*ABC of clinical haematology***Bleeding disorders, thrombosis, and anticoagulation**

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Blood within the vascular tree remains fluid throughout life, but if a blood vessel is damaged, blood will clot in a rapid localised response. Failure of clotting leads to bleeding disorders; thrombosis is inappropriate clotting within blood vessels. The haemostatic system is complex, and many congenital and acquired conditions can disturb its correct functioning.

Bleeding disorders**History**

Personal and family history is as important as laboratory investigation in assessing bleeding disorders. Easy bruising, nose bleeds (especially in children), and menorrhagia are common and do not necessarily signify a haemostatic defect unless they are persistent and severe. Small bruises on the limbs in response to minor trauma and simple easy bruising are especially common in elderly people and those receiving long term corticosteroids.

Large bruises after minimal trauma and on the trunk may indicate an important haemostatic defect. Abnormally prolonged bleeding from minor cuts and scratches and delayed recurrence of bleeding are also important, as is gum bleeding if there is no gingival disease and if it is unrelated to the trauma of brushing. Repeated nose bleeds lasting more than 10 minutes despite compression suggest a local cause or an underlying bleeding disorder.

The haemostatic response to previous haemostatic challenges is informative, especially in mild conditions when spontaneous bleeding is rare. A history of excessive bleeding or recurrence of bleeding after dental extractions, circumcision, tonsillectomy, other previous surgical operations, and childbirth should be sought, as should a history of unexplained anaemia, gastrointestinal bleeding without the demonstration of a cause, and previous blood transfusion.

A drug history should be taken to assess intake of aspirin and non-steroidal anti-inflammatory drugs, and appropriate questioning will suggest causes for acquired haemostatic disorders, such as excessive alcohol intake, liver disease, or renal disease.

An inherited bleeding condition will result in a family history of the condition and suggest a pattern of inheritance—for example, autosomal dominant inheritance (both sexes affected) or X linked inheritance (only males affected).

In severe coagulation factor deficiency, such as haemophilia A or B, bleeding occurs primarily into muscles and joints, whereas in platelet disorders and von Willebrand's disease bleeding tends to be mucocutaneous—for example, nose bleeds, menorrhagia, and gum and gastrointestinal bleeding.

Laboratory investigation

The vast majority of important bleeding disorders can be excluded if the findings are all normal for blood and platelet counts; blood film; prothrombin time; activated partial thromboplastin time; fibrinogen or thrombin time; and bleeding time. These tests will reveal quantitative platelet disorders and congenital or acquired deficiency of coagulation factors, which can be confirmed by specific assay. The tests will not, however, detect all bleeding disorders, especially those due

History in bleeding disorders

- Abnormal bruising
- Abnormal bleeding from cuts and abrasions
- Nose bleeds
- Menorrhagia
- Haemarthrosis
- Bleeding after dental extraction
- Bleeding during childbirth
- Bleeding during surgery
- Previous anaemia and transfusions
- Drug history
- Family history

Persistent menorrhagia sufficient to cause iron deficiency anaemia may indicate a bleeding disorder if no structural uterine abnormality is present

Screening tests for bleeding disorders

<i>Test</i>	<i>Abnormality detected</i>
Blood count and film	Anaemia, leukaemia, disseminated intravascular coagulation
Platelet count	Thrombocytopenia
Activated partial thromboplastin time	Deficiency of all coagulation factors except VII, especially factors VIII and IX; heparin
Prothrombin time	Deficiency of factors I, II, V, VII, and X; warfarin
Thrombin time or fibrinogen	Hypofibrinogenaemia or dysfibrinogenaemia; heparin; fibrin degradation products
Bleeding time	Test of platelet-vessel wall interaction

to vascular causes and mild von Willebrand's disease, and patients with a strong personal or family history of the condition, despite normal screening investigation, should be referred for special management.

Congenital disorders

Haemophilia A and B are rare conditions with a combined incidence of about 1:10 000 of the population. They are due to a deficiency of coagulation factors VIII (haemophilia A) and IX (haemophilia B). As the genes for both proteins are on the X chromosome, both haemophilias have sex linked inheritance—the daughters of a man with haemophilia are therefore obligate carriers. Patients with severe haemophilia (less than 2% factor VIII or IX) have spontaneous bleeding into muscles and joints that can lead to a crippling arthropathy. Patients with moderate (2-5%) and mild (>5%) conditions usually bleed only after trauma or surgery. Management is highly specialised and consists of preventing or treating bleeding episodes with plasma derived or recombinant clotting factors.

Clinical features of coagulation factor deficiency and platelet type/von Willebrand's disease

	<i>Coagulation defect</i>	<i>Platelet/von Willebrand's disease</i>
<i>Bruises</i>	Large, on body and limbs	Small
<i>Bleeding from cuts</i>	Not severe	Profuse
<i>Nose bleeds</i>	Not common	Common, often prolonged and severe
<i>Gastrointestinal bleeding</i>	Uncommon, no underlying lesion	Common
<i>Haemarthrosis</i>	Common in severe haemophilia	Very uncommon
<i>Haematuria</i>	Common	Rare
<i>Bleeding after dental extraction and surgery</i>	Delayed 12-24 hours after haemostatic challenge	From time of challenge

Von Willebrand's disease is a common bleeding disorder with an incidence of up to 1% in some populations. Most cases are mild, with bleeding only after a haemostatic challenge. Inheritance is autosomal dominant, with males and females equally affected. The condition is due to a reduction or structural abnormality of von Willebrand's factor, which has the dual role of promoting normal platelet function and stabilising coagulation factor VIII. Von Willebrand's disease can give normal results on screening tests, and diagnosis may require specialist investigation. Most patients with mild disease respond to desmopressin (DDAVP), but clotting factor concentrates are needed for a minority.

Acquired disorders

Most proteins of the coagulation cascade and their regulators and inhibitors necessary for haemostasis are synthesised in the liver. Acquired abnormalities can be due to impaired synthesis, increased consumption, or rarely the formation of autoantibodies against coagulation proteins. Liver disease can cause a severe bleeding disorder, with prolongation of the prothrombin time particularly, often with coexistent thrombocytopenia due to excessive pooling of platelets in an enlarged spleen. Malabsorption of vitamin K from the gut can cause a coagulation disorder similar to that caused by ingestion of warfarin. Disseminated intravascular coagulation is a rare cause of an acquired severe systemic failure of haemostasis with simultaneous microvascular thrombosis and generalised bleeding. Overwhelming bacterial infections—for example, meningococcal septicaemia or disseminated malignancies (such

Patients who have unexplained abnormalities on screening investigations should be referred for special management

Clinical severity of haemophilia A and B

<i>Factor value*</i>	<i>Bleeding tendency</i>
<0.02	Severe—frequent spontaneous bleeding into joints, muscles, and internal organs
0.02-0.05	Moderate—some “spontaneous” bleeds, bleeding after minor trauma
>0.05	Mild—bleeding only after significant trauma or surgery

*Normal value of factors VIII and IX is 0.5-1.5

Acute haemarthrosis of knee joint.

Pathological bruising in von Willebrand's disease.

Acquired bleeding disorders

<i>Disease</i>	<i>Pathophysiology</i>
Liver disease and cirrhosis	Decreased synthesis of coagulation factors, thrombocytopenia
Gastrointestinal malabsorption	Vitamin K deficiency
Shock/sepsis/malignancy	Disseminated intravascular coagulation, increased consumption of coagulation factors and platelets
Renal disease	Acquired platelet dysfunction
Lymphoproliferative disorders/spontaneous	Acquired autoantibodies to specific coagulation factors (inhibitors)
Amyloidosis	Acquired factor X deficiency, blood vessel infiltration

as prostatic, pancreatic, and acute promyelocytic leukaemia)—are the most common causes. Renal disease causes a variable bleeding disorder primarily due to platelet dysfunction; advancing age, prolonged use of steroids, and vitamin C deficiency can all result in excessive bruising. Abnormal bleeding has been reported with myeloproliferative, myelodysplastic, and lymphoproliferative disorders.

Thrombosis

Arterial thrombosis

Arterial thrombosis results in myocardial infarction, stroke, and peripheral vascular disease. Atherosclerotic lesions form in the vessel wall, resulting in narrowing and subsequent plaque rupture, which cause vessel occlusion. Risk factors for atherosclerosis include smoking, hypertension, diabetes, hypercholesterolaemia, hyperlipidaemia, and hyperfibrinogenemia. Platelet deposition occurs on a ruptured atherosclerotic plaque, and the antiplatelet drug aspirin is widely used in the treatment and secondary prophylaxis of arterial thrombosis.

Venous thrombosis

Venous thrombosis results in deep vein thrombosis and pulmonary embolism and is due to a combination of blood stasis and hypercoagulability. The clinical diagnosis of venous thromboembolic disease is notoriously unreliable, and objective confirmation with ultrasonography or venography for deep vein thrombosis and ventilation perfusion scanning or pulmonary angiography for pulmonary embolus must be performed. Recently it has become clear that venous thrombosis is frequently due to a combination of environmental factors (such as surgery and pregnancy), with an underlying genetic predisposition due to inherited deficiencies or abnormalities of the proteins of the natural anticoagulant pathway, which functions to inhibit or limit thrombin formation.

The incidence of the recently described condition activated protein C resistance is 3–5% in white populations, and it is thus the commonest cause of an inherited predisposition to venous thrombosis (thrombophilia), despite being rare in other ethnic groups. All the hereditary thrombophilic conditions are autosomally dominantly inherited and are present in up to 50% of cases of venous thrombosis, particularly when recurrent, familial, or at a young age. Detection of one of these conditions should not only influence the future management of the individual with regard to thromboprophylaxis and anticoagulation but also initiate family screening. Unfortunately the presence of active thrombosis and treatment with both heparin and warfarin make testing for the above conditions unreliable, and testing should be delayed until active thrombosis has resolved and anticoagulants have been discontinued, although the genetic test for the factor V Leiden defect is not affected.

An acquired predisposition to both arterial and venous thrombosis occurs in the antiphospholipid syndrome, which can either be primary or secondary to an underlying collagen vascular disorder. Laboratory diagnosis of this condition entails the detection of antibodies to cardiolipin or a lupus anticoagulant, or both. The latter causes in vitro a prolonged activated partial thromboplastin time and a prolonged dilute Russell's viper venom test, which corrects with excess phospholipids, but is paradoxically associated in vivo with thrombosis. Lupus anticoagulants can also be induced by infections and drugs, and in these circumstances are not usually associated with thrombosis.

Contrast venogram showing extensive thrombosis with intraluminal filling defects and vessel occlusion.

Risk factors for venous thrombosis

Environmental

- Immobility
- Surgery, trauma
- Pregnancy, puerperium
- Long distance travel
- Use of combined oral contraceptives

Inherited

- Antithrombin deficiency
- Protein C deficiency
- Protein S deficiency
- Activated protein C resistance, factor V Leiden mutation

Acquired

- Antiphospholipid antibody, lupus anticoagulant
- Malignancy
- Myeloproliferative diseases

Clinical features of familial thrombophilia

- Family history of venous thromboembolism
- First episode at early age
- Recurrent venous thromboembolism
- Unusual site of thrombosis—for example, cerebral, mesenteric
- Thrombosis during pregnancy or puerperium
- Spontaneous venous thrombosis without environmental or acquired risk factor
- Recurrent superficial thrombophlebitis

Anticoagulation

Warfarin

Warfarin is an oral anticoagulant that results in the synthesis by the liver of non-functional coagulation factors II, VII, IX, and X, as well as proteins C and S, by interfering with vitamin K metabolism.

Warfarin prolongs the prothrombin time, and dosage monitoring is achieved by a standardised form of this test, the international normalised ratio.

Recommended target ranges and duration of treatment have been published; an international normalised ratio of 2 to 3 is adequate for most cases.

Recommended international normalised ratio ranges

2.0-3.0

- Treatment of deep vein thrombosis and pulmonary embolism
- Atrial fibrillation
- Mitral stenosis with embolism
- Transient ischaemic attack

3.0-4.5

- Recurrence of deep vein thrombosis or pulmonary embolism while taking warfarin
 - Mechanical prosthetic heart valves
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Warfarin treatment requires regular monitoring as over-treatment carries an important haemorrhagic risk, and warfarin requirements may be affected by intercurrent illness or concurrent drug treatment. Dental extraction or minor surgery is usually safe if the international normalised ratio is less than 2.5, whereas for major surgery warfarin should be discontinued and parenteral heparin substituted.

In pregnancy warfarin is absolutely contraindicated from six to 12 weeks of gestation as it may damage the fetus. Because warfarin crosses the placenta and affects the fetus heparin is increasingly being substituted throughout pregnancy as the drug of choice for thromboprophylaxis.

Reversal of a high international normalised ratio can be addressed in several ways, depending on the circumstances. In the absence of bleeding, omitting warfarin is usually sufficient. Minor bleeding episodes can be treated with local measures and small doses of vitamin K. Life threatening bleeding requires resuscitation of the patient together with treatment with coagulation factor concentrate; fresh frozen plasma can be used if concentrate is not available but is less effective.

Heparin

Heparin is a parenterally active anticoagulant that acts by potentiating the antithrombotic effects of antithrombin and can be used for both prophylaxis and treatment of venous thromboembolic disease. Unfractionated heparin is usually given intravenously and is monitored by prolongation of the activated partial thromboplastin time. It has a narrow therapeutic range with complex pharmacokinetics and great interpatient variation in dose requirements. Newer, low molecular weight heparins are replacing unfractionated heparin for both prophylaxis and treatment of venous thromboembolic disease. They can be administered by once daily subcutaneous injection without monitoring.

Intracerebral bleeding in patient taking warfarin.

Reversal of oral anticoagulation

<i>Condition</i>	<i>Treatment</i>
INR > 4.5 without bleeding	Stop warfarin transiently and review
INR > 4.5 with minor bleeding	Stop warfarin and consider small doses of intravenous vitamin K
Life threatening bleeding	Stop warfarin; give intravenous vitamin K 5 mg; give factor II, IX, X, and VII concentrate (50 units/kg factor IX) if available (if concentrate is unavailable give 15-25 ml/kg fresh frozen plasma)
Unexpected bleeding at any INR	Consider unsuspected underlying structural lesion

INR = international normalised ratio

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