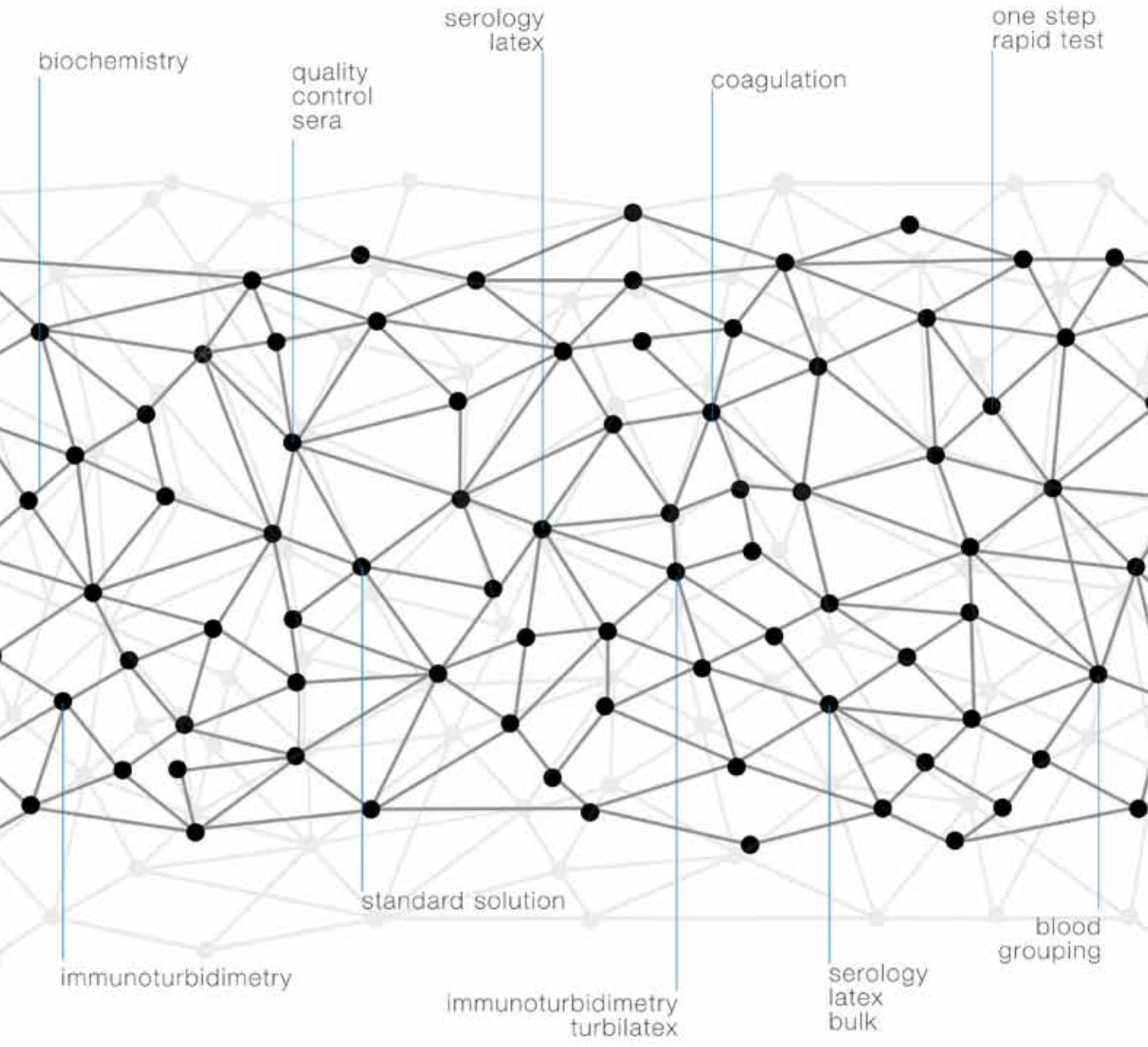
CHRONOLAB

CHRONOLAB SYSTEMS



Acquired disorders of coagulation

Vickie McDonald

Abstract

Normal coagulation is a delicate balance between pro- and antithrombotic mechanisms. Haemorrhage results from dysfunctional/absent procoagulant mechanisms and can be caused by inherited or acquired factors. The most common acquired abnormalities seen in the clinical setting are covered in this article, including vitamin K deficiency, warfarin therapy, liver disease, direct oral anticoagulants, disseminated intravascular coagulation, platelet disorders and vascular disorders. Patients bleeding on warfarin therapy need urgent international normalized ratio testing and reversal with vitamin K and/or prothrombin complex concentrate. Patients bleeding while taking direct oral anticoagulants need a wider approach. Liver disease results in complex haemostatic changes, and the management of bleeding depends on the site and severity of bleeding. Disseminated intravascular coagulation can complicate many clinical situations and needs prompt action when patients are bleeding. Acquired dysfunction of platelets is commonly encountered in clinical practice, often in association with drug therapy such as aspirin.

Keywords Antiplatelet drugs; apixaban; bleeding; dabigatran; direct oral anticoagulants; disseminated intravascular coagulation; edoxaban; liver disease; rivaroxaban; vascular abnormalities; vitamin K deficiency; warfarin

Key points

- Acquired disorders of coagulation are more common than inherited disorders in general clinical practice
- Anticoagulants and antiplatelet drugs are commonly prescribed and frequently a cause for bruising and bleeding
- Where there is major bleeding, the effects of warfarin should be reversed with prothrombin complex concentrate and vitamin K
- Detecting the presence of the new direct oral anticoagulants is not always easy. Management of major bleeding is complex and should be undertaken in conjunction with a specialist

Introduction

The normal coagulation process is a delicate balance between pro- and antithrombotic mechanisms involving coagulation factors, platelets and the vascular endothelium. When there is deficiency or dysfunction of elements of coagulation, haemorrhagic disorders result. Acquired disorders of coagulation are much more common than inherited disorders, and while they can share common laboratory abnormalities, there are a wide range of causes (Table 1), with varying clinical presentations. Assessment of patients with bleeding or bruising requires careful history-taking and a thorough investigation before performing laboratory investigations.

History

Establish the type of bleeding, precipitating factors and severity and frequency of bleeding. The patient's medical history can provide a clue to, for example, liver or kidney disease. A thorough drug history is critical.

Examination

Look for evidence of associated systemic disease, such as signs of liver disease or lymphadenopathy. Examine the mucosal surfaces such as the skin, mouth and joints for bruises, petechiae and signs of bleeding. Bruises suggestive of an abnormal bleeding tendency are usually large, and occur with minimal trauma and in atypical sites, such as the trunk.

Investigations

Initial investigations should include:

- full blood count and blood film examination
- coagulation screen
  - prothrombin time (PT)
  - activated partial thromboplastin time (APTT)

Causes of acquired disorders of coagulation

- Vitamin K deficiency and warfarin (or other vitamin K antagonists)
- Liver disease
- Direct oral anticoagulant drugs
- Disseminated intravascular coagulation
- Massive blood loss and massive transfusion
- Platelet disorders
  - Drugs
  - Uraemia
  - Cardiopulmonary bypass
  - Myeloproliferative neoplasms
- Vascular disorders
  - Corticosteroids
  - Henoch–Schönlein purpura
  - Scurvy (vitamin C deficiency)

Causes of abnormal coagulation in liver disease

- Defective synthesis of coagulation factors and natural anticoagulants
  - Includes protein C and S
- Thrombocytopenia due to portal hypertension, hypersplenism and reduced thrombopoietin production
- Vitamin K deficiency from malabsorption
  - Leading to reduced factors II, VII, IX and X
- Abnormal fibrinolysis and/or intravascular coagulation
  - Can lead to reduced fibrinogen

Table 1

Vickie McDonald *MA PhD MRCP FRCPath is a Consultant Haematologist at Guy's and St Thomas' NHS Foundation Trust, London, UK.*
Competing interests: none declared.

- Clauss fibrinogen
- if PT or APTT are prolonged, a 50/50 mix of the patient's plasma with normal plasma to distinguish between an inhibitor and a clotting factor deficiency

- renal and liver function.

Additional investigations, such as factor assays or platelet studies, depend on the initial history, examination and baseline investigations.

Vitamin K deficiency and warfarin therapy

Vitamin K is essential for the function of coagulation factors II, VII, IX and X and anticoagulant proteins C and S. Deficiency occurs as a result of malabsorption or dietary deficiency and leads to a prolonged PT. Neonates are born with a low vitamin K concentration and are at risk of haemorrhage if this is not supplemented.[1]

Warfarin inhibits the effect of vitamin K on clotting factors, thereby reducing functional factor concentrations. Its effect on coagulation is monitored by the international normalized ratio (INR). Warfarin is affected by many things including diet and other drugs, so the INR can fluctuate over time. The risk of major haemorrhage in patients taking warfarin is about 2% per year and goes up with increasing INRs.

The management of bleeding when taking warfarin depends on the INR and severity of bleeding.[2] With an isolated high INR and no bleeding, warfarin should be suspended until the INR falls back into range. If the INR is over 5.0, small doses (1 or 2 mg orally) of vitamin K may be needed, with the INR retested 24 hours later. For major bleeding, rapid reversal with prothrombin complex concentrate (PCC), which contains factors II, VII, IX and X, is required. PCC acts quickly and a repeat INR can be performed 10 minutes after administration to see its effect; however, the response lasts only a few hours, and vitamin K should be given alongside to establish a more durable reduction in the INR.[2] Fresh frozen plasma (FFP) is no longer recommended for the reversal of warfarin.[2] PCC is associated with potential for thrombosis so is used with caution in some groups.

Liver disease

Abnormal haemostasis in liver disease is usually multifactorial (Table 1) and not all patients have associated bleeding.[3]

Laboratory abnormalities that can be seen include:

- prolonged PT: owing to vitamin K deficiency leading to reduced synthesis of factors II, VII, IX and X
- prolonged APTT and PT: from reduced synthesis of all clotting factors
- reduced fibrinogen because of disseminated intravascular coagulation (DIC)
- prolonged thrombin time due to dysfibrinogenaemia
- reduced protein C and S concentrations
- low platelet count.

The management of bleeding depends on its site and severity. Vitamin K 10 mg (orally or intravenously) for 3 days can help patients who have vitamin K deficiency. In life-threatening or major bleeding, any potential source of bleeding, such as varices, should be sought and treated. Platelets should be given if the platelet count is below $50–100 \times 10^9$/litre, but recovery can be poor if splenomegaly is present. FFP can be used to replace clotting factors in major haemorrhage when the PT (±APTT) is prolonged, but large volumes are often required. PCC has been used off-licence in patients with liver disease who are bleeding, but this use should be discussed with a haematologist or expert in this area. In addition, fibrinogen replacement with cryoprecipitate (or off-licence use of fibrinogen concentrate) may be required in those patients with low fibrinogen concentration.

Direct oral anticoagulants

The advent of the direct oral anticoagulants is changing the face of anticoagulation. These medicines directly inhibit either factor IIa (e.g. dabigatran) or Xa (e.g. rivaroxaban, apixaban, edoxaban). They have more predictable pharmacokinetics than warfarin with fewer drug interactions, and are reported to have preferable major bleeding rates (particularly intracranial bleeding) compared with warfarin. They all affect coagulation testing, but in a variable manner (summarized in Table 2). Monitoring of these drugs is not routine; if required, it should be discussed with a haematologist.

Minor bleeding episodes when taking these drugs can usually be managed with drug cessation. The management of major bleeding on these drugs is briefly summarized in Table 2.[4] Drug cessation and simple local measures are first line, with the additional of tranexamic acid and supportive transfusions as required. Off-licence use of PCC should be considered, except in the case of dabigatran, for which the reversal agent idarucizumab (Praxbind®) should be used.[5] Dabigatran can also be removed from the circulation with dialysis. Studies of reversal agents for Xa inhibitors are underway, and these cannot be removed by dialysis.

Effects of direct oral anticoagulants on standard coagulation assays and management of major bleeding

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Effect on PT	Prolongs	Prolongs but not sensitive at low concentrations	Prolongs	Prolongs
Effect on APTT	Prolongs but varied results	Prolongs but varied results	Prolongs but varied results	Prolongs but varied results
Management of major bleeding	• Local haemostatic measures • Tranexamic acid • Reversal with idarucizumab • Consider dialysis	• Local haemostatic measures • Tranexamic acid • PCC[a]	• Local haemostatic measures • Tranexamic acid • PCC[a]	• Local haemostatic measures • Tranexamic acid • PCC[a]

APTT, activated partial thromboplastin time; PCC, prothrombin complex concentrate; PT, prothrombin time.
[a] Off-licence use.

Table 2

Disseminated intravascular coagulation

DIC results from inappropriate and excessive activation of the haemostatic system (see Further reading). It can lead to thrombosis, haemorrhage or both; purpura fulminans is the syndrome of DIC with skin necrosis. There are many triggers, including trauma, infection, malignancy and placental abruption.

Activation of coagulation leads to microthrombus formation with subsequent consumption of clotting factors and increased breakdown of fibrin. The clotting factors become depleted, platelets are consumed, and fibrin deposition in the circulation reduces tissue perfusion and causes mechanical haemolysis. The patient can bleed from any site, but this is often mucocutaneous. The clotting screen shows a prolonged APTT, with or without a prolonged PT, and low fibrinogen. In addition, investigations show thrombocytopenia, anaemia from red cell breakdown (microangiopathic haemolytic anaemia) and raised D-dimer concentrations. Emergency management is discussed in *MEDICINE* 2017; 45(5).

Massive blood loss

Causes of abnormal clotting after massive blood loss include dilution, hypocalcaemia and acidosis; these are discussed in *Blood transfusion* on pages 244–250 of this issue and also in the article on Emergency management in *MEDICINE* 2017; 45(5).

Acquired disorders of platelet function

Acquired platelet disorders (listed below) are much more common than congenital ones (see *Inherited Bleeding Disorders* on pages 229–232 of this issue):

- **Antiplatelet drugs** (e.g. aspirin) irreversibly acetylate platelet cyclooxygenase, impairing thromboxane A2 production and platelet aggregation. The effects of aspirin last approximately 7–10 days. Low-dose aspirin can prevent thrombosis, but can lead to haemorrhage, especially from the gastrointestinal tract. Other antiplatelet drugs include dipyridamole, which inhibits phosphodiesterase, clopidogrel and glycoprotein (GP)IIb/IIIa inhibitors.
- **Uraemia** can result in a functional defect in platelets that may improve with dialysis or desmopressin (DDAVP).
- **Cardiopulmonary bypass circuits** can result in platelet trauma, leading to thrombocytopenia, platelet fragmentation and platelet function abnormalities (see Further reading). With excessive bleeding, platelet transfusions can be required.
- **Myeloproliferative disorders** can be associated with abnormal platelet function, which can result in thrombosis or haemorrhage (see Further reading). Haemostasis usually improves with correction of the platelet count.

Vascular disorders

Intact vascular endothelial function and the ability of vessels to contract are essential in controlling blood loss. Abnormal vessel walls can result in excessive bleeding and routine clotting tests are normal. Acquired disorders include corticosteroid-induced purpura, Henoch–Schönlein purpura and scurvy, which leads to an acquired collagen abnormality. ◆

KEY REFERENCES

1 Shearer MJ. Vitamin K deficiency bleeding (VKDB) in early infancy. *Blood Rev* 2009; **23:** 49–59.
2 Keeling D, Baglin T, Tait C, et al. Guidelines on oral anticoagulation with warfarin – fourth edition. *Br J Haematol* 2011; **154:** 311–24.
3 Lisman T, Caldwell SH, Burroughs AK, et al. Hemostasis and thrombosis in patients with liver disease: the ups and downs. *J Hepatol* 2010; **53:** 362–71.
4 Makris M, Van Veen J, Tait C, et al. Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol* 2012; **16:** 35–46.
5 Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015; **373:** 511–20.

FURTHER READING

Linden MD. The hemostatic defect of cardiopulmonary bypass. *J Thromb Thrombolysis* 2003; **16:** 129–47.
Tefferi A. Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol* 2012; **87:** 285–93.