Inherited bleeding (haemostatic) and clotting (thrombotic) disorders are rare but sometimes encountered by anaesthetists during emergency or elective surgeries. The perioperative management of these uncommon conditions can be challenging. In this article, we discuss the most common inherited coagulation disorders, their pathophysiology, and perioperative anaesthetic considerations.

Inherited bleeding disorders

The most frequent inherited bleeding disorders and their inheritance are summarized in Table 1. Of all the congenital bleeding disorders, haemophilia and von Willebrand’s disease (VWD) are the most common.

Pathophysiology and diagnosis

Haemophilia

Haemophilia can be classified as haemophilia A, B, or C depending on the deficiency of the coagulation factors VIII, IX, or XI respectively. Haemophilia A and B are inherited as X-linked recessive (XLR) disorders due to mutation in the long arm of chromosome X at F8 and F9 genes, respectively.1 As with any XLR disorder, males are affected and females are carriers. One-third of the patients presenting with haemophilia have no family history.

Factors VIII and IX mainly play an important role in the intrinsic pathway of the clotting cascade. These factors are required for thrombin generation and fibrin formation. The plasma concentration of factors VIII and IX can be expressed in IU ml⁻¹ or as percentages of normal pooled plasma. 1 IU is the concentration of coagulation factor in 1 ml of normal pooled plasma. The normal value is 0.5–1.5 IU ml⁻¹ or 50–150%.

Diagnosis of haemophilia is usually suspected when bleeding symptoms occur spontaneously or after trauma. The risk of bleeding increases as the factor levels decrease (Table 2). Patients usually present with bleeding into the weight-bearing joints (knees, ankles and elbows), muscles and rarely the genitourinary system. The most common cause of death is intracranial bleed. The routine clotting screen may be normal and the only abnormality may be a prolonged activated partial thromboplastin time. The definitive diagnosis is made only by a factor level assay.

Von Willebrand’s disease

VWD is the most common of inherited bleeding disorders. The prevalence of VWD is one in 100 but is asymptomatic in the majority of patients and is clinically significant in only one in 10 000 patients.2,3 VWD is caused by either a quantitative or qualitative defect in von Willebrand’s factor (VWF). VWF is a plasma glycoprotein which plays a vital role in platelet adhesion, aggregation, and also acts as a carrier for factor VIII and thereby decreasing its clearance from plasma. VWF is synthesized in bone megakaryocytes and vascular endothelium and stored in Weibel–Palade bodies in the endothelial cells. Deficiency of VWF leads to easy bruising from trivial trauma; in particular, bleeding from mucosal surfaces, that is, epistaxis, gums, and bowel. Depending upon the type of VWD, patients can have prolonged bleeding after surgery. Of all blood groups, people with blood group O tend to have low VWF levels.

VWD is classified by the International Society on Thrombosis and Haemostasis (ISTH) based on quantitative or qualitative defect of VWF into three types.2 In type 1 VWD, there is a quantitative defect, whereas in type 2 VWD, there is a qualitative defect. Type 2 is further subclassified into four types (type 2A, 2B, 2M, 2N) depending upon the associated platelet binding and function, factor VIII binding
capacity, and number of high molecular weight VWF multimers. In type 3 VWD, there is a complete absence of VWF. Type 1 VWD is a mild–moderate bleeding disorder, whereas type 3 VWD is a severe bleeding disorder. VWD shows autosomal inheritance (dominant or recessive) depending on the subtype. Often the only abnormality is a prolonged bleeding time as normal screening tests do not rule out VWD (Table 3). In general, lab diagnosis of VWD is made with quantitative factor VIII, VWF, collagen binding assays, ristocetin cofactor activity, and multimeric analysis. The qualitative assays include tests such as glycoprotein binding assay, ristocetin cofactor activity (VWF:RCo), and ristocetin-induced platelet agglutination.3

**Anaesthetic considerations**

**Preoperative assessment**

A detailed history about the type of haemophilia and VWD and its severity must be obtained. Prior information about response to DDAVP, use of recombinant factors VIII and IX, and previous transfusion of blood will be useful. A complete blood count, coagulation profile and fibrinogen level, and specific factor assays must be done if indicated. All patients must be evaluated for the presence of transfusion-related infections such as HIV and hepatitis B and C. Examination for the presence of joint deformities, contractures, and a thorough airway assessment. Preoperative assessment ideally must be done by a team of haematologist, surgeon, and anaesthetist, so that a tailored individual plan is formulated and discussed with the patient.

**General principles**

- Multidisciplinary management comprising haematologist, surgeon, anaesthetist, physiotherapist, and occupational therapist.
- Liaison with laboratory services to ensure that appropriate factor concentrates are available and in sufficient quantity.
- Elective surgery scheduled early during the week and preferably in the morning.
- Preoperative clotting screen and specific factor assays depending on the type of bleeding disorder and preoperative transfusion of recombinant factors 30–60 min before the surgical procedure.
- Perioperative avoidance of mucosal trauma, i.m. injections, maintenance of normothermia, and pressure point care.
- Care with vascular access and invasive monitoring. Consider early use of ultrasound.
- Avoidance of tachycardia and hypertension.
- Risk–benefits for neuraxial block and regional blocks need to be assessed individually and in general avoided.
- Early mobilization, consider mechanical deep venous thrombosis prophylaxis. Risk–benefits of pharmacological methods must be considered and discussed with the surgeon and haematologist.
- Multimodal pain management, avoid non-steroidal anti-inflammatory drugs.

**Specific management**

**Haemophilia**

Before introduction of viral inactivation methods, the most common cause of death in haemophilic was due to transfusion of transmitted viral infections such as Hepatitis C and HIV. The general move over the years has been away from pooled plasma products to recombinant factors.

Patients with haemophilia need 80–100% correction of their factor VIII before any major surgical procedure and this must be confirmed before surgery. Postoperatively, levels should be maintained for up to 6 weeks after orthopaedic procedures and 1–2 weeks for other procedures.1,4,5

**Factors and blood products**

(i) Recombinant factors VIII and IX: this is mainly helpful in haemophilia A and B. Commercial preparations of factors VIII

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**Table 1** Inherited bleeding disorders. XLR, X-linked recessive; AD, autosomal-dominant; AR, autosomal-recessive; VWF, von Willebrand’s factor

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Primary defect</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilia A</td>
<td>XLR</td>
<td>Factor VIII deficiency</td>
<td>1/5000 male births</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>XLR</td>
<td>Factor IX deficiency</td>
<td>1/25 000 male births</td>
</tr>
<tr>
<td>Haemophilia C</td>
<td>AR/AD</td>
<td>Factor XI deficiency</td>
<td>1/10 000</td>
</tr>
<tr>
<td>Von Willebrand’s disease</td>
<td>AR/AD</td>
<td>VWF qualitative or quantitative defect</td>
<td>&lt; 1/million</td>
</tr>
<tr>
<td>Rare bleeding disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor II, V, VII, X, XIII deficiency</td>
<td>AR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysfibrinogenaemia</td>
<td>AD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Grading of severity of haemophilia

<table>
<thead>
<tr>
<th>Haemophilia (A, B, or C)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>% activity of factors</td>
<td>5–40</td>
<td>1–5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Factor levels (IU ml⁻¹)</td>
<td>0.05–0.40</td>
<td>0.01–0.05</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Table 3** Screening blood tests in haemophilia and von Willebrand’s disease (VWD)

<table>
<thead>
<tr>
<th>Test</th>
<th>Haemophilia</th>
<th>VWD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Normal</td>
<td>Normal or reduced</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>Normal</td>
<td>Normal or prolonged</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Activated partial thromboplastin time</td>
<td>Prolonged</td>
<td>Normal or prolonged</td>
</tr>
</tbody>
</table>
Anaesthetic considerations

and IX as lyophilized powder are available. It is free from the risk of disease transmission as seen with blood products, but the limiting factor being its cost. The dosage of factors is as follows:

- Each FVIII unit per kilogram of body weight infused i.v. will raise the plasma FVIII level by \( \sim 2\% \) (t\(_{1/2}\) factor VIII = 8–12 h).
- No of units of FVIII required = weight of patient \( \times \% \) factor level desired \( \times 0.5 \).
- Each FIX unit per kilogram of body weight infused i.v. will raise the plasma FIX level \( \sim 1\% \) (t\(_{1/2}\) factor IX = 18–24 h).
- No of units of FIX required = weight of patient \( \times \% \) factor level desired.

Patients must be screened for the presence of inhibitors to factor VIII or IX. Depending upon the amount of inhibitors present, patients are classified as low risk (inhibitor level \( < 5 \) Bethesda units ml\(^{-1}\)) or high risk (\( > 5 \) Bethesda units ml\(^{-1}\)). The low-risk group requires higher dose of the deficient factor, but the high-risk group requires approved alternative regimens like recombinant activated factor VII (rFVIIa) or Factor Eight Inhibitor Bypassing Activity (FEIBA).

(ii) Intermediate and high purity factor VIII concentrates: plasma derived, can have other non-factor VIII proteins, alternative when recombinant factors are not available.

(iii) Cryoprecipitate: it is a source of factor VIII, VWF, factor XIII, and fibrinogen. It carries a risk of transmission of blood-borne infections and must be used only when recombinant factors are not available. Methylene blue-treated non-UK sourced cryoprecipitate is used for children < 16 yr old.

(iv) Prothrombin complex concentrate (PCC): it is a combination of blood clotting factors II, VII, IX, and X, protein C and S. Although the current main indication of PCC is for emergency reversal of warfarin therapy, PCC were initially developed for treatment of haemophilia B; they have been sparingly used after the development of highly purified and recombinant factors. Its thrombogenic calculated units are based on factor IX levels. The dosage is 15–50 units kg\(^{-1}\) (maximum 5000 units stat). Most PCC contain heparin to prevent activation of the factors. The plasma-derived activated PCCs (FEIBA) are licensed for use in patients with inhibitors to factor VIII and IX. Commercially available products include Beriplex\(^{\text{®}}\) and Octaplex\(^{\text{®}}\) and differ in the concentrations of the factors, manufacturing process, methods for viral inactivation, and dosage.

(v) Recombinant factor VIIa: it can bind to the surface of activated platelets, thereby directly activating factor X and leading to an improved generation of thrombin. rFVIIa has been shown to be effective in achieving haemostasis in haemophilia patients with inhibitors in about 80% of cases. The thrombogenic activity of rFVIIa is optimized when fibrinogen levels and pH are within the normal range. It is also licensed for use in platelet dysfunctional disorders (Glanzmann’s thromboasthenia) and FVII deficiency.

Fresh-frozen plasma is no longer used in perioperative management of haemophilia as it carries the risk of blood-borne infections and volume overload.

Pharmacological options

(i) Desmopressin (1-desamino-8- d-arginine vasopressin) or DDAVP: is an analogue of vasopressin hormone; it acts by releasing VWF which in turn forms a complex with factor VIII, thereby preventing its breakdown. It is mainly used in treatment of mild form of haemophilia A and VWD. DDAVP produces a two- to five-fold increase in factor VIII levels which may be sufficient in mild haemophilia for minor surgery. It is ineffective in severe haemophilia A or in haemophilia B. It is available as intranasal spray, oral or sublingual tablet, or i.v. preparation. The peak effect of i.v. dose is at 60 min and s.c./intranasal is 90–120 min. The i.v./s.c dose is 0.3 \( \mu \)g kg\(^{-1}\). Adult nasal spray dosage of 300 \( \mu \)g is equivalent to the standard i.v. dose of 0.2 \( \mu \)g kg\(^{-1}\). A dose of 300 \( \mu \)g for those over 50 kg and 150 \( \mu \)g for those up to 50 kg is suggested. DDAVP is not approved for use in children < 2 yr or in pregnant women.

(ii) Tranexamic acid: it is a synthetic derivative of amino acid lysine. Its antifibrinolytic action is due to competitive inhibition of conversion of plasminogen to plasmin which degrades fibrin. The plasma half-life is 2 h. The optimal dosage is unknown and has been successfully used in a wide dose range. It can be used orally (15–25 mg kg\(^{-1}\) 8th hourly) or i.v. (10 mg kg\(^{-1}\) 8th hourly). Conventional oral dosage is 3 g in three divided doses. It should be avoided in patients with haematuria due to obstructive uropathy. It is helpful in both haemophilia and VWD.

Von Willebrand’s disease

The majority of cases of VWD do not need blood components to control haemorrhage, pharmacological management would suffice. In the high-risk subtypes, it is recommended that the VWF:RCo level is maintained at about 100 IU dl\(^{-1}\) perioperatively and > 50 IU dl\(^{-1}\) in the immediate postoperative period. The FVIII plasma concentration should be above 100 IU dl\(^{-1}\) to cover major surgery and sustained above 50 IU dl\(^{-1}\) in the postoperative period. Major surgery requires treatment for 7–14 days and minor surgery for 1–5 days.

(i) DDAVP: it is approved for use in VWD type 1 and is of no use in type 3 VWD; its use in type 2 VWD must be discussed with a haematologist because of variable effect according to subtypes and its capacity to cause thrombocytopenia. DDAVP must be given at least 90 min before operation in the above-mentioned doses. Further doses may not be beneficial due to rapid tachyphylaxis. DDAVP infusion can cause hypotension, facial flushing, and hypotraemia. Consider fluid restriction.

(ii) Antifibrinolytics: Tranexamic acid in the above mentioned doses may be useful.
(iii) VWF/factor VIII concentrates: indicated in severe cases, type 3 VWD, and qualitative defects of VWF. These concentrates are derived from pooled plasma and are subjected to viral inactivation methods. Various preparations with different ratios of VWF/factor VIII:C and fibrinogen levels are available (Humate P® and Alphanate SD/HT®). Products like recombinant factor VIII which contain no VWF are not used in VWD. Venous thromboembolism (VTE) can occur with replacement therapy.³

Allo-antibody formation occurs in 10–15% of type III VWD. In patients with inhibitors, there is very limited experience reported in the literature but recombinant VIIIa (rVIIa) and continuous infusion of high doses of rFVIII have been successfully used.

(iv) Platelet infusions: should be considered if bleeding persists, despite DDAVP and replacement VWF concentrates.

(v) Cryoprecipitate: unpredictable effect. Risk of transmissible infections. Should not be used for management of VWD unless other treatment modalities have failed.

Special population and situations

Regional anaesthesia

Although there are guidelines about the use of regional anaesthesia in patients on anticoagulants, there are no clear-cut guidelines in patients with coagulation disorders. There are case series and reports of central neuraxial blocks with catheters in haemophiliac patients undergoing lower limb orthopaedic surgeries after correction of factor levels, but there are no randomized controlled trials. Therefore, the risk–benefit ratio must be assessed individually on a case-to-case basis. The minimum ‘safe’ factor levels and platelet count for neuraxial block in both the obstetric and general populations and evidence-based recommendations for neuraxial techniques in the setting of haemophilia and VWD cannot be offered.⁶

Obstetrics patients with haemophilia

Females are usually carriers as haemophilia is an XLR disorder. All female relatives of a patient with haemophilia must be screened to document FVIII level. Once the carriers are identified, they must be educated and counselled about the risk of having a child with haemophilia and other reproductive options. Such patients should be managed with a multidisciplinary team right from the antenatal period. Sex of the child and therefore the haemophilia status may be identified by polymerase chain reaction around 10 weeks of gestation or by ultrasound around 18–20 weeks. Factor VIII and IX levels must be measured immediately before delivery and post-partum with an aim to maintain above 0.5 IU ml⁻¹. Controversies exist about the mode of delivery. Instrumental delivery poses a high risk of intracranial haemorrhage in a fetus with confirmed haemophilia status. Elective Caesarean section must be debated individually according to the risk to mother and child taking into consideration the haemophilia status of the fetus. There is no contraindication to normal vaginal delivery; however, prolonged labour must be avoided. There is no evidence that routine ultrasound screening or prophylactic administration of clotting factors reduces the risk of intracranial haemorrhage in the newborn.

Labour analgesia

The risk of neuraxial analgesia must be assessed individually after checking platelet and factor VIII levels (>0.5 IU ml⁻¹). Other options need to be considered like remifentanil patient controlled analgesia (PCA) with continuous monitoring of heart rate and oxygen saturation.

Von Willebrand's disease

In pregnancy, VWF begins to increase from 6 weeks of gestation and increases by three- to four-fold by the third trimester. Levels of VWF must be assessed at 34–36 weeks in type 1 and 2 VWD. VWF activity (VWF:RCo) >40 IU dl⁻¹ is required for safe vaginal delivery and >50 IU dl⁻¹ for Caesarean section.³ Post-Caesarean section patients usually need treatment with DDAVP or VWF concentrates for a week to maintain haemostasis. Similarly, patients with post-partum haemorrhage must receive active management with suitable replacement therapy. Monitoring of VWF and factor VIII must be done within 24 h post-partum as levels of VWF decline rapidly back to baseline.

Labour analgesia

Epidural analgesia may be considered in type 1 VWD after thorough evaluation of coagulation profile and VWF levels. The risk–benefit ratio must be assessed and must be performed by a senior anaesthetist. Epidural anaesthesia is not recommended in type 2 or 3 VWD.

Other recessively inherited coagulation disorders

Deficiency of fibrinogen, prothrombin, clotting factors V, VII, X, XI, and XIII are recessively inherited and are very rare with prevalence ranging from one in two million for factor II (prothrombin) and factor XIII (FXIII) deficiency to one in 500,000 for factor VII (FVII) deficiency. Replacement factors such as fibrinogen concentrates (RiaSTAP®, rFVIIa (NovoSeven®), and F XIII (Corifact®) are available and must be considered along with the use of PCC and cryoprecipitate.

Inherited clotting disorders

(Trombophilias)

Thrombotic and embolic events cause significant mortality and morbidity. Thrombotic tendency can be caused by either inherited or acquired defects in the clotting cascade. Venous thrombosis has an annual incidence of one in 1000. Deficiencies of antithrombin, protein C, and protein S account usually for <5% of venous thrombosis in all age groups. The inherited thrombophilias are listed in Table 4.⁷
## Antithrombin deficiency

Antithrombin functions primarily by inactivating thrombin and activated factor X and secondarily by inactivating factors VII, IX, and XII. The normal levels of antithrombin are 70–132% and <60% results in thrombosis.

## Protein C and protein S deficiency

Protein C mainly functions by inactivating activated factors V and VIII and stimulating plasminogen activator. Protein S is a cofactor of protein C, which enhances its action. The normal levels of protein C and protein S are 70–164% and 63–160%, respectively, and any level below the normal is thrombotic.

## Factor V Leiden mutation

Factor V mainly acts as a cofactor for activated factor X. Activity of factor V is limited by activated protein C which degrades it. The factor V Leiden mutation results in resistance to activated protein C thereby causing thrombosis.

## Abnormalities of fibrinolytic system

In normal subjects, plasminogen is converted to plasmin which lysed clots. It is mainly activated by tissue plasminogen activator (tPA) and inhibited by plasminogen activator inhibitor (PAI). Deficiency of plasminogen, tPA, or excess of PAI may lead to a hypercoagulable state (Table 5). Qualitative defects in fibrinogen (dysfibrinogenemia) may also lead to thrombosis.

## Treatment

Anticoagulants such as unfractionated heparin, low molecular weight heparin (LMWH) and warfarin are the mainstay of treatment. Specific conditions, replacement factors are available like cryoprecipitates, protein C, and antithrombin. Fresh-frozen plasma is rarely used as a source of anticoagulants and may be used in the case of their deficiency. Consideration should be given to preoperative placement of inferior vena cava (IVC) filters in high-risk patients undergoing high-risk surgery with anticipated prolonged immobility.

### Table 4 Inherited thrombophilias

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Factor</th>
<th>Inheritance</th>
<th>Life time probability of thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess procoagulants</td>
<td>† Factors VII, VIII, IX, XI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal cofactors (mutations)</td>
<td>Factor V Leiden</td>
<td>AD</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>Prothrombin</td>
<td>AD</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>Dysfibrinogenaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficiency of anticoagulants</td>
<td>† Antithrombin (AT)</td>
<td>AD</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>† Protein C</td>
<td>AD</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>† Protein S</td>
<td>AD</td>
<td>8.5</td>
</tr>
<tr>
<td>Abnormalities of fibrinolysis</td>
<td>† tPA (tissue plasminogen activator)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>† Plasminogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>† PAI (plasminogen activator inhibitor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other allied inherited conditions</td>
<td>Hyperhomocysteinaemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5 Diagnosis

<table>
<thead>
<tr>
<th>Defect</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfibrinogenaemia</td>
<td>Prolonged thrombin time (normal: 18–22 s)</td>
</tr>
<tr>
<td>Fibrinolysis defect</td>
<td>Prolonged euglobulin clot lysis time (normal: 90–240 min)</td>
</tr>
<tr>
<td>Anticoagulant deficiency</td>
<td>Normal thrombin time and euglobulin clot lysis time</td>
</tr>
</tbody>
</table>

## Preoperative assessment

A detailed coagulation screen must be done to evaluate the diagnosis and to monitor treatment as patients are on anticoagulation. The decision to administer fresh-frozen plasma before surgery must be done in consultation with the haematologist. (Fresh-frozen plasma is only used for factor V deficiency and plasma exchange in patients with thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome.)

## General principles

- As for bleeding disorders, multidisciplinary team management, elective scheduled surgery, ultrasound for vascular access, and multimodal analgesia.
- Preoperative clotting screen/anti-Xa levels depending on the medication used to bridge perioperative anticoagulation.
- Bridging therapy with unfractionated/LMWHs for high-risk patients.
- Avoid dehydration and promote early mobilization, use of mechanical compression devices.

## Anaesthetic considerations

Choice of general anaesthesia vs regional anaesthesia should be individualized as per patient and surgery. Guidelines exist for regional anaesthesia in a patient on anticoagulation by American and European societies of regional anaesthesia. In high-risk patients, warfarin must be converted to heparin before surgery with monitoring of coagulation. The use of mechanical measures like graduated
elastic stockings and intermittent pneumatic compression devices must be used. A plan for restarting anticoagulants after surgery must be discussed with the surgeons and haematologist.

**Conclusion**

Patients with inherited coagulation disorders can have the same perioperative outcome as a normal patient if care is taken to maintain the deficient factor levels in bleeding disorders or time anticoagulation in clotting disorders in the perioperative period. Also the availability of recombinant factor VIIa has revolutionized treatment in complicated haemophilia patients with inhibitors.

**Declaration of interest**

None declared.

**References**


Please see multiple choice questions 17–20.