Bleeding Disorders

Related synonyms: bleeding diathesis, clotting disorder, coagulation disorder, coagulopathy, haemostatic disorder

Bleeding disorders are usually taken to mean coagulopathies with reduced clotting of the blood but also encompass disorders characterised by abnormal platelet function or blood vessel walls that result in increased bleeding. Bleeding disorders may result from faults at many different levels in the coagulation process. They can range from severe and life-threatening conditions, such as haemophilia A, to much milder variants. Some bleeding symptoms (e.g., bruising without obvious cause, nosebleeds and heavy menstrual bleeding) are quite common in the general population and there is phenotypical variation even among individuals with defined bleeding problems. Investigation of mild bleeding problems often fails to provide a diagnosis.

The coagulation cascade

When a blood vessel is injured, a series of biochemical reactions is brought into play. This has been presented in the past as a coagulation 'cascade', describing a series of reactions necessary to achieve haemostasis by the development of a clot, stopping its formation at the right time and eventually facilitating clot dissolution when the vessel has healed. The scientific literature has moved towards the concept of a cell-based model which has more relevance to in vivo mechanisms (see below).

Nevertheless, the coagulation cascade is still useful in describing the sequence of events that occur in vitro and on which laboratory tests of coagulation are based.

Most of the proteins required for the cascade are produced by the liver as inactive precursors (zymogens) which are then modified into clotting factors. There are two routes for activation of the coagulation system: an intrinsic and an extrinsic pathway. The intrinsic pathway is activated by contact with collagen from damaged blood vessels (or indeed any negatively charged surface). The extrinsic pathway is activated by contact with tissue factor from the surface of extravascular cells.

Both routes end in a final common pathway - the proteolytic activation of thrombin and the cleaving of fibrinogen to form a fibrin clot. The intrinsic pathway is the main 'player' in this scenario, with the extrinsic pathway acting as an enhancer.

The cell-based model
The original cascade proposed by McFarlane in 1964 has been developed over the ensuing decades. A newer model describes the complex formed by tissue factor and factor VII. These participate in the activation of factor IX, indicating that the intrinsic and extrinsic coagulation pathways are linked almost from the outset. The new cascade model identifies a role for endothelial cells and details the influence of host factors, including the role of inflammation in coagulation.

Three stages are identified in the cell-based model in which it is envisaged that most of the processes involved occur at the cell surface level:

- **Initiation** - tissue injury exposes tissue factor (TF) to plasma. TF-expressing cells are found in the blood vessel walls but can also be induced in monocytes and TF-bearing microparticles derived from monocytes and platelets.
- **Amplification** - small amounts of thrombin induce platelet activation and aggregation and promote activation of factors V, VIII and XI on platelet surfaces.
- **Propagation** - this involves the formation of proteins (e.g., tenase, prothrombinase) ending in the formation of the thrombin clot.

Platelets are identified as having three functions - control of thrombin generation, support of fibrin formation and regulation of fibrin clot retraction. It has been postulated that different populations of platelets, with distinct surface properties, are involved in these coagulant functions.\(^4\)
Classification

Bleeding disorders can be classified as either congenital or acquired:

Congenital bleeding disorders

- Von Willebrand's disease (vWD) is the most common inherited bleeding disorder. Usually the condition is mild without spontaneous bleeding. It occurs equally in men and women and is caused by reduced production or abnormality of Von Willebrand's factor (vWF) that both promotes normal platelet function and stabilises factor VIII.
- Haemophilia A (factor VIII deficiency) and haemophilia B (factor IX deficiency or Christmas' disease) are the most well-known congenital bleeding disorders as well as notable examples of X-linked genetic disease.
- Other inherited bleeding disorders affecting the coagulation pathway are much rarer and inherited in an autosomal recessive fashion; for example, prothrombin (factor II) deficiency is found in about 1 in 2 million individuals.
- Platelet function disorders: rare autosomal recessive disorders affecting platelet membrane glycoproteins and causing abnormal platelet adhesion (eg, Bernard-Soulier syndrome), aggregation (eg, Glanzmann's thrombasthenia) or secretion.

Acquired disorders

- Liver disease and cirrhosis cause reduced synthesis of clotting proteins and thrombocytopenia.
- Vitamin K deficiency due to dietary deficiency, gastrointestinal malabsorption or absence of gut bacteria in infancy (vitamin K deficiency bleeding of the newborn).
- Shock, sepsis or malignancy can all cause an increased bleeding tendency, often through the final common pathway of disseminated intravascular coagulopathy (DIC) where simultaneous microvascular thrombosis and generalised bleeding occur due to massive consumption of coagulation factors or damage to vessel walls (for example, in meningococcal septicaemia).
- Renal disease: causes platelet dysfunction and reduced aggregation.
- Autoimmune: circulating autoantibodies to coagulation factors (eg, in lymphoma and systemic lupus erythematosus) or to platelets (as in immune thrombocytopenic purpura).
- Amyloidosis: where factor X deficiency occurs as well as hyperfibrinolysis and local infiltration of blood vessels.
- Vitamin C deficiency leads to weakened collagen and blood vessel fragility but can also cause diffuse haemorrhage in surgical patients.
- Advanced age can be associated with fragile veins.
- Prolonged steroid use is reputed to be associated with hypercoagulability and increased bleeding tendency. However, one study found that this effect was likely to be of limited clinical consequence.

Remember that some diseases can be associated with both bleeding and thrombosis - eg, polycythaemia vera and essential thrombocythaemia.

Presentation

Symptoms

- Bruising may be spontaneous or recurrent:
  - Large bruises on sun-exposed areas of limbs in the elderly are usually due to cumulative ultraviolet vessel damage to underlying elastin and are rarely significant.
  - Large bruises on the trunk are more indicative of a bleeding disorder.

- Prolonged bleeding:
  - After minor cuts or abrasions.
  - Nosebleeds lasting >10 minutes despite adequate compression (especially in children).
  - Severe menorrhagia causing anaemia, with normal uterus.
  - Bleeding from gums without gingival disease and unrelated to brushing.
  - Following dental extraction.
  - Postpartum haemorrhage.
  - After injections or surgical procedures.
Also enquire regarding:

- Current medication:
  - Including aspirin, clopidogrel, non-steroidal anti-inflammatory drugs, warfarin and other anticoagulants.
  - Complementary and alternative medicines - eg, garlic tablets, milk thistle.
  - Remember drug interactions between warfarin and other medications that prolong the international normalised ratio (INR).

- Family history of bleeding tendency.
- Alcohol intake.
- Other constitutional symptoms - eg, malaise, weight loss.
- Past history of thrombosis (can be suggestive of thrombophilia).
- Previous blood transfusions.
- Renal or hepatic impairment.

**Signs**

Systemically look for:

- Pallor.
- Sepsis.
- Haemodynamic status.
- Lymphadenopathy or hepatosplenomegaly.

Check:

- Skin, palate and gums for:
  - Bruising.
  - Petechia (non-blanching haemorrhagic spot <2 mm diameter).
  - Purpura (2-10 mm diameter).
  - Ecchymosis (>10 mm diameter).

- Fundi for retinal haemorrhages.
- Joints for haemarthrosis.
- Rectal or vaginal examination may be appropriate.

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<th>Coagulation factor defects</th>
<th>Platelet disorders and von Willebrand's disease</th>
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<td>Bruising on trunk and limbs</td>
<td>Large bruises</td>
<td>Small bruises</td>
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<tr>
<td>Bleeding from cuts</td>
<td>Relatively slight</td>
<td>Profuse</td>
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<tr>
<td>Nosebleeds</td>
<td>Uncommon</td>
<td>Common, frequently profuse and of long duration</td>
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<td>Gastrointestinal bleeding</td>
<td>Uncommon</td>
<td>Common</td>
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<tr>
<td>Haematuria</td>
<td>Common</td>
<td>Rare</td>
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<tr>
<td>Haemarthrosis</td>
<td>In severe haemophilia</td>
<td>Very rare</td>
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<tr>
<td>Bleeding after surgery or dental extraction</td>
<td>Up to a day's delay before bleeding occurs</td>
<td>Immediate bleeding</td>
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Investigations[1, 17]

- FBC, blood film and platelet count - may detect leukaemia, lymphoma, thrombocytopenia or abnormal platelets.
- Consider checking U&Es to exclude uraemia causing a platelet disorder.
- Consider LFTs to detect hepatic cause of acquired coagulation factor deficiency and alcohol-related damage.
- Bone marrow biopsy.

A coagulation screen usually involves taking blood in a mixture of citrate, EDTA and clotted sample bottles. It includes:

- **Activated partial thromboplastin time (APTT):**
  - This measures the **Intrinsic pathway** (which includes factors I, II, V, VIII, IX, X, XI and XII) and the common pathway.
  - A plasma sample is used and the intrinsic pathway is activated by adding phospholipid, an activator such as kaolin (which acts as a negatively charged surface) and calcium ions. The formation of prothrombinase complexes on the surface of the phospholipid enables the formation of thrombin and a subsequent clot. The result is reported as the time in seconds for this reaction.
  - The test is used to assess the overall competence of the coagulation system, as a routine test to monitor heparin therapy and as a pre-operative screen for bleeding tendencies. It will also reveal possible coagulation factor deficiencies, as in haemophilia A and B.

- **Prothrombin time (PT):**
  - This assesses the **extrinsic and final common pathway** of the coagulation cascade, thus can detect factor I, II, V, VII or X deficiency or the effects of warfarin.
  - It is performed by adding thromboplastin and calcium ions to a plasma sample. The time for clot formation is measured.
  - Prolonged time suggests the presence of an inhibitor to, or a deficiency of, one or more coagulation factors, the presence of warfarin, the existence of vitamin K deficiency or liver dysfunction.
  - The INR, used to monitor warfarin, is derived by comparing the patient's prothrombin time to that of a standardised sample.

- **Thrombin clotting time test:**
  - This measures the rate of a patient's clot formation compared with a normal plasma control. The plasma is first depleted of platelets and a standard amount of thrombin added.
  - The test is used in the diagnosis of DIC and other conditions that can affect fibrinogen level, such as liver disease.

- **Thromboelastometry:**
  - This is not generally part of the conventional screen but is increasingly recognised as important in the emergency situation[18].
  - It can help to differentiate between surgical or traumatic blood loss and coagulopathy and its use can guide the use of haemostatic therapy.

If the above tests are all normal, the vast majority of common haemostatic disorders will have been excluded. However, if symptoms persist and/or there is a suggestion of family history, patients should be referred to a haematologist for further tests which may include:

- The platelet function analyser (PFA), which has largely replaced the in vivo bleeding time test (see below), although it is not specific for, or predictive of, any particular disorder and its limitations need to be taken into account.[19, 20]
- **Bleeding time** - this tests the interaction between the platelets and the vessel walls. A standardised spring-loaded lancet is used to make a small cut in the patient's forearm and the time for the bleeding to stop is then measured. The test is not useful as a screening test, as it has a high false positive result. It is sometimes used in the investigation of vWD, although it has been largely superseded by the PFA.
- **Fibrinogen** - the level can be determined by immunological or functional assay. It is usually performed when APTT or PT screening tests are prolonged. The main disorders detected are afibrinogenaemia or hypofibrinogenaemia (due to absence or a low level of fibrinogen production) and dysfibrinogenaemia (due to a molecular alteration of fibrinogen, causing poor function). Differences in the level of fibrinogen measured by the two methods are suggestive of dysfibrinogenaemia[1].
- **Specific factor assays** - factors VIII or IX to determine severity of haemophilia; factor VIII and vWF in vWD.
- **Gene analysis looking for specific gene defects.**
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<th>Haemostasis tests in bleeding disorders[1, 21]</th>
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<tr>
<td><strong>Haemophilia A</strong></td>
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<td>Platelet count</td>
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<td>Normal</td>
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| **Haemophilia B**                            |
| Platelet count | Prothrombin time | Activated partial thromboplastin time | Bleeding time | Thrombin time | Additional tests |
| Normal                     | Normal          | Prolonged                              | Normal        | Normal        | Factor IX low    |

| **Von Willebrand's disease**                  |
| Platelet count | Prothrombin time | Activated partial thromboplastin time | Bleeding time | Thrombin time | Additional tests |
| Normal                     | Normal          | Prolonged or normal                   | Prolonged     |               | Von Willebrand's factor and factor VIII activity low and impaired ristocetin-induced platelet aggregation |

| **Liver disease**                             |
| Platelet count | Prothrombin time | Activated partial thromboplastin time | Bleeding time | Thrombin time | Additional tests |
| Low                        | Prolonged       | Prolonged                              | Normal (rarely prolonged) |               |                      |

| **Disseminated intravascular coagulopathy**   |
| Platelet count | Prothrombin time | Activated partial thromboplastin time | Bleeding time | Thrombin time | Additional tests |
| Low                        | Prolonged       | Prolonged                              | Grossly prolonged |               |                      |

| **Massive transfusion**                       |
| Platelet count | Prothrombin time | Activated partial thromboplastin time | Bleeding time | Thrombin time | Additional tests |
| Low                        | Prolonged       | Prolonged                              | Normal        |               |                      |

| **Oral anticoagulants**                       |
| Platelet count | Prothrombin time | Activated partial thromboplastin time | Bleeding time | Thrombin time | Additional tests |
| Normal                     | Grossly prolonged | Prolonged                              | Normal        |               |                      |

| **Heparin**                                  |
| Platelet count | Prothrombin time | Activated partial thromboplastin time | Bleeding time | Thrombin time | Additional tests |
| Normal (rarely low) | Mildly prolonged | Prolonged                              | Prolonged     |               |                      |

### Management

Management is dependent on the underlying condition - see separate Haemophilia A (Factor VIII Deficiency), Haemophilia B (Factor IX Deficiency) and Von Willebrand's Disease articles.

Whilst the sex-linked nature of haemophilia results in those affected being predominantly male, women are much more likely to present with mild bleeding disorders due to the demands of menstruation and childbirth. Menorrhagia can be tackled by standard means - see separate Menorrhagia article.

### Prevention

Those with serious inherited bleeding disorders may want genetic counselling and prenatal diagnosis[22].

### Further reading & references

- Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders; United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO)
- The Haemophilia Society
- Canadian Hemophilia Society


15. Karnath B; Easy Bruising and Bleeding in the Adult Patient, 2005.


21. Handbook of Diagnostic Hemostasis and Thrombosis Tests; University of Washington Department of Laboratory Medicine Reference Laboratory Services, 2005


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