an antibody (most often a lupus anticoagulant but occasionally a specific inhibitor of one of the coagulation factors, typically factor VIII). Willebrand disease may present with anormal APTT

- Platelet function has historically been assessed by the bleeding time, measured as the time to stop bleeding after astandardised incision.
- However, most centres have abandoned the use of this test.
- Platelet function can be assessed in vitro by measuring aggregation in response to various agonists,
- Coagulation screening tests are also performed in patients with suspected DIC, when clotting factors and platelets are consumed, resulting in thrombocytopenia

  and prolonged PT and APTT.

In addition, there is evidence of active coagulation with consumption of fibrinogen and generation of fibrin degradation products (D-dimers).

- Note, however, that fibrinogen is an acute phase protein which may also be elevated in inflammatory disease.

- The international normalised ratio (INR) is validated only to assess the therapeutic effect of coumarin anticoagulants, including warfarin. INR is the ratio of the patient's PT to that of a normal control, raised to the power of the international sensitivity index (ISI)
- Monitoring of heparin therapy is, on the whole, only required with unfractionated heparins.
- Therapeutic anticoagulation prolongs the APTT relative to a control sample by a ratio of approximately 1.5–2.5
- Low molecular weight heparins have such a predictable dose response that monitoring of the anticoagulant effect is not required, except in patients with renal impairment (glomerular filtration rate less than 30 mL/min). When monitoring is indicated, an anti-Xa activity assay rather than APTT should be used

Thrombotic disorders

- Measurement of plasma levels of D-dimers derived from fibrin degradation is useful in excluding the diagnosis of active venous thrombosis in some patients .

Venous thrombosis

- While the most common presentation of venous thromboembolic disease (VTE) is with deep vein thrombosis (DVT) of the leg and/or pulmonary embolism similar principles apply to rarer manifestations such as jugular vein thrombosis, upper limb DVT, cerebral sinus thrombosis and intra-abdominal venous thrombosis (e.g. Budd–Chiari syndrome;
- DVT has an annual incidence of approximately 1 : 1000 in Western populations and the case mortality is

1–3%. It is increasingly common with ageing, and many of the deaths are related to coexisting medical conditions,such as active cancer.

Clinical assessment

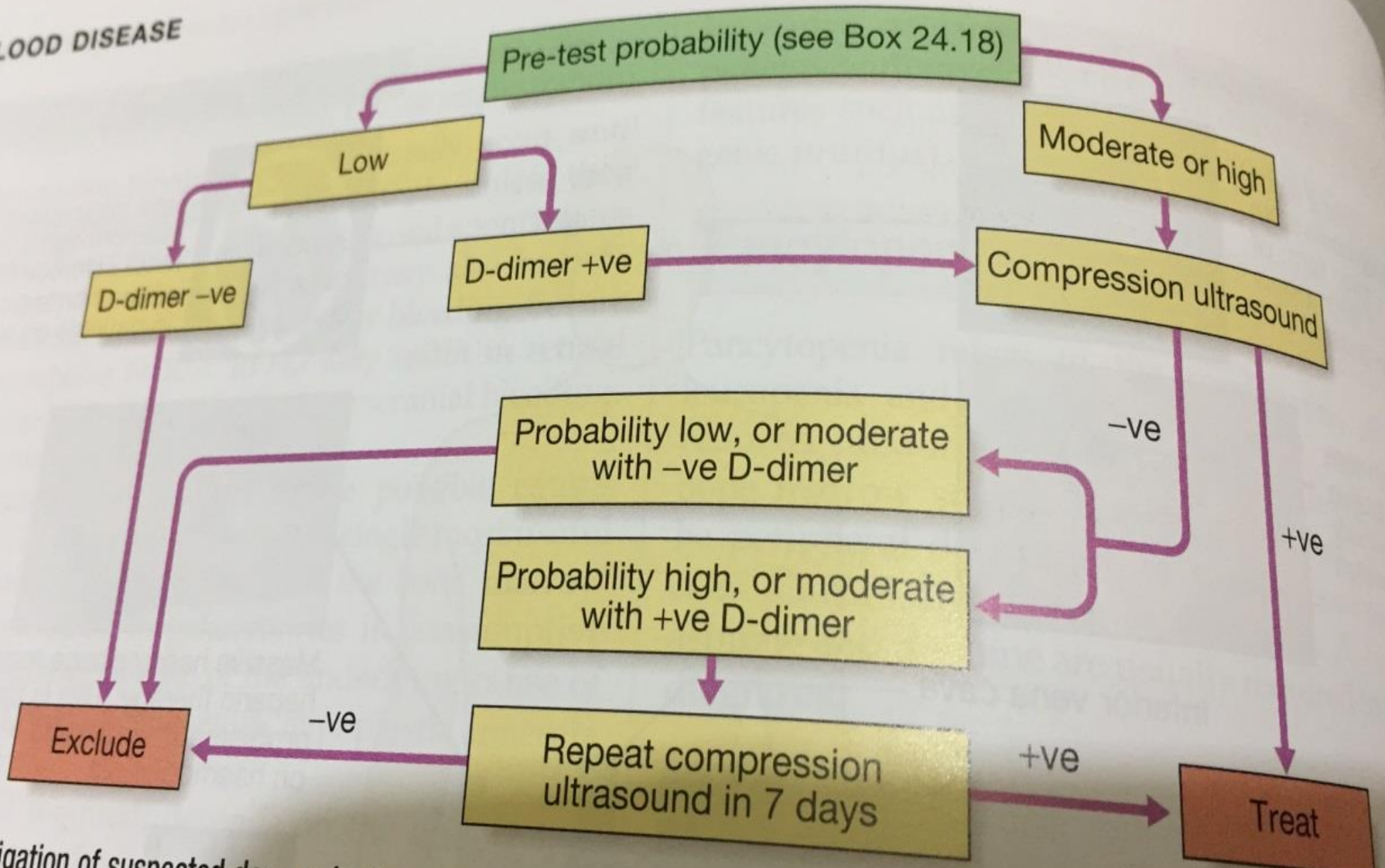
- Lower limb DVT characteristically starts in the distal veins, causing pain, swelling, an increase in temperature and dilatation of the superficial veins. Often, however, symptoms and signs are minimal.
- It is typically unilateral but may be bilateral, and clot may extend proximally into the inferior vena cava.
- Bilateral DVT is more commonly seen with underlying malignancy or anomalies of the inferior vena cava.
- The differential diagnosis of unilateral leg swelling includes a spontaneous or traumatic calf muscle tear or a ruptured Baker's cyst, both characterise by sudden onset and localised tenderness. Infective cellulitis is usually distinguished by marked skin erythema and heat localised within a well-demarcated area of the leg and may be associated with an obvious source of entry of infection (e.g. insect bite, leg ulcer).
- Risk factors for DVT should be considered and examination should include assessment for malignancy.

- Symptoms and signs of PE should be sought particularly in those with proximal thrombosis; asymptomatic PE is thought to be present in approximately 30% of patients with lower limb DVT.
- Clinical criteria can be used to rank patients according to their likelihood of DVT or PE: for example, by using scoring systems such as the Wells score

Management

- The management of leg DVT includes elevation and analgesia. Thrombolysis may be considered for limbthreatening DVT, but the mainstay of treatment is anticoagulation with low molecular weight heparin (LMWH), followed by a coumarin anticoagulant, such as warfarin.
- An alternative is the oral Xa inhibitor, rivaroxaban, which has a rapid onset of action and can be used immediately from diagnosis without the need for LMWH.
- Treatment of acute VTE with LMWH should continue for at least 5days.
- If a coumarin is being introduced, the heparin should continue until the INR has been in the target range for 2 days.
- Patients who have had a DVT and have a strong contraindication to anticoagulation, and those who, despite therapeutic anticoagulation, continue to have new pulmonary emboli,should have an inferior vena cava filter inserted to prevent life-threatening PE.

- The optimal initial duration of anticoagulation is between 6 weeks and 6 months. Patients who have thrombosis in the presence of a temporary risk factor, which is then removed, can usually be treated for shorter periods (e.g. 3 months) than those who sustain unprovoked thrombosis.



5 Investigation of suspected deep vein thrombosis. Pre-test probability is calculated in Box 24.18.

- **Post-thrombotic syndrome is** due to damage of venous valves by the thrombus. It results in persistent leg swelling, heaviness and discoloration.
- The most severe complication of this syndrome is ulceration around the medial malleolus.

Antithrombin deficiency

- Antithrombin (AT) is a serine protease inhibitor (SERPIN) which inactivates the activated coagulation factors IIa, IXa, Xa and XIa. Heparins, fondaparinux and idraparinux achieve their therapeutic effect by potentiating the activity of AT.
- Familial deficiency of AT is inherited as an autosomal dominant; homozygosity for mutant alleles is not compatible with life. Around 70% of affected individuals will have an episode of VTE before the age of 60 years and the relative risk for thrombosis compared with the background population is 10–20.

- Pregnancy is a high-risk period for VTE and this requires fairly aggressive management with doses of LMWH which are greater than the usual prophylactic doses (≥ 100 U/kg/day). AT concentrate (either plasmaderived or recombinant) is available; this is required for cardiopulmonary bypass and may be used as an adjunct to heparin in surgical prophylaxis.
- Protein C and S are vitamin K-dependent natural anticoagulants involved in switching off coagulation factor activation (factors Va and VIIIa) and thrombin generation . Inherited deficiency of either protein C or S results in a prothrombotic state with a fivefold relative risk of VTE compared with the background population.

Factor V Leiden

- Factor V Leiden results from mutation which prevents the cleavage and hence inactivation of activated factor V. This results in a relative risk of venous thrombosis .

Antiphospholipid syndrome

- Antiphospholipid syndrome (APS) is a clinicopathological entity in which a constellation of clinical conditions, alone or in combination, is found in association with apersistently positive test for an antiphospholipid antibody.
- The mechanisms underlying the clinical features of APS are not clear.
- In clinical practice, two types of test are used, which detect: antibodies (called an anticardiolipin antibody test) those which interfere with coagulation tests like the APTT or the dilute Russellviper venom time (called a lupus anticoagulant test).
- The term antiphospholipid antibody encompasses both a lupus anticoagulant and an anticardiolipin antibody;
- individuals may be positive for one or both of these activities.

- Arterial thrombosis, typically stroke, associated with APS should be treated with warfarin, as opposed to aspirin. APS-associated VTE is one of the situations in which the predicted recurrence rate is high enough to indicate long-term anticoagulation after a first event

Table 27.3 Clinical associations of lupus anticoagulant and anticardiolipin antibodies.

Venous thrombosis: deep venous thrombosis/pulmonary embolism, renal, hepatic, retinal veins
Arterial thrombosis
Recurrent fetal loss
Thrombocytopenia
Livedo reticularis

N.B. Recurrent fetal loss may also occur in other types of thrombophilia.

Disseminated intravascular coagulation

- Disseminated intravascular coagulation (DIC) may complicate a range of illnesses . It is characterised by systemic activation of the pathways involved in coagulation and its regulation.
- This may result in the generation of intravascular fibrin clots causing multi organ failure, with simultaneous coagulation factor and platelet consumption causing bleeding.
- There is consumption of platelets, coagulation factors (notably factors V and VIII) and fibrinogen.
- The lysis of fibrin clot results in production of fibrin degradation products (FDPs), including D-dimers.

investigations

- Measurement of coagulation times (APTT and PT), along with fibrinogen,
- platelet count and FDPs, helps in the assessment of prognosis and aids clinical decision-making with regard to both bleeding and thrombotic complications.

Management

- Therapy is primarily aimed at the underlying cause.These patients will often require intensive care to deal with concomitant issues, such as acidosis dehydration, renal failure and hypoxia.
- Blood component therapy, such as fresh frozen plasma, cryoprecipitate and platelets, should be given if the patient is bleeding or to cover interventions with high bleeding risk, but should not be prescribed routinely based on coagulation tests and platelet counts alone.
- Prophylactic doses of heparin should be given, unless there is a clear contraindication.Established thrombosis should be treated cautiously with therapeutic doses of unfractionated heparin, unless clearly contraindicated. Patients with DIC should not, in general, be treated with antifibrinolytic therapy, e.g. tranexamic acid.

Thrombotic thrombocytopenic purpura

- Like DIC and also heparin-induced thrombocytopenia thrombotic thrombocytopenic purpura (TTP) is a disorder in which thrombosis is accompanied by paradoxical thrombocytopenia.
- TTP is characterised by a pentad of findings, although few patients have all five

Components:

1. thrombocytopenia
2. microangiopathic haemolytic anaemia
3. neurological sequelae
4. fever
5. renal impairment.

- It is an acute autoimmune disorder mediated by antibodies The features are of microvascular occlusion by platelet thrombi affecting key organs, principally brain and kidneys. It is a rare disorder (1 in 750 00 perannum), which may occur alone or in association with drugs (ticlopidine, ciclosporin), HIV, shiga toxins and malignancy.
- It should be treated by emergency plasma exchange.
- Corticosteroids, aspirin and rituximab also have a role in management.
- Untreated mortality rates are 90% in the first 10 days, and even with appropriate therapy, the mortality rate is 20–30% at 6 months.