Bleeding

By dr Alaa sadiq

Bleeding

- Bleeding can be due to congenital or acquired abnormalities in the clotting system.
- History and examination help to clarify the severity and underlying cause of the bleeding.
- Normal bleeding is seen following surgery and trauma.
- Pathological bleeding occurs when structurally abnormal vessels rupture or when a vessel is breached in the presence of a defect in haemostasis.
- This may be due to a deficiency or dysfunction of platelets, to the coagulation factors, or occasionally to excessive fibrinolysis,which is most commonly observed following therapeutic thrombolysis .

Clinical assessment

- 'Screening' blood tests do not reliably detect all causes of pathological bleeding (e.g.von Willebrand disease, scurvy, certain anticoagulant drugs
- A careful clinical evaluation is the key to diagnosis of bleeding disorders
- It is important to consider the following:

Site of bleeding. Bleeding into muscle and joints, along with retroperitoneal and intracranial haemorrhage, indicates a likely defect in coagulation factors.

Purpura, prolonged bleeding from superficial cuts, epistaxis, gastrointestinal haemorrhage or menorrhagia is more likely to be due to thrombocytopenia, a platelet function disorder or von Willebrand disease.

Recurrent bleeds at a single site suggest a local structural abnormality.

Duration of history. It may be possible to assess whether the disorder is congenital or acquired.

Precipitating causes. Bleeding arising spontaneously indicates a more severe defect than bleeding that occurs only after trauma.

Surgery. Ask about operations. Dental extractions,tonsillectomy and circumcision are stressful tests of the haemostatic system. Immediate post-surgical bleeding suggests defective platelet plug formation and primary haemostasis; delayed haemorrhage is more suggestive of a coagulation defect.

- In postsurgical patients, persistent bleeding from a single site is more likely to indicate surgical bleeding than a bleeding disorder.

Family history. While a positive family history may be present in patients with inherited disorders, the absence of affected relatives does not exclude a hereditary bleeding diathesis; about one-third of cases of haemophilia arise in individuals without afamily history, and deficiencies of factor VII, X andXIII are recessively inherited.

- Recessive disorders are more common in cultures where there is consanguineous marriage.

Drugs. Use of antithrombotic anticoagulant and fibrinolytic drugs must belicited.

- Drug interactions with warfarin and drug-induced thrombocytopenia should be considered.
- Some ‘herbal’ remedies may result in a bleeding diathesis.
- Clinical examination may reveal different patterns of skin bleeding.
- Petechial purpura is minor bleeding into the dermis that is flat and non-blanching .
- Petechiae are typically found in patients with thrombocytopenia or platelet dysfunction.
- Palpable purpura occurs in vasculitis Ecchymosis, or bruising, is more extensive bleeding into deeper layers of the skin.

- The lesions are initially dark red or purple but become yellow as haemoglobin is degraded.
- Retroperitoneal bleeding presents with a flank haematoma.
- Telangiectasia of lips and tongue points to hereditary haemorrhagic telangiectasia .
- Joints should be examined for evidence of haemarthroses.
- A full examination is important, as it may give clues to an underlying associated systemic illness such as a haematological or other malignancy, liver disease, renal failure, connective tissue disease and possible causes of splenomegaly.
- If the patient has a history that is strongly suggestive of a bleeding disorder and all the preliminary screening tests give normal results, further investigations, such as measurement of von Willebrand factor and assessment of platelet function, should be performed

Thrombocytopenia (low platelet count)

- A reduced platelet count may arise by one of two mechanisms:
- • decreased or abnormal production (bone marrow failure and hereditary thrombocytopathies
- increased consumption following release into the circulation (immune-mediated, DIC or sequestration).
- Spontaneous bleeding does not usually occur until the platelet count falls below 20 × 109/L, unless their function is also compromised.
- Purpura and spontaneous bruising are characteristic but there may also be oral, nasal, gastrointestinal or genitourinary bleeding.
- Severe thrombocytopenia (< 10 × 109/L) may result in retinal haemorrhage and potentially fatal intracranial bleeding, but this is rare.

- A blood film is the single most useful initial investigation. Examination of the bone marrow may reveal increased megakaryocytes in consumptive causes of thrombocytopenia, or the underlying cause of bone marrow failure in leukaemia, hypoplastic anaemia or myelodysplasia.
- Treatment (if required) depends on the underlying cause.
- Platelet transfusion is rarely required and is usually confined to patients with bone marrow failure and platelet counts below 10 × 109/L, or to clinical situations with actual or predicted serious haemorrhage.

Disorders of primary haemostasis

- The initial formation of the platelet plug also known as ‘primary haemostasis’) may fail in thrombocytopenia , von Willebrand disease and also in platelet function disorders and diseases affecting the vessel wall.

Vessel wall abnormalities

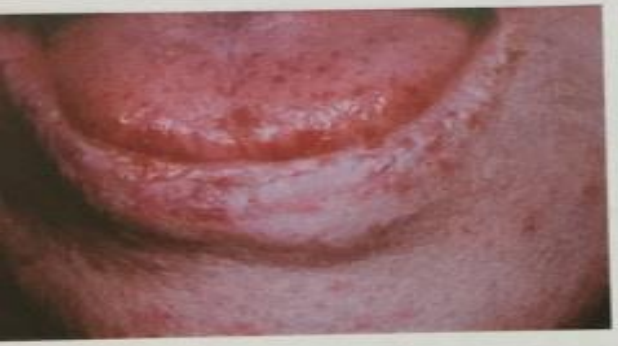
- Vessel wall abnormalities may be:

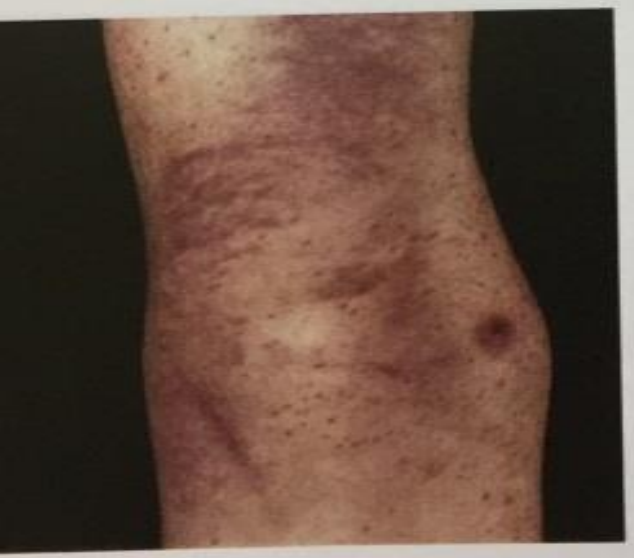
1. congenital, such as hereditary haemorrhagic telangiectasia
2. acquired, as in a vasculitis or scurvy.

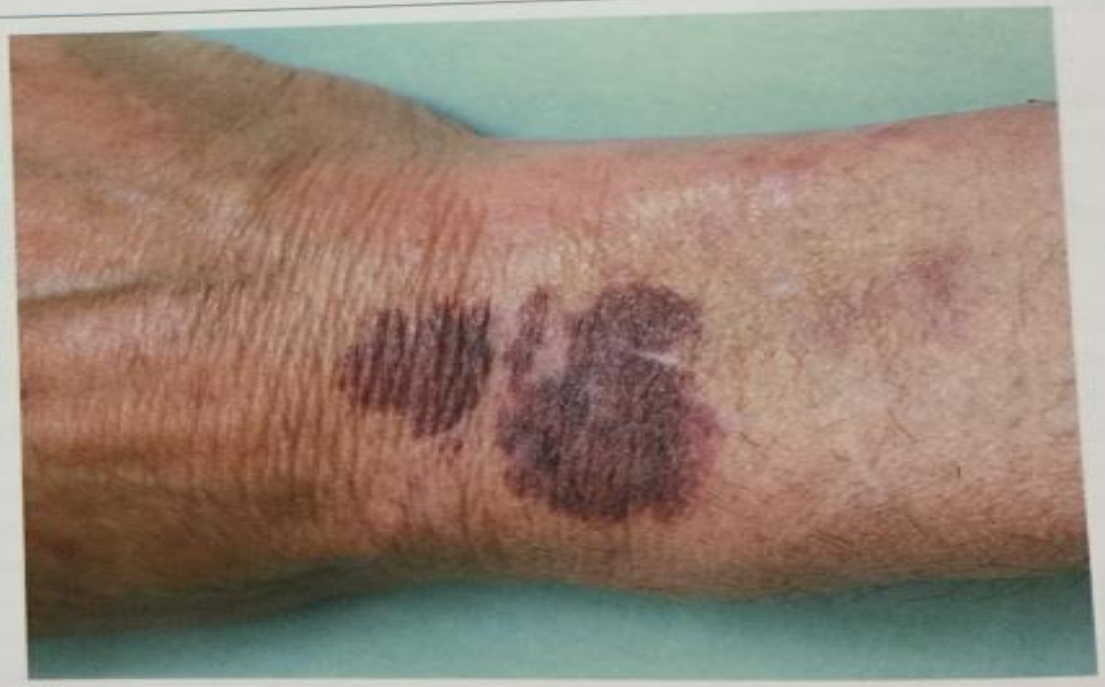
Hereditary haemorrhagic telangiectasia

- Hereditary haemorrhagic telangiectasia (HHT) is a dominantly inherited condition
- Telangiectasia and small aneurysms are found on the fingertips, face and tongue, and in the nasal passages, lung and gastrointestinal tract.
- A significant proportion of these patients develop larger pulmonary arteriovenous malformations (PAVMs) that cause arterial hypoxaemia due to a right-to-left shunt.
- These predispose to paradoxical embolism, resulting in stroke or cerebral abscess. All patients with HHT should be screened for PAVMs; if these are found, ablation by percutaneous embolisation should be considered. Patients present either with recurrent bleeds, particularly epistaxis, or with iron deficiency due to occult gastrointestinal bleeding.

- Treatment can be difficult because of the multiple bleeding points but regular iron therapy often allows the marrow to compensate for blood loss.
- Local cautery or laser therapy may prevent single lesions from bleeding.







(b)

Figure 25.1 **(a)** Hereditary haemorrhagic telangiectasia: the characteristic small vascular lesions are obvious on the lips and tongue. **(b)** Senile purpura. **(c)** Characteristic perifollicular petechiae in vitamin C deficiency (scurvy).

Ehlers–Danlos disease

- Vascular Ehlers–Danlos syndrome is a rare autosomal dominant disorder (1/100 000) which results in fragile blood vessels and organ membranes, leading to bleeding and organ rupture.
- The diagnosis should be considered when there is a history of bleeding but normal laboratory tests.

Scurvy

- Vitamin C deficiency affects the normal synthesis of collagen and results in a bleeding disorder characterised by petechial haemorrhage, bruising and subperiosteal bleeding. The key to diagnosis is the dietary history .

Platelet function disorders

- Bleeding may result from thrombocytopenia or from congenital or acquire abnormalities of platelet function. The most common acquired disorders are iatrogenic, resulting from the use of aspirin, clopidogrel, dipyridamole and the IIb/IIIa inhibitors to prevent arterial thrombosis .
- Inherited platelet function abnormalities are relatively rare.
- Congenital abnormalities may be due to deficiency of the membrane glycoproteins, e.g. Glanzmann's thrombasthenia (IIb/IIIa) or Bernard–Soulier disease (Ib), or due to the presence of defective platelet granules, e.g. a deficiency of dense (delta) granules giving rise to storage pool disorders.
- Apart from Glanzmann's thrombasthenia, these conditions are mild disorders, with bleeding typically occurring after trauma or surgery but rarely spontaneously.
- Glanzmann's is an autosomal recessive condition associated with a variable but often severe bleeding disorder.

- These conditions are usually managed by local mechanical measures, but antifibrinolytics, such as tranexamic acid, may be useful and, in severe bleeding, platelet transfusion may be required.
- Recombinant VIIa is licensed for the treatment of resistant bleeding in Glanzmann’s thrombasthenia.

Idiopathic thrombocytopenic purpura

- Idiopathic thrombocytopenic purpura (ITP) is mediated by autoantibodies, most often directed against the platelet membrane glycoprotein IIb/IIIa, which sensitise the platelet, resulting in premature removal from the circulation by cells of the reticulo-endothelial system.
- It is not a single disorder; some cases occur in isolation while others are associated with underlying immune dysregulation in conditions such as connective tissue diseases, HIV infection, B cell malignancies, pregnancy and certain drug therapies. However, the clinical presentation and pathogenesis are similar, whatever the cause of ITP

Clinical features and investigations

- The presentation depends on the degree of thrombocytopenia.
- Spontaneous bleeding typically occurs only when the platelet count is below 20 ×109/L. At higher counts, the patient may complain of easy bruising or sometimes epistaxis or menorrhagia.
- Many cases with counts of more than 50 × 109/L are discovered by chance.
- In adults, ITP more commonly affects females and may have an insidious onset.
- Unlike ITP in children, it is unusual for there to be a history of a preceding viral infection.
- Symptoms or signs of a connective tissue disease may be apparent at presentation or emerge several years later.
- Patients aged over 65 years should have a bone marrow examination to look for an accompanying B cell malignancy and appropriate autoantibody testing performed if a diagnosis of connective tissue disease is likely.

HIV testing should be considered.

- The peripheral blood film is normal, apart from a greatly reduced platelet number, whilst the bone marrow reveals an obvious increase in megakaryocytes

Management

- Many patients with stable compensated ITP and a platelet count of more than 30 × 109/L do not require treatment to raise the platelet count, except at times of increased bleeding risk, such as surgery and biopsy.
- First-line therapy for patients with spontaneous bleeding is with prednisolone

  1 mg/kg daily to suppress antibody production and inhibit phagocytosis of sensitised platelets by reticuloendothelial cells.
- Administration of intravenous immunoglobulin (IVIg) can raise the platelet count by blocking antibody receptors on reticuloendothelial cells, and is combined with corticosteroid therapy if there is severe haemostatic failure or a slow response to steroids alone.
- Persistent or potentially lifethreatening bleeding should be treated with platelet transfusion in addition to the other therapies.

- The condition may become chronic, with remissions and relapses.
- Relapses should be treated by reintroducing corticosteroids.
- If a patient has two relapses, or primary refractory disease, splenectomy is considered,
- Splenectomy produces complete remission in about 70% of patients and improvement in a further 20–25%, so that, following splenectomy, only 5–10% of patients require further medical therapy.
- If severe thrombocytopenia with or without significant bleeding persists despite splenectomy, second-line therapy with the thrombopoietin analogue romiplostim or the thrombopoietin receptor agonist eltrombopag should be considered
- Low-dose corticosteroid therapy, immunosuppressants such as rituximab, ciclosporin and tacrolimus should be considered in cases where the approaches above are ineffective.

Coagulation disorders

- Coagulation factor deficiency may be congenital or acquired, and may affect one or several of the coagulation factors Inherited disorders are almost uniformly related to decreased synthesis, as a result of mutation in the gene in coagulation.
- Von Willebrand disease is the most common inherited bleeding disorder.
- Haemophilia A and B are the most common single coagulation factor deficiencies, but inherited deficiencies of all the other coagulation factors are seen.
- Acquired disorders may be due to under-production (e.g. in liver failure), increased consumption(e.g. in disseminated intravascular coagulation) or inhibition of function (such as heparin therapy or immune inhibitors of coagulation, e.g. acquired haemophilia A).

24.66 Causes of coagulopathy

Congenital

X-linked
- Haemophilia A and B

Autosomal
- Von Willebrand disease
- Factor II, V, VII, X, XI and XIII deficiencies
- Combined II, VII, IX and X deficiency
- Combined V and VIII deficiency
- Hypofibrinogenaemia
- Dysfibrinogenaemia

Acquired

Under-production
- Liver failure

Increased consumption
- Coagulation activation
  - Disseminated intravascular coagulation (DIC)
- Immune-mediated
  - Acquired haemophilia and von Willebrand syndrome
- Others
  - Acquired factor X deficiency (in amyloid)
  - Acquired von Willebrand syndrome in Wilms tumour

Drug-induced

Inhibition of function
- Heparins
- Argatroban
- Fondaparinux
- Rivaroxaban
- Apixaban
- Dabigatran

Inhibition of synthesis
- Warfarin

Table 24.3 Screening tests used in the diagnosis of coagulation disorders (see also Fig. 24.10)

Screening tests	Abnormalities indicated by prolongation	Most common cause of coagulation disorder
Thrombin time (TT)	Deficiency or abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs	DIC Heparin therapy
Prothrombin time (PT)	Deficiency or inhibition of one or more of the following coagulation factors: VII, X, V, II, fibrinogen	Liver disease Warfarin therapy DIC
Activated partial thromboplastin time (APTT or PTTK)	Deficiency or inhibition of one or more of the following coagulation factors: XII, XI, IX (Christmas disease), VIII (haemophilia), X, V, II, fibrinogen	Haemophilia, Christmas disease (+ conditions above)
Fibrinogen quantitation	Fibrinogen deficiency	DIC, liver disease

DIC, disseminated intravascular coagulation; FDPs, fibrin degradation products.
N.B. Platelet count and the test-