Perioperative management of coagulopathies / bleeding dyscrasias in the pediatric patient

Introduction

This is a rather broad topic. For the syllabus, I have focused on the following:

- General considerations concerning perioperative management
- Platelet disorders
- Coagulation disorders

Emphasis has been placed on the inherited bleeding disorders because pediatric anesthesiologists will encounter children who have these diseases. However, these challenging disorders are uncommon and many anesthesiologists might be a little vague about the intricacies of perioperative management. This review draws from published work. Selected references are provided.

Topics that are not addressed include:

- Rare inherited bleeding disorders (but references provided)
- Vascular bleeding disorders
- Blood product transfusion issues
- Cardiopulmonary bypass surgery
- Antifibrinolytic prophylaxis

Normal coagulation

**Coagulation cascade:** The coagulation cascade describes the initiation of coagulation as it occurs in test tubes and is useful in explaining how coagulation tests work.

**Cellular model:** By contrast, the newer cellular model of coagulation proposed by Hoffman, et al. enables a better understanding of the clotting process as it occurs in vivo.

The basic pre-conditions for clot formation are activators and accelerators, localizing matrix, sufficient substrate and stabilizing factors (Fig. 1). Clot formation overshoot is prevented by several limiting control mechanisms and the activity of the counterbalancing fibrinolytic system.

**Figure 1.** Thrombin generation (Modified from: Innerhofer P, et al. *Best Pract Res Clin Anaesth* 2010;24:1-14.)

![Diagram of Thrombin Generation](image)

Tissue factor-bearing cells expose tissue factor to the blood stream, resulting in complex formation with circulating VIIa. By activating factors X and V a small amount of thrombin is formed. This initial thrombin activates platelets and factors XI, IX, X and co-factors VIII and V resulting in a thrombin burst necessary for cleavage of fibrinogen. The formed fibrin monomers polymerize spontaneously and are finally cross-linked by means of XIIIa.
Primary hemostasis: the platelet plug

Exposure of subendothelial collagen initiates platelet spreading, platelet adhesion and shape change, platelet granule secretion and initial platelet aggregation. Platelet adhesion is initiated at high blood shear rates by platelet glycoprotein Ib (GPIb) receptor complex binding with von Willebrand Factor (vWF). Other platelet receptors also bind to subendothelial collagen. The platelets are then activated, primarily by collagen and the small amount of thrombin that is built up during the initiation of coagulation.

Upon activation, platelets change shape and expose negatively charged phospholipids on their surface membrane that play an important role in secondary hemostasis. Activated platelets also release the contents of the their α-granules and dense granules. These substances promote platelet aggregation and endothelial smooth muscle vasoconstriction at the site of injury. Platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptors are activated during platelet activation and bind with fibrinogen, thereby cross-linking adjacent platelets together. Platelet aggregation and thrombin generation (from secondary hemostasis) together form a fibrin clot that is limited to areas of vascular injury. Neighboring intact endothelial cells produce platelet aggregation inhibitors and vasodilators, thereby preventing propagation of the platelet aggregate beyond the site of injury.

Secondary haemostasis: thrombin and clot formation

During initiation of coagulation, the exposed tissue factor (TF) and circulating FVIIa form the TF/FVIIa complex. This TF/FVIIa complex catalyzes two reactions. The first is the activation of FX to FVa. Free FVa is rapidly broken down by natural inhibitors which are abundant in the environment of the TF-bearing cell. However, FVa present on the surface of the TF-bearing cell is relatively protected and can catalyze the conversion of a small amount of prothrombin into thrombin. This small amount of thrombin, although insufficient to sustain the cleavage of fibrinogen into fibrin, is potent enough to fully activate platelets. The second reaction catalyzed by TF/FVIIa is the activation of FIX to activated FIX (FIXa). FIXa is less vulnerable to proteolysis than FVa and diffuses away from the TF-bearing cell to bind with the negatively-charged phospholipid surface membrane of activated platelets.

The surface of activated platelets is vital for further coagulation factor assembly. During activation, platelets α-granules release FV that is converted by thrombin to activated FV (FVa). Thrombin also acts to dissociate vWF from circulating FVIII, thus releasing activated FVIII (FVIIIa) onto the activated platelet surface. Additionally, activated platelets express high-affinity binding sites for FIXa and FXa. When FIXa reaches and binds to the activated platelet surface, it joins FVIIIa to form the ‘tenase’ complex (FVIIIa/FIXa). In parallel, thrombin-induced FIXa activates FIXa. The ‘tenase’ complex activates large amounts of FXa, which may then join with its co-factor, FVa, to form the ‘prothrombinase’ complex (FXa/FVa). This ‘prothrombinase’ complex is responsible for the large-scale conversion of prothrombin to the thrombin (thrombin burst) necessary for the formation of a stable fibrin cross-linked clot.

Every activated platelet exposes several thousand glycoprotein receptors (GPIIb/IIIa) for effective binding of fibrinogen. Following sufficient thrombin generation, fibrinogen is cleaved and the resulting fibrin monomers spontaneously polymerize to form uncross-linked fibrin. Stability of the formed platelet/fibrin clot determines effective cessation of bleeding. The main stabilising factors are the thrombin-induced factors FXIIIa and thrombin-activatable fibrinolysis inhibitor (TAFIa). FXIIIa stabilises the clot by catalysing fibrin cross-linking (cross-linked fibrin) and incorporating antifibrinolytic proteins into the clot. TAFIa decreases fibrinolysis by reducing fibrin’s binding sites for plasminogen and tissue plasminogen activator (t-PA).

Uncontrolled thrombosis is life-threatening, thus regulation is exerted at multiple levels of the process. Tissue factor pathway inhibitor (TFPI) modulates the initiation phase of blood coagulation by inhibiting the actions of the TF/FVIIa complex. The anticoagulant protein, antithrombin (AT), is a powerful inhibitor of both FXa and thrombin and limits the coagulation process to the site of vascular injury. Protein C (PC), another important anticoagulant protein, is activated by thrombin once it has bound to the membrane protein, thrombomodulin, on the surface of intact endothelial cells. When activated, it inhibits coagulation through the breakdown of FVa and FVIIIa.
**Tertiary hemostasis (fibrinolysis)**

Plasmin eliminates clot by cleaving fibrin into its degradation products, the smallest of which are measured as D-dimers. Plasminogen is converted to plasmin by several mechanisms. These include tissue plasminogen activator (t-PA), which binds to fibrin via lysine binding sites. t-PA only activates plasminogen that is bound to fibrin thus limiting fibrinolysis to the site of clot formation.

**Age and coagulation**

When assessing the results of haemostatic investigations it is important to be aware that there are physiological differences between the coagulation systems of infants and children and those of adults and these differences are most significant in young infants. For instance, the levels of several clotting factors are considerably lower in healthy full-term infants at birth when compared to adults, with premature infants showing even more pronounced reductions. In general, the postnatal maturation of the coagulation system towards adult status is accelerated in premature infants when compared with full-term babies, and by 6 months of age most components of the coagulation system in premature infants begin to approach adult values. This is reflected in alterations in thrombin regulation in children compared to adults, which are thought to be one of the reasons that children are protected from thromboembolism compared to adults. There is also apparent platelet hypofunction in newborn babies. It is therefore essential that gestational and/or postnatal age is taken into consideration when interpreting coagulation results.

**Acquired bleeding disorders: causes**

The development of an acquired disorder of coagulation or platelet function in a hospitalized child is generally much more common than congenital disorders.

(i) **Vitamin K deficiency** is probably the most common acquired bleeding disorder of childhood and it can result in any degree of bleeding from minor bruising through to severe life-threatening hemorrhage. It usually results from liver dysfunction, gastro-intestinal disorders and from drug therapy, particularly antibiotics and oral anticoagulants. Neonatal vitamin K deficiency can cause hemorrhagic disease of the newborn where bleeding can vary from bruising or petechiae in the first few days of life through to severe and life-threatening intracranial haemorrhage and/or gastrointestinal bleeding. It can be prevented by IM vitamin K soon after birth.

(ii) **Severe liver disease** often results in a coagulation disorder, caused by impaired synthesis of coagulation factors and clearance of activated clotting factors, enhanced fibrinolysis and there can also be an acquired platelet function defect. However, the liver has large reserves so often only 10–15% of children have significant bleeding.

(iii) **Dys- or hypo-fibrinogenaemia** can occur in some systemic diseases in childhood, including renal or liver disease, and following drug therapy (e.g.: l-asparaginase, sodium valproate).

(iv) **Disseminated intravascular coagulation (DIC)** usually occurs in critically ill children. There are many causes, including severe infections, tissue or vascular injury or intravascular haemolysis (ABO incompatible transfusion, liver disease and malignancy). DIC can cause profuse bleeding into the skin, gastro-intestinal tract and central nervous system.

(v) **Coagulation inhibitors** are rare in children who do not have an underlying inherited coagulation disorder. They can occur in association with malignancy or occasionally post-surgery. Inhibitors to phospholipid are more common but are rarely associated with an excess bleeding risk except when the anti-phospholipid antibody is directed against prothrombin (FII) and results in consumption of FII. These usually follow viral infections in otherwise well children and are generally transient. A FII level should therefore be requested in any child with bruising and a poor correction of a prolonged APTT with 50:50 mix with normal plasma especially if there is also a prolonged PT. It is unusual for this transient bleeding diathesis to require treatment.

(vi) **Platelet dysfunction** causing temporary bruising is common following ingestion of nonsteroidal anti-inflammatory drugs or aspirin. Acquired platelet dysfunction is also often noted with uremia, liver disease and after cardiopulmonary bypass.
(vii) **Thrombocytopenia** can result from increased platelet destruction, hemodilution and decreased platelet production.

**Investigation of child with abnormal bruising / bleeding: basic principles**

Initial assessment includes obtaining a comprehensive history, examining the patient and performing baseline investigations, including complete blood count (CBC), activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time and fibrinogen assay.

A CBC and blood film should exclude hematological causes of bleeding or bruising, such as thrombocytopenia or bone marrow failure syndromes, and will also allow morphological examination of platelets.

If there is prolongation of either the APTT or PT, the test should be repeated using a mix with equal volumes of test and normal plasma to differentiate between a factor deficiency and a circulating inhibitor. Lupus-like inhibitors are a relatively common cause of a prolonged APTT in children and are usually a transient postviral phenomenon of no consequence.

A prolonged thrombin time may indicate hereditary or acquired fibrinogen abnormalities (dysfibrinogenemia or hypofibrinogenemia) or elevated fibrin/fibrinogen degradation products as seen in DIC. A Clauss fibrinogen assay should be performed rather than relying on a fibrinogen value derived from the PT on the coagulation analyzer.

Finally, biochemical screens should be undertaken, with particular emphasis on hepatic and renal functions.

If these baseline investigations are normal, consider the following disorders:

- Mild von Willebrand disease
- Mild haemophilia A or B
- Mild factor XI or other single factor deficiency
- Factor XIII deficiency
- α2 antiplasmin deficiency
- Plasminogen activation inhibitor-1 deficiency
- Glanzmann thrombasthenia
- Platelet storage pool disease
- Platelet release defect
- Collagen disorders
- Vitamin C deficiency

Bleeding disorders can be complex and all such cases should, at the very least, be discussed with a pediatric hematology department. High levels of certain factors (e.g.: FVIII – an acute phase reactant) may well mask mild deficiencies of the other factors. Therefore, in cases in which a hemostatic disorder is part of the differential diagnosis it is necessary to perform all factor assays even when the screen is normal. A simplified scheme for guiding further investigation is suggested in Table 1 (from: Khair K, et al. *Br J Haematol.* 2006;133:221-31).
### Table 1: Investigation of abnormal bruising or bleeding

<table>
<thead>
<tr>
<th>Baseline tests</th>
<th>Possible abnormality</th>
<th>Further investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal platelet count &amp; normal coagulation</td>
<td>See text for details</td>
<td>Factor assays&lt;br&gt;VWD screen&lt;br&gt;PFA-100&lt;br&gt;Platelet aggregation / nucleotides&lt;br&gt;Flow cytometry for glycoprotein expression&lt;br&gt;FXIII activity&lt;br&gt;α2 antiplasmin level&lt;br&gt;PAI-1 activity</td>
</tr>
<tr>
<td>Low platelet count</td>
<td>See text for details</td>
<td>Monospot/viral serology&lt;br&gt;Bone marrow aspirate&lt;br&gt;Platelet associated IgG&lt;br&gt;Autoantibodies&lt;br&gt;Fanconi screen&lt;br&gt;Platelet aggregation / nucleotides&lt;br&gt;Flow cytometry for glycoprotein expression</td>
</tr>
<tr>
<td>Abnormal coagulation PT APTT TT ↑ N N</td>
<td>• Factor VII deficiency&lt;br&gt;• Liver disease&lt;br&gt;• Vitamin K deficiency</td>
<td>Measurement of PT-based factors</td>
</tr>
<tr>
<td>N ↑ N</td>
<td>• Deficiency of FVIII (haemophilia A or VWD), factors IX, XI, XII or contact factors&lt;br&gt;• Lupus anticoagulant or other coagulation factor inhibitor</td>
<td>Measurement of APTT-based factors, VWD screen&lt;br&gt;DRVVT, ACL, anti-β2GP1 antibodies</td>
</tr>
<tr>
<td>N N ↑</td>
<td>• Hypofibrinogenaemia&lt;br&gt;• Dysfibrinogenaemia</td>
<td>Reptilase time + other thrombin time corrections</td>
</tr>
<tr>
<td>↑ ↑ N</td>
<td>• Deficiency of factors II, V, X&lt;br&gt;• Vitamin K deficiency&lt;br&gt;• Liver disease&lt;br&gt;• Massive transfusion&lt;br&gt;• Oral anticoagulants</td>
<td>PT- and APTT-based factors, INR</td>
</tr>
<tr>
<td>N ↑ ↑</td>
<td>• Heparin</td>
<td>Reptilase time and other thrombin time corrections</td>
</tr>
<tr>
<td>↑ ↑ ↑</td>
<td>• Disseminated intravascular coagulation&lt;br&gt;• Large amount of heparin&lt;br&gt;• Severe hypo- or afibrinogenaemia</td>
<td>D-dimers, Reptilase time and other thrombin time corrections</td>
</tr>
</tbody>
</table>

PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; N, within normal range; ↑, prolonged; VWD, von Willebrand disease; DRVVT, dilute Russell Viper Venom time; ACL, antinuclear antibodies; INR, international normalised ratio; PFA-100, platelet function analyser closing time; anti-β2GP1 antibodies.

### Anesthetic management: general considerations

**Preoperative coagulation screening tests**

Debate in the literature about the appropriate use of preoperative coagulation screening tests has continued for at least two decades. Many now think the indiscriminate use of routine coagulation
testing in the preoperative setting is not helpful and may cause unnecessary further testing and delay of surgery. They suggest coagulation testing should be restricted to well-defined circumstances.

Some of the issues relevant to this debate are:

(i) Inherited bleeding defects are rare

The incidence of mild von Willebrand disease (VWD) is 1:1,000, severe VWD =1:10,000, haemophilia A =1:10,000, and hemophilia B =1:60,000. Severe, clinically relevant, deficiencies of FII, FV, FVII, FX, FXI, fibrinogen and platelets are even rarer with an incidence varying between 1:300,000 and 1:2,000,000. The majority of patients with these bleeding disorders will be aware of their diagnosis through either a personal or family history of bleeding. Indiscriminate screening by routine coagulation testing will therefore only very rarely identify previously undetected individuals.

(ii) Abnormal coagulation tests are common

In contrast, prolongation of the APTT is a common occurrence, usually due to mild FXII deficiency or the presence of a lupus anticoagulant, neither of which is associated with a bleeding tendency. Moderate and severe FXII deficiency was found in 2.3-10.3% of individuals. Lupus anticoagulant can be found in 1.2–3.8% of healthy individuals. Other causes of a prolonged APTT not associated with a bleeding tendency include high molecular weight kininogen deficiency and prekallikrein deficiency.

Finally, a normal range is calculated by the mean +2 standard deviations of measurements in healthy, non-bleeding subjects and by definition 2.5% of measurements in normal individuals will show a prolonged clotting time. Therefore, if routine coagulation testing is done to identify previously undiagnosed bleeding disorders, it is much more likely to identify a prolonged routine coagulation test that is not associated with a bleeding tendency. In practice, this can lead to further unnecessary testing and postponement or delay of the surgery.

(iii) Routine coagulation tests fail to identify inherited bleeding disorders

Routine coagulation tests can be normal in the presence of mild or severe bleeding disorders. The most common of these is mild VWD. Mild haemophilia A or B may also be missed if an insensitive reagent/analyser combination is used, or during an acute phase response where a temporarily high FVIII level may lead to shortening of the APTT. Other conditions that cannot be detected by routine coagulation testing but may be associated with clinically significant bleeding include the rare inherited bleeding disorders such as FXIII and α2 antiplasmin deficiency and platelet function disorders.

(iv) Routine coagulation tests are poor predictors of perioperative blood loss

Multiple studies have shown that PT and APTT have limited value as preoperative screening tests. There is poor positive predictive value and low likelihood ratio for bleeding with an abnormal coagulation test, whereas the perioperative bleeding rates were similar in patients with and without abnormal coagulation tests.

(v) A history of bleeding is common

A bleeding history is subjective and common symptoms are found in up to 25% of a healthy population without bleeding disorders including epistaxis, gum bleeding, and post-partum hemorrhage. The use of a standardized bleeding questionnaire has been suggested as being better than indiscriminate coagulation testing as a screening tool for perioperative bleeding, and there are suggestions that in patients with congenital bleeding disorders (e.g., VWD), a structured history is at least as informative as laboratory testing to predict bleeding. Published British, German, Italian and American guidelines all recommend using a standardized bleeding questionnaire. Pediatric-specific questionnaires (e.g.: for tonsil/adenoid surgery) are described; parental input is often required. History may be less reliable in young infants who have encountered few hemostatic challenges.

Relevant questionnaire items include:

- Known coagulopathy (bleeding history of the patient and relatives indicating severe bleeding diathesis)
• Epistaxis without obvious reasons
• Hematoma, petechia at torso/unnatural location without other reasons
• Wound-healing defects.
• Prolonged bleeding after abrasion/cut, during or after previous surgery, during or after teeth extraction, after vaccinations, umbilical cord stump.
• Abnormal blood and blood product requirement after previous surgery.
• Hypermenorrhea requiring more than seven tampons per day, bleeding for more than 7 days since menarche.
• Medication affecting coagulation: pain killers, anti-thrombotic and anti-platelet drugs, over-the-counter drugs and dietary factors.

Recommendations for preoperative coagulation screening tests

Many argue, based on the available evidence, that a reasonable approach to assessing the perioperative bleeding risk is as follows:

1. Take a structured bleeding history.
2. Only perform coagulation tests (and consider hematology consult) if:
   - Patient with a personal history of bleeding identified by structured history taking or a family history of bleeding or known inherited bleeding disorder.
   - Neither patient nor family able to provide a satisfactory history.
   - Patient with acute illnesses such as sepsis or conditions that can be associated with a coagulopathy such as chronic liver disease.
   - Patient taking drugs that impair hemostasis. If the drug can be stopped and surgery delayed until drug effect has gone, then testing may not be necessary. If drug cannot be stopped or surgery cannot be delayed, then testing should be performed.
   - To determine patient’s baseline coagulation status prior to procedures that will perturb coagulation (e.g.: cardiopulmonary bypass, surgeries associated with major blood loss and transfusions).

Some guidelines recommend PT, APTT and platelet count before surgery in children even in case of a negative bleeding history for the following reasons:

- Possibility to detect hemorrhagic disorders, especially in children who can have a negative history for bleeding.
- Necessity of a baseline test in case of perioperative complications.
- Usefulness of the pre-operative platelet count to detect heparin-induced thrombocytopenia in patients who will receive heparin.

(Italian Society for Haemostasis and Thrombosis, 2009)

Preoperative management

Patients may present to the anesthesiologist with: (i) abnormal laboratory coagulation test(s) and a negative bleeding history, (ii) known diagnosis of a bleeding disorder, (iii) history suspicious for possible bleeding disorder, (iv) symptoms and signs suggestive of a bleeding disorder, (v) unexpected excessive bleeding after trauma or surgery.

- Consultation with a hematologist may be very helpful.
- Consider obtaining baseline serum concentration of iron and ferritin to assess iron stores, because individuals with bleeding disorders may be iron deficient, particularly post-pubertal females.
- Consider screening for hepatitis B and C and perhaps HIV if the patient with a chronic bleeding disorder has received blood products in the past.
- Elective cases should be scheduled early in the day, when availability of hospital resources and expertise are optimal.
- Perioperative hemostasis management plan should be clearly defined and understood by all relevant parties. Hemostasis management is likely to impact pre-, intra- and post-operative care. Excellent communication between the different teams caring for the patient is vital.
Intraoperative anesthetic management

- Ensure appropriate hemostatic agents are immediately available.
- Ensure appropriate coagulation tests for monitoring therapy are available.
- Prepare for the possibility of rapid and/or sustained blood loss.
- Concerns about bruising and bleeding may influence the following: positioning of the patient, airway management, invasive monitoring, choice of anesthetic technique, pain management.
- Avoid drugs that adversely affect platelet or coagulation factor function.

Regional anesthesia and bleeding disorders

The anesthesiologist should carefully discuss the risks and benefits of regional anesthesia with the patient, the hematologist, and the perioperative team.

A literature review (Choi, et al.) in 2009 concluded “there is a paucity of published data regarding the provision and safety of neuraxial techniques in patients with common bleeding diatheses. Based on reports of only 507 neuraxial techniques, of which 406 were in the obstetric population, hemorrhagic complications after neuraxial techniques in patients with known hemophilia, vWD, or immune thrombocytopenia (ITP) appear infrequent when factor levels are more than 0.5 IU mL\(^{-1}\) for Factor VIII levels, VW Factor levels, and Ristocetin Co-factor Activity levels, or when the platelet count is more than 50 x 10\(^9\) L\(^{-1}\) before block performance. The minimum ‘safe’ factor levels and platelet count for neuraxial blockade remain undefined in both the obstetric and general populations and evidence-based recommendations for neuraxial techniques in the setting of hemophilia, vWD, or ITP cannot be offered.” Published guidelines are summarized below.

Table 2. Guidelines for neuraxial techniques in hemophilia, VWD, and thrombocytopenia

<table>
<thead>
<tr>
<th>Society</th>
<th>Date</th>
<th>Disease</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOGC</td>
<td>2006</td>
<td>Hemophilia</td>
<td>Neuraxial techniques safe when coagulation factors normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VWD</td>
<td>Neuraxial techniques safe when coagulation factors normal</td>
</tr>
<tr>
<td>UKHCDO</td>
<td>2006</td>
<td>Hemophilia</td>
<td>Neuraxial techniques safe when coagulation factors &gt;0.5 IU mL(^{-1}) Use midline technique with minimum local anesthetic concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VWD Type 1</td>
<td>Neuraxial techniques safe when coagulation factors &gt;0.5 IU mL(^{-1}) Use midline technique with minimum local anesthetic concentration</td>
</tr>
<tr>
<td>UKHCDO</td>
<td>2004</td>
<td>VWD</td>
<td>Neuraxial techniques safe when coagulation factors &gt;0.5 IU mL(^{-1}) Avoid neuraxial techniques in patients with vWD Types II &amp; III</td>
</tr>
<tr>
<td>BCSH</td>
<td>2003</td>
<td>ITP</td>
<td>Platelet count &gt;80 x 10(^9) L(^{-1}) recommended for neuraxial techniques</td>
</tr>
<tr>
<td>BCSH</td>
<td>2003</td>
<td>Thrombocytopenia</td>
<td>Platelet count &gt;50 x 10(^9) L(^{-1}) recommended for neuraxial techniques and major surgical procedures</td>
</tr>
<tr>
<td>ASCO</td>
<td>2001</td>
<td>Thrombocytopenia</td>
<td>Platelet count &gt;40–50 x 10(^9) L(^{-1}) recommended for neuraxial techniques and major surgical procedures</td>
</tr>
</tbody>
</table>

ASCO = American Society for Clinical Oncology; BCSH = British Committee for Standards in Haematology; SOGC = Society of Obstetrics and Gynaecology of Canada; UKHCDO = United Kingdom Haemophilia Doctors Organization.


Suggested reading

26. Choi S, Brull R. Neuraxial techniques in obstetric and non-obstetric patients with common


Platelet disorders

Platelets and primary hemostasis

The primary physiological role of platelets is to support hemostasis at sites of vascular injury by forming platelet plugs that arrest blood loss (Fig. 2).

Normally, disc-shaped platelets circulate in the bloodstream without adhering to the endothelium of the vessel wall. When the endothelium is damaged, the following occurs:

**Platelet adhesion:** Platelets bind to subendothelial collagen at the site of injury via the integrin α2β1 and GPVI membrane glycoprotein receptors and, at high shear, to collagen-immobilized von Willebrand factor (VWF) via the GPIb-IX-V complex.

**Platelet activation:** Platelet adhesion initiates platelet activation via intracellular signaling pathways. Adherent platelets alter their cytoskeleton, changing to become irregular spheres with filopodia spreading to increase surface contact. The contents of dense δ-granules (e.g., ADP and serotonin) and α-granules (e.g., adhesive proteins and growth factors) are secreted. Thromboxane A2 (TxA2), formed from arachidonic acid via the actions of cyclooxygenase-1 and thromboxane synthase, is released from the cell. Exposure of phospholipids on surface membrane on the platelet promote the assembly of coagulation factor complexes (tenase and prothrombinase) that accelerate the generation of thrombin.

**Platelet aggregation:** ADP, TxA2, and thrombin bind to their specific membrane receptors, initiating signaling pathways that allow adjacent activated platelets to aggregate via integrin αIIbβ3 (GPIIb-IIIa) receptor binding with fibrinogen and VWF.

There are age-related differences in platelet function. Term and preterm newborns, when compared older children and adults, show decreased platelet activation responses that persist for the first 2 to 4 weeks after delivery. This hyporesponsiveness includes decreased aggregation, decreased granule secretion, and decreased expression of activation markers in response to in vitro agonists and results from impaired receptor-mediated signal transduction. However, both in vivo bleeding times and ex vivo PFA-100 closure times are shorter in term neonates than in older children and adults—findings that correlate with higher hematocrit and increased von Willebrand factor activity in these newborns.

![Figure 2: Platelet plug formation at the site of vessel wall damage.](image)
A simplified diagram of adhesion, activation, and aggregation of platelets in response to exposed subendothelium in support of hemostasis. Note that alpha granules store and secrete >300 proteins involved in clot formation and wound healing, and that dense granules secrete serotonin and polyphosphate and other small molecules in addition to ADP.

VWF, von Willebrand factor; TxA2, thromboxane A2. (*) interactions involving VWF that occur only at high shear.

**Clinical manifestations of failure of primary hemostasis**

When platelet adhesion, activation, or aggregation processes fail, hemostasis is impaired. Symptomatic patients generally present with mucosal or cutaneous bleeding.

**Mucosal bleeding** usually manifests as epistaxis, gingival bleeding or extensive oral mucous membrane bleeding (“wet purpura”), hematuria, or in postpubertal females, excessive menstrual bleeding. The presence of “wet purpura” is widely perceived as a risk factor for potentially life-threatening hemorrhage.

**Cutaneous bleeding** usually appears as petechiae or superficial ecchymoses. Patients who have thrombocytopenia may also have persistent, profuse bleeding from superficial cuts. Petechiae, the pinhead-sized, red, flat, discrete lesions caused by extravasation of red cells from skin capillaries and often occurring in crops in dependent areas, are highly characteristic of decreased platelet number or function. Petechiae are nontender and do not blanch under pressure. They are asymptomatic and not palpable. Purpura describes purplish discolorations of the skin due to the presence of confluent petechiae. Ecchymoses are nontender areas of bleeding into the skin that are typically small, multiple, and superficial and can develop without noticeable trauma. Ecchymoses often have a variety of colors due to the presence of extravasated blood (red or purple) and the ongoing breakdown of heme pigment in the extravasated blood by skin macrophages (green, yellow, or brown).

This pattern of bleeding differs from that of patients who have disorders of coagulation factors, such as hemophilia. Patients who have thrombocytopenia tend to have less deep bleeding into muscles or joints, more bleeding after minor cuts, less delayed bleeding, and less postsurgical bleeding. In addition, patients who have coagulation factor disorders tend not to have petechiae. Although rare, bleeding into the central nervous system is the most common cause of death due to thrombocytopenia. When such bleeding occurs, it is often preceded by a history of head trauma.

**Platelets and hemostasis: the perioperative period**

Anesthesiologists encounter the following management challenges:

- Thrombocytopenia (defined as <150 x 10^9/L)
- Bleeding history (typically mucocutaneous)
- Active bleeding

Bleeding may be due to decreased platelet number or abnormal platelet function or both.

**Thrombocytopenia**

Other than nutritionally acquired anemia, isolated thrombocytopenia is the most commonly acquired blood disorder in the pediatric population. Thrombocytopenia is the most common coagulation problem in the ICU with an incidence of 15% to 60% depending on the definition used, population evaluated, and period of ICU stay studied. In the ICU, counts <100 x 10^9/L have been associated with a 10-fold increased risk of bleeding compared to those between 100 and 150 x 10^9/L. Lower platelet counts are associated with an even higher risk of hemorrhage, especially counts below 50 x 10^9/L.

Figure 3 illustrates the relationship between platelet count and bleeding in children.

**Figure 3:** Relationship between major bleeding and platelet count.
Causes of thrombocytopenia

These are listed below:

*Increased Platelet Destruction*
- **Immune-mediated**
  - Immune thrombocytopenic purpura
  - Neonatal alloimmune thrombocytopenia
  - Neonatal autoimmune thrombocytopenia
  - Autoimmune diseases
  - Drug-induced
- **Platelet activation/consumption**
  - Disseminated intravascular coagulation
  - Hemolytic-uremic syndrome
  - Thrombotic thrombocytopenic purpura
  - Kasabach-Merritt syndrome
  - Necrotizing enterocolitis
  - Thrombosis
- **Mechanical platelet destruction**
- **Platelet sequestration**
  - Chronic liver disease
  - Type 2B and platelet-type von Willebrand disease
  - Malaria

* Dilutional thrombocytopenia*
  - Massive IV fluid or non-platelet blood product administration

*Decreased Platelet Production*
- **Infection**
- **Cyanotic congenital heart disease**
- **Bone marrow failure or infiltrate**
  - Acute lymphoblastic leukemia and other malignancies
  - Acquired aplastic anemia
  - Fanconi pancytopenia
  - Drugs, toxins
- **Nutritional deficiencies**
- **Genetically impaired thrombopoiesis**
  - Thrombocytopenia with absent radii syndrome
  - Congenital amegakaryocytic thrombocytopenia
  - Wiskott-Aldrich syndrome
In addition, platelet autoantibodies may induce thrombocytopenia by inhibiting proplatelet antigen specificity against platelet. The increased platelet destruction results from autoantibodies, mostly are of the IgG class with an annual incidence of symptomatic cases estimated to be between 3 and 8 cases per 100,000 children.

The increased platelet destruction results from autoantibodies, mostly are of the IgG class with specificity against platelet-specific antigens, in particular, glycoproteins IIb/IIa and Ib/IX. Cellular immune mechanisms are also involved; the production of antiplatelet antibodies by B cells requires antigen-specific, CD4-positive, T-cell help. Cytotoxic T cells play a role in the destruction of platelets. In addition, platelet autoantibodies may induce thrombocytopenia by inhibiting proplatelet production of maternal IgG antiplatelet antibodies against the foreign antigen. These antibodies across the placenta into the fetal circulation and destroy the baby’s platelets, resulting in fetal and neonatal thrombocytopenia (analogous to hemolytic disease of the newborn). In contrast to Rh sensitization, NAIT often develops in the first pregnancy of an at-risk couple. The most serious complication of NAIT is intracranial hemorrhage (ICH), which occurs in approximately 10% to 20% of affected newborns, with up to 50% of these events occurring in-utero. Affected newborns typically present with petechiae, bruising, and bleeding, but are otherwise healthy. Platelet counts are often less than 10x10^9/L. The platelet count typically falls in the first few days after birth, but then rises over the next 1 to 4 weeks as the alloantibody concentration declines. Prevention of ICH is an emergency. Term infants are transfused using washed and irradiated maternal platelets, or HPA compatible platelets. Random donor platelets are HPA1b1b/5a5a, compatible in >90% of cases. Treatment with intravenous gamma globulin (IVIG) has also been shown to be effective.

Thrombocytopenia in childhood

**Immune thrombocytopenia purpura** (ITP) is the most common immune-mediated pediatric thrombocytopenia, with an annual incidence of symptomatic cases estimated to be between 3 and 8 cases per 100,000 children.
Inherited Disorders of Platelet Function

Inherited disorders of platelet function are caused by herbal medications with anti-platelet effects, such as feverfew. Antiepileptics, particularly valproic acid, can cause thrombocytopenia, platelet dysfunction, and acquired von Willebrand disease. Selective serotonin reuptake inhibitors can cause platelet dysfunction.

Although more commonly seen in adults, platelet function in children may also be compromised in systemic disease, including renal failure, sepsis, myelodysplastic syndromes, and leukemia.

Inherited platelet disorders encompass both function disorders and thrombocytopenia (see below).

**Inherited Disorders of Platelet Function**
Abnormalities of receptors for adhesive proteins
- GP Ib–IX–V complex (Bernard–Soulier syndrome*#, platelet-type von Willebrand disease*)
- GP IIb–IIIa (αIIbβ3; Glanzmann thrombasthenia#)
- GP Ia-IIa (α2β1)
- GP VI

Abnormalities of receptors for soluble agonists
- Thromboxane A2 receptor
- P2Y12 receptor
- α2-adrenergic receptor

Abnormalities of platelet granules
- δ-granules (δ-storage pool deficiency, Hermansky–Pudlak syndrome, Chediak–Higashi syndrome, thrombocytopenia with absent radii syndrome*#)
- α-granules (Gray platelet syndrome*, ARC syndrome*, Quebec platelet disorder*, Paris–Trousseau–Jacobsen syndrome*)#
- α- and δ-granules (α, δ-storage pool deficiency)

Abnormalities of signal-transduction pathways
- Primary secretion defects

Abnormalities of the arachidonic acid/thromboxane A2 pathway
- Gαq deficiency
- Partial selective PLC-β2 deficiency
- Defects in pleckstrin phosphorylation
- Defects in Ca2+ mobilization

Abnormalities of cytoskeleton
- MYH9-related disorders (May–Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, Epstein syndrome*)
- Wiskott–Aldrich syndrome*#
- X-linked thrombocytopenia*

Abnormalities of membrane phospholipids
- Scott syndrome

*These disorders usually present with thrombocytopenia in addition to functional abnormalities.
# Indicates the more common inherited platelet disorders.

Inherited Thrombocytopenias

Small platelets
- Wiskott–Aldrich syndrome*
- X-linked thrombocytopenia

Normal-sized platelets
- Congenital amegakaryocytic thrombocytopenia
- Amegakaryocytic thrombocytopenia with radio-ulnar synostosis
- Thrombocytopenia with absent radii*
- Familial platelet disorder and predisposition to acute myeloid leukemia*
- Autosomal dominant thrombocytopenia

Large platelets
- Bernard–Soulier syndrome*
- DiGeorge/Velocardiofacial syndrome
- Platelet-type von Willebrand disease*
- Gray platelet syndrome*
- ARC syndrome
- MYH9-related disorders*
- X-linked thrombocytopenia with thalassemia
Paris–Trousseau–Jacobsen syndrome
Benign Mediterranean macrothrombocytopenia
Dyserythropoietic anemia with thrombocytopenia

*These disorders may present with functional abnormalities in addition to thrombocytopenia.

The prevalence of inherited platelet disorders is unknown. A survey of pediatric centers in Germany, Austria, and Switzerland estimated two affected children per million population.

Most affected individuals present with symptoms and signs of mucocutaneous bleeding. These disorders may go undetected in young children unless a family history prompts early testing or until a hemostatic challenge results in bleeding. The consideration of congenital thrombocytopenia should be greater in patients who have a prolonged history of asymptomatic abnormal platelet counts or a family history of thrombocytopenia. Investigation of a child with a suspected platelet disorder can be difficult because the possible causes of mucocutaneous bleeding are many, and specialized testing is often difficult to access or interpret.

**Bernard–Soulier syndrome** is autosomal recessive and therefore most commonly seen in consanguineous families. There is thrombocytopenia and platelet dysfunction and results in a moderate or severe bruising/bleeding tendency from infancy.

**Wiskott–Aldrich Syndrome** is an X-linked immune-deficiency disorder associated with eczema. The more severe forms may present with bruising within the first 6 months of life that may precede the onset of recurrent infections.

**Gray platelet syndrome** results in severe bruising and bleeding from an early age. There is mild thrombocytopenia and examination of the blood film by light or electron microscopy usually makes the diagnosis, as agranular platelets are seen.

**Glanzmann thrombasthenia (GT)** is autosomal recessively inherited and is more commonly seen in consanguineous families. It is the most severe of the dysfunction disorders in which the platelet number and morphology is normal. The defect is in the platelet membrane glycoprotein IIb/IIIa, the main fibrinogen receptor on the platelet surface. Effective platelet aggregation and clot propagation cannot occur. The glycoprotein expression is absent in type 1 GT and there is dysfunctional glycoprotein receptor in type 2 GT. Typically, GT presents in infancy, with severe, often spontaneous bleeding usually from the mucous membranes, which can be life threatening if there is a delay in treatment. Petechiae are common, especially following restriction for venesection and bruising is usually extensive following even trivial injury.

**Platelet storage pool disorders** can be idiopathic or part of a more complex disorder. Generally, there is mild to moderate bruising tendency but in some children there is brisk bleeding following trauma or surgery. Hermansky Pudlak syndrome is autosomal recessive and includes oculocutaneous albinism. Albinism, susceptibility to infection and mental retardation are feature of Chediak Higashi syndrome.

**Diagnostic investigation of a suspected bleeding disorder**

It is not uncommon for anesthesiologists to care for patients who have thrombocytopenia or a personal or family history of bleeding. Although consultation with a hematologist is invaluable, the anesthesiologist can often make substantial progress towards characterizing a platelet disorder by performing a thorough history and physical examination and by requesting some commonly available laboratory tests.

The initial evaluation of a child with a suspected platelet disorder should begin with a detailed medical and bleeding history, including family history. Standardized, validated bleeding questionnaires may be useful in assessing the significance of bleeding symptoms in individual patients. The Pediatric Bleeding Questionnaire (PBQ) is a standardized questionnaire for mucocutaneous bleeding in children with type 1 VWD that has been shown to be potentially useful for assessing bleeding severity in children with other platelet disorders. The PBQ summates scores
for 13 bleeding symptoms, graded according to severity from -1 or 0 to 4, and including a pediatric-specific category (umbilical stump bleeding, cephalohematoma, post-circumcision bleeding, venipuncture bleeding, conjunctival hemorrhage, macroscopic hematuria). The higher the score, the greater the risk of bleeding.

An algorithm (Figure 4) developed for the investigation of suspected platelet disorders provides a sequential approach to evaluating both platelet function abnormalities and thrombocytopenia. Investigation begins with a clinical evaluation and laboratory testing that is generally available, including platelet counting, peripheral blood cell morphology, and aggregometry. Based on results of initial investigations, the algorithm recommends specialized testing for specific diagnoses, including flow cytometry, immunofluorescence microscopy, electron microscopy, and mutational analysis.

**Figure 4:** Algorithm for evaluation of children with suspected platelet disorders.

Suggested investigations are in gray boxes and potential results in hatched boxes. The circles and dotted circles contain diagnoses and suspected diagnoses, respectively.

BSS, Bernard–Soulier syndrome; CAMT, congenital amegakaryocytic thrombocytopenia; ATRUS, amegakaryocytic thrombocytopenia with radio-ulnar synostosis; FPD/AML, familial platelet disorder and predisposition to acute myelogenous leukemia; GT, Glanzmann thrombasthenia; GPS, gray platelet syndrome; SGD, storage granule disorder; TAR, thrombocytopenia with absent radii; THC2, autosomal dominant thrombocytopenia; XLT, X-linked thrombocytopenia. Some rare disorders are not included in the algorithm.


**Platelet count**

A platelet count that does not make sense clinically should be confirmed. Spurious thrombocytopenia can be caused by improper collection or inadequate anticoagulation of the blood sample, resulting in
platelet clumps that are counted as leukocytes by automated cell counters. Automated cell counters underestimate platelet counts when platelet size is outside the established reference range. Similarly, the mean platelet volume obtained from an automated cell counter may under or over estimate platelet size as the largest and smallest platelets are excluded from the analysis.

Screening tests for platelet disorders

Considering the challenges of testing children for abnormalities of primary hemostasis, there is yet no ideal simple, inexpensive, sensitive screening test that reliably identifies patients requiring specialized testing of platelet function. Although both bleeding times and PFA-100 closure times (Platelet Function Analyzer-100; Siemens, Marburg, Germany) have been used for this purpose, these tests are not adequately sensitive to rule out the need for further testing in patients with mucocutaneous bleeding, or in the pre-operative screening of unselected pediatric patients. In most studies, the lack of specificity has limited their usefulness and, although they may have a role in the comprehensive evaluation of primary hemostatic abnormalities, these tests should be considered optional.

Whole blood coagulation tests such as the thromboelastograph (TEG) and rotational thromboelastometry (ROTEM) provide global assessment of hemostasis and clot lysis in whole blood. In addition to measuring the rate of clot formation, clot strength, and subsequent lysis, the contribution of platelet function and platelet interaction with clotting factors is also assessed. These tests do not appear to be useful as screening tests for platelet disorders and do not demonstrate age-related developmental changes in the hemostatic system. They have been used for monitoring hemostasis during cardiac and transplant surgery, as well as in evaluation of hypercoagulable states.

Platelet Function Testing

The most common method of assessing platelet function is LTA, in which the optical density of a rapidly stirred sample of citrated platelet-rich plasma is measured by a photometer.

Upon addition of agonists (e.g., ADP, epinephrine, collagen, arachidonic acid, the stable TxA2 mimetic U46619), the platelets change shape from discs to more rounded forms with extended filipodia, resulting in a transient, small decrease in light transmission that is followed by an increase as the platelets aggregate in a fibrinogen-dependent manner. Typically, the increase in light transmission (% aggregation) is measured. The secondary aggregation response observed with higher concentrations of ADP and epinephrine is due to TxA2 formation and secretion of granule contents. Platelet agglutination stimulated by ristocetin, which changes the conformation of plasma VWF allowing it to bind to GPIb–IX–V, is also measured by LTA. Although many preanalytical and analytical variables affect the results, and international surveys have shown that there is a wide variation in methods, LTA remains the gold standard platelet function test.

Perioperative management of suspected platelet disorders

Elective surgery:

- Investigate the cause. If necessary, consult a hematologist. In a fair proportion of cases, the cause of the platelet dysfunction will remain unclear.
- If possible, avoid drugs that impair platelet function. (See reviews by Levy, et al. and Vandermeulen, et al. for details on drug action and duration of effect.)
- Consider therapies that enhance clot formation (e.g.: antifibrinolytics, topical hemostatic agents) or improve platelet number/function (e.g.: desmopressin & VWD, corticosteroids & ITP).

Emergency Surgery:

Patients who have severe thrombocytopenia and/or platelet dysfunction and critical bleeding require immediate transfusion of platelets regardless of the cause of the platelet disorder. If the platelet disorder is due to platelet antibodies, the platelet dose may need to be increased and the therapeutic effect may be shorter.
Recommended reading

von Willebrand Disease

von Willebrand Factor (VWF)

VWF has two functions, as follows: (1) it attaches to subendothelial collagen and to platelets, promoting formation of a platelet plug at the site of injury of small blood vessels, and (2) it binds and transports factor VIII.

VWF gene

The gene for VWF is at the tip of the short arm of chromosome 12. It is exceptionally large, about 178 kilobases. A signal peptide and propeptide are encoded by about 80 kilobases and the mature subunit by the remainder.

VWF structure and function

VWF is synthesized in endothelial cells and megakaryocytes, first as a precursor polypeptide consisting of a signal peptide, a propeptide and a large subunit. Repeated domains in the subunit are illustrated below (Figure 5).

![Diagram of VWF structure](image)

**Figure 5:** VWF within the cell consists of a signal peptide, a propeptide and a mature subunit with repeating domains. There are three collagen binding sites at D’, A1 and A3 domains. Factor VIII binds at the D’ domain. Platelet GP Ib binds at the A1 domain. Platelet GP IIB/IIIa binds at the C1 domain.

In the endoplasmic reticulum, subunits join end-to-end by disulfide bonds to form dimers. In the Golgi apparatus, dimers link by additional disulfide bonds to form large multimers of differing sizes. Mature VWF is stored in alpha granules in megakaryocytes and platelets, and in Weibel-Palade bodies in endothelial cells. VWF is secreted from endothelial cells into the plasma. After secretion, the propeptide separates and circulates briefly. In the plasma, VWF multimers are subject to cleavage by a metalloprotease, ADAMTS-13 (which is deficient in thrombotic thrombocytopenic purpura.)

VWF is essential for the adhesion of platelets to the subendothelium at high fluid shear rates. VWF binds to subendothelial collagen and then to platelets at their glycoprotein Ib (GPIb) site. High molecular weight (HMW) VWF multimers bind to GPIB far better than do smaller ones. After platelets activate, another binding site, glycoprotein IIb/IIa (GPIIb/IIa), becomes available to VWF. Binding of VWF at GPIIb/IIa helps bridge the adherence of platelets to each other. Binding of VWF to FVIII is not dependent on multimer size.

VWF circulates as a coil of multimers. Upon stimulation, it uncoils into a long string, exposing many GP Ib binding sites.

**Normal variation in VWF levels**

**Environment:** Levels of VWF and of FVIII are increased by: (1) adrenalin release as in strenuous exercise or stress, (2) inflammatory conditions, (3) severe liver disease, (4) high levels of thyroid hormones as in hyperthyroidism and (5) high levels of estrogen and progesterone as in pregnancy.

**Genetics:** (1) Levels are higher in persons with blood groups A and B compared to blood group O. VWF is less glycosylated in group O persons (therefore, more susceptible to proteases). Levels of the protease ADAMTS-13, which cleaves VWF, are higher in group O persons. (2) Levels of VWF are higher in persons of black African descent than in Caucasians.
von Willebrand Disease (VWD)

VWD is caused by deficient or defective plasma VWF and >20 VWD variants have been described. There are three types of VWD:

- **Type 1**: partial quantitative deficiency of essentially normal VWF (±75% of cases)
- **Type 2**: qualitative deficiency of defective VWF (±25% of cases)
- **Type 3**: complete quantitative deficiency (virtually absent) VWF (<5% of cases)

### Influence of mutations on VWF

<table>
<thead>
<tr>
<th>Type of mutation</th>
<th>Consequence at molecular level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene deletion or null allele</td>
<td>Decreased VWF quantity</td>
</tr>
<tr>
<td>Missense</td>
<td>Decreased VWF quantity Function VWF abnormality</td>
</tr>
<tr>
<td></td>
<td>Abnormal range of multimer sizes</td>
</tr>
</tbody>
</table>

### VWD types: defect and genetics

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect</th>
<th>Genetics / comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Decreased amount VWF, normal multimers. Bleeding risk inversely related to VWF level.</td>
<td>Usually dominant</td>
</tr>
<tr>
<td>2A</td>
<td>Decreased large multimers (decreased formation or increased destruction) causes decreased GP1b binding.</td>
<td>Usually dominant, missense (A2, A1 domain)</td>
</tr>
<tr>
<td>2B</td>
<td>Increased affinity for platelet GP1b (gain-of-function). Decreased HMW multimers.</td>
<td>Usually dominant, missense (A1 domain). ± thrombocytopenia</td>
</tr>
<tr>
<td>2M</td>
<td>Decreased affinity for platelets. Normal multimers.</td>
<td>Usually co-dominant (A1 domain)</td>
</tr>
<tr>
<td>2N</td>
<td>Decreased affinity for FVIII. Increased proteolysis of unbound FVIII results in mild bleeding.</td>
<td>Recessive. Homozygous or doubly heterozygous (D'-D3 domain)</td>
</tr>
<tr>
<td>3</td>
<td>Absence of VWF. Increased proteolysis of unbound FVIII increases bleeding.</td>
<td>Recessive. Homozygous or doubly heterozygous.</td>
</tr>
</tbody>
</table>

### Laboratory testing

**Screening Tests**

Screening tests are of limited value for VWD.

- **Complete blood count (CBC)**. Thrombocytopenia, specifically in type 2B VWD.
- **Activated partial thromboplastin time (aPTT)**. The aPTT is often normal, but may be prolonged when the factor VIII level is reduced to below 30-40 IU/dL, as can be seen in severe type 1 VWD, type 2N VWD, or type 3 VWD.
- **Prothrombin time (PT)**. The PT is normal in VWD.
- **PFA closure time**. Lacks sensitivity in persons with mild bleeding.
- **Bleeding time**. Unreliable in children.
**Hemostasis Factor Assays**

The following specific hemostasis factor assays should be performed even if the screening tests are normal and are essential for the diagnosis of VWD (Table 3).

- **VWF:RCo.** Functional VWF assay (ristocetin cofactor activity), i.e., ability of VWF to agglutinate platelets, initiated by the antibiotic ristocetin. Normal range is 50-200 IU/dL.

- **VWF:Ag.** Quantity of VWF protein (antigen) in the plasma, measured antigenically using ELISA or latex immunoassay (LIA). Normal range is 50-200 IU/dL.

- **Factor VIII:C level.** Functional FVIII assay, i.e., activity of FVIII. Normal range is 50-150 IU/dL.

If abnormalities in the three tests above are identified, specialized coagulation laboratories may also perform the following assays to determine the subtype of VWD:

- **VWF multimer analysis.** SDS-agarose electrophoresis is used to determine the complement of VWF multimers in the plasma. Normal plasma contains VWF ranging from dimers to multimers >40. HMW multimers are decreased or missing in types 2A and 2B VWD. Other patterns differentiate subtypes of type 2A VWD.

- **Ristocetin-induced platelet agglutination (RIPA).** Agglutination of platelets by VWF at a low ristocetin concentrations (~0.5 mg/mL) is abnormal and may indicate VWD type 2B (mutation in VWF A1 domain) or a platelet defect called pseudo VWD (mutation in platelet GP1b receptor). In both cases there is enhanced VWF-platelet binding.

- **Binding of FVIII by VWF (VWF:FVIII B).** Ability of VWF to bind FVIII. Essential in order to identify type 2N VWD.

- **Collagen binding assay (VWF:CB).** Ability of VWF to bind to collagen (a sub-endothelial matrix component). Used in some laboratories to help define functional VWF discordance (i.e., to help distinguish types 1 and 2 VWD). Normal range is approximately 50-200 IU/dL.

**Table 3. Classification of VWD based on specific VWF tests**

<table>
<thead>
<tr>
<th>VWD type</th>
<th>VWF:RCo</th>
<th>VWF:Ag</th>
<th>VWF RCo: Ag</th>
<th>FVIII:C (IU/dl)</th>
<th>Multimers</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low</td>
<td>Low</td>
<td>&gt;0.6</td>
<td>±1.5x VWF:Ag</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>Low</td>
<td>Low</td>
<td>&lt;0.6</td>
<td>Low or normal</td>
<td>Fewer HMW</td>
<td>RIPA decreased</td>
</tr>
<tr>
<td>2B</td>
<td>Low</td>
<td>Low</td>
<td>&lt;0.6</td>
<td>Low or normal</td>
<td>Fewer HMW</td>
<td>RIPA excessive</td>
</tr>
<tr>
<td>2M</td>
<td>Low</td>
<td>Low</td>
<td>&lt;0.6</td>
<td>Low or normal</td>
<td>Normal</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>2N</td>
<td>Normal</td>
<td>Normal</td>
<td>&gt;0.6</td>
<td>Low (&lt;30)</td>
<td>Normal</td>
<td>Low VWF:FVIII B</td>
</tr>
<tr>
<td>3</td>
<td>Absent</td>
<td>Absent</td>
<td></td>
<td>Low (&lt;10)</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical presentation**

**Prevalence vWD in children**

1:100 – have low vWF (<50 IU/dL) (with or without bleeding/bruising history)

1:1,000 – present with bleeding/bruising

1:10,000 – referred to hematology clinic (ie: severe bleeding)

**Bleeding**

Bleeding history depends on disease severity. Symptoms may only become apparent on hemostatic challenge. Type 3 VWD is often apparent early in life, whereas mild type 1 VWD may not be diagnosed until adulthood, despite a history of bleeding episodes. Neonates have increased VWF
activity and more HMW multimers. Consequently, VWD is unlikely to present in the neonatal period unless it is type 3 VWD.

Individuals with VWD primarily manifest excessive mucocutaneous bleeding (bruising, epistaxis, menorrhagia, etc.) and do not tend to experience musculoskeletal bleeding unless the FVIII:C level is <10 IU/dL, as can be seen in type 2N or type 3 VWD. (See Table 4.)

**Table 4:** VWD: bleeding episodes.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Type 1 (n=671)</th>
<th>Type 2 (n=497)</th>
<th>Type 3 (n=66)</th>
<th>Normal (n=500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>61</td>
<td>63</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>32</td>
<td>32</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>Dental extraction</td>
<td>31</td>
<td>39</td>
<td>53</td>
<td>5</td>
</tr>
<tr>
<td>Hematomas</td>
<td>13</td>
<td>14</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Minor wound bleed</td>
<td>36</td>
<td>40</td>
<td>50</td>
<td>0.2</td>
</tr>
<tr>
<td>Gum bleeding</td>
<td>31</td>
<td>35</td>
<td>56</td>
<td>7</td>
</tr>
<tr>
<td>Post surgery bleeding</td>
<td>20</td>
<td>23</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Postpartum bleeding</td>
<td>17</td>
<td>18</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>5</td>
<td>8</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Joint bleeding</td>
<td>3</td>
<td>4</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>2</td>
<td>5</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral bleed</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

**Management of bleeding**

The two main treatments are desmopressin (DDAVP) and clotting factor concentrates containing both VWF and FVIII (VWF/FVIII concentrate). Individuals with VWD should receive prompt treatment for severe bleeding episodes.

**Desmopressin**

Most individuals with type 1 VWD and some with type 2 VWD respond to intravenous (0.3 mcg/kg) or intranasal (150-300 mcg/kg) treatment with desmopressin, which promotes release of stored VWF and raises levels three- to fourfold. (See "platelet disorders" section for further information about desmopressin.)

Following VWD diagnosis, a desmopressin challenge is advisable to assess VWF response. Desmopressin is the preferred treatment for acute bleeding episodes or to cover surgery. In persons who are intolerant to desmopressin or have a poor VWF response, clotting factor concentrate is required.

Desmopressin therapy for type 2B VWD is controversial because the drug can cause or worsen thrombocytopenia. Type 2M patients have a poor response to desmopressin, type 2N patients may respond but the FVIII level drops rapidly because of increased vulnerability to proteolysis. Therefore, concentrates usually required. Desmopressin is not effective in type 3 VWD.

**Intravenous infusion of VWF/FVIII Clotting Factor Concentrates**

In those who are non-responsive to desmopressin (ie: VWF deficiency is not sufficiently corrected), and for those in whom desmopressin is contraindicated, bleeding episodes can be prevented or
controlled with intravenous infusion of virally inactivated plasma-derived clotting factor concentrates containing both VWF and FVIII. Such concentrates are prepared from pooled blood donations from many donors. Concentrates with a ratio of >2:1 for VWF:RCo : FVIII activity are preferred. Haemate P/Humate-P and Alphanate are FDA approved for surgical prophylaxis. Studies report the median half-life of VWF:RCo is 11.3 hours for Haemate P and 6.5 hours for Alphanate.

Dosing can be calculated as follows: (i) Define vWF:RCo plasma level required, (ii) Measure patient’s vWF:RCo level, (iii) Calculate dose using general guide that 1 IU of VWF:RCo/kg increases plasma VWF:RCo by 2 percentage points. For example, a dose of 30 IU/kg will raise plasma VWF:RCo by 60 IU/dL.

**Table 5: VWF/FVIII clotting factor concentrates: dosing for procedures**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>vWF:RCo U/kg</th>
<th>Target plasma vWF:RCo</th>
<th>Infusions</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>50</td>
<td>100% initially</td>
<td>DOS &amp; daily until healed</td>
<td>FVIII + vWF:RCo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Later &gt;50%</td>
<td>(typically 7-10 days)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>30-50</td>
<td>&gt;50%</td>
<td>DOS &amp; 1-2 days until healed</td>
<td>FVIII + vWF:RCo</td>
</tr>
<tr>
<td>Dental</td>
<td>30</td>
<td>&gt;50%</td>
<td>DOS</td>
<td>Nil</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>50</td>
<td>100% initially</td>
<td>DOS &amp; daily for 3-4 days</td>
<td>FVIII + vWF:RCo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Later &gt;50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural catheter</td>
<td>50</td>
<td>100% initially</td>
<td>DOS &amp; daily as needed</td>
<td>FVIII + vWF:RCo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Later &gt;50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>30-50</td>
<td>&gt;50%</td>
<td>DOS &amp; daily as needed</td>
<td>FVIII + vWF:RCo</td>
</tr>
</tbody>
</table>

DOS: day of surgery

**Indirect Treatments**

In addition to treatments that directly increase VWF levels, individuals with VWD often benefit from indirect hemostatic treatments, including:

- Fibrinolytic inhibitors
- Hormonal treatments (i.e., the combined oral contraceptive pill for treatment of menorrhagia)

**Perioperative management of patients with VWD**

**Evaluation of bleeding risk**

A thorough history is essential. A pediatric bleeding questionnaire (PBQ) has been validated as a tool for assessing the risk of bleeding in children with type 1 VWD. The PBQ generates a bleeding score. This score can be combined with VWF:Ag and family history of bleeding to provide, by Bayesian analysis, the final odds of a patient having VWD.

**Management for elective surgery**

Management will depend on the type of surgery, severity and type of VWD and the response observed following a desmopressin challenge. Guidance from a hematologist is recommended.

A general guide is as follows:

**Major surgery:** All VWD types will require VWF/FVIII concentrates. Antifibrinolytic useful adjunct therapy. Very rarely, platelet transfusions may be required. Type 3 VWD patients who have homozygosity for large deletions may form allo-antibodies to VWF (anti-VWF). rFVIIa has been suggested for these patients.
Minor surgery: Severe type 1, most type 2 variants, and type 3 will require VWF/FVIII concentrates and antifibrinolytic. Desmopressin and antifibrinolytic may suffice for responders with mild type 1 or mild type 2A.

Dental care: Antifibrinolytics are particularly useful for mucous bleeding and may be adequate for patients with mild VWD who are undergoing dental care.

Emergency surgery: Same protocol as for major surgery.

Acquired VWD

This disorder is uncommon in children. It is associated with the following disease states: clonal hemoproliferative diseases, neoplasia, immunological disease, drugs and diseases such as uremia and congenital heart disease.

The likely mechanisms involved include:
- Defective VWF synthesis and/or release (hypothyroidism)
- Adsorption of VWF on cell surfaces (neoplasia, lymphoproliferative disorders)
- Auto-antibody to VWF (immunological diseases)
- Proteolytic degradation of VWF (uremia, drugs)
- Mechanical degradation of VWF by high shear stress (aortic stenosis)

Treatment options include:
- Treating the underlying disease
- Desmopressin as first choice for increasing VWF levels
- VWF/FVIII concentrates and/or IVIgG for non-responders.

Suggested reading


Hemophilia

Hemophilia A and B, together with VWD, represent 95% to 97% of all the inherited deficiencies of coagulation factors. The remaining deficiencies (fibrinogen, FII, FV, combined FV+FVIII, FVII, FX, FXI and FXIII) are generally transmitted as autosomal recessive traits and are quite rare in most populations, with the prevalence ranging from 1:500,000 for FVII deficiency to 1:2,000,000 for FII and FXIII deficiencies.

Hemophilia definition

- Hemophilia is an X-linked congenital bleeding disorder with a frequency of about one in 10,000 births.
- Hemophilia is caused by a deficiency of coagulation factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B) related to mutations of the clotting factor gene.
- Hemophilia A is more common than hemophilia B, representing 80-85% of the total.

Clinical presentation

- Easy bruising in early childhood;
- Spontaneous bleeding (particularly into the joints and soft tissue)
- Excessive bleeding following trauma or surgery.
- A family history of bleeding is commonly obtained. Hemophilia generally affects males on the maternal side. However, both FVIII and FIX genes are prone to new mutations, and as many as 1/3 of all patients may not have a family history of these disorders.
- Screening tests will show a prolonged APTT in severe and moderate cases but may not show prolongation in mild hemophilia. A definitive diagnosis depends on factor assay to demonstrate deficiency of FVIII or FIX.
- The severity of bleeding manifestations in hemophilia is generally correlated with the clotting factor level as shown in the following table.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Factor VIII Clotting Activity</th>
<th>Symptoms</th>
<th>Usual Age of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Frequent spontaneous bleeding (joint, muscle); abnormal bleeding after minor injuries, surgery, or tooth extractions</td>
<td>Age ≤2 years *Median age: 1 month</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>1%-5%</td>
<td>Spontaneous bleeding is rare; abnormal bleeding after minor injuries, surgery, or tooth extractions</td>
<td>Age &lt;5 years *Median age: 8 months</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;5%-35%</td>
<td>No spontaneous bleeding; abnormal bleeding after major injuries, surgery, or tooth extractions</td>
<td>Often later in life. *Median age: 36 months</td>
</tr>
</tbody>
</table>

* Median age data from United States Center for Disease Control

Bleeding Manifestations in Hemophilia

**Serious**
- Joints (hemarthrosis)
- Muscle/soft tissue
- Mouth/gums/nose
- Hematuria

**Life threatening**
- CNS
- GI
- Neck/throat
- Severe trauma

**Sites of bleeding**
- Hemarthrosis: 70-80%
- Muscle/soft tissue: 10-20%

**Joint bleeding**
- Knee: 45%
- Elbow: 30%
Management of bleeding
dyscracias

Other major bleeds; 5-10%
CNS bleeds: <5%

Ankle: 15%
Shoulder: 3%
Wrist: 3%
Hip: 2%
Other: 2%

Most newborns were diagnosed in the first month of life and the sites of hemorrhage included circumcision, head bleeds (of which half were intracranial) and heel sticks. Infants presenting beyond the first 6 months of life primarily manifest head injuries (with only 8% being intracranial) and mouth and joint bleeding.

Carriers
Being an X-linked disorder, the disease typically affects males, while females are carriers.

- Most carriers are asymptomatic.
- About 10% of carriers may have clotting factor levels in the hemophilia range – mostly in the mild category – but in rare instances, carriers can be in the moderate or severe range due to extreme lyonization.
- Carriers with factor levels in the hemophilia range may have bleeding manifestations commensurate with their degree of clotting factor deficiency, particularly during trauma and surgery.
- Menorrhagia is a common manifestation among those with significantly low factor levels (<30%). Birth control pills and antifibrinolytic agents are useful in controlling symptoms.

General principles of care pertinent to the anesthesiologist

- USA patients: survival and morbidity is reduced if patient managed at a hemophilia treatment center.
- Prevention of bleeding should be the goal.
- Acute bleeds should be treated early (within two hours, if possible).
- Clotting factor concentrate replacement or DDAVP should be given to achieve appropriate factor levels prior to any invasive procedures.
- Avoid use of drugs that affect platelet function, particularly acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors. The use of paracetamol/acetaminophen is a safe alternative for analgesia.
- Intramuscular injections, difficult phlebotomy, and arterial punctures must be avoided.

Management of bleeding

- Many patients carry easily accessible identification indicating the diagnosis, severity, inhibitor status, type of product used, and contact information of the treating physician/clinic. This will facilitate management in an emergency.
- In severe bleeding episodes, especially in the head, neck, chest, and gastrointestinal and abdominal regions that are potentially life-threatening, treatment should be initiated immediately, even before assessment is completed.
- The half-life of factors VIII and IX are decreased in infants and young children younger than 6 years owing to an age-related increased volume of distribution and accelerated plasma clearance.
- If bleeding does not resolve, despite adequate treatment, clotting factor level should be monitored and inhibitors should be checked if the level is unexpectedly low.
- Administration of desmopressin can raise FVIII level sufficiently high (2-8 times baseline levels) in patients with mild to moderate hemophilia A.
- Antifibrinolytic drugs (e.g., tranexamic acid, epsilon aminocaproic acid) for 5-10 days is effective as adjunctive treatment for mucosal bleeds (e.g., epistaxis, mouth bleed) and is used to decrease the use of coagulation products in dental extractions. These drugs should be avoided in renal bleeding as unlysed clots in the renal pelvis and ureter can behave like stones resulting in ureteric colic and obstructive nephropathy. Antifibrinolytic drugs should not be given concurrently with non-activated or activated prothrombin complex concentrates because of potential thrombotic complications.
• Certain COX-2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis.

Prophylaxis
Prophylaxis is the administration of clotting factors at regular intervals to prevent bleeding.
• Primary prophylaxis aims to keep clotting factor level >1%, thereby reducing spontaneous bleeding and better preserving of joint function.
• Primary prophylaxis is recommended standard of care for all children with hemophilia, with therapy started before the onset of recurrent joint hemorrhage. Currently, the most commonly suggested protocol for prophylaxis is the infusion of 25 IU/kg of clotting factor concentrates three times a week for those with hemophilia A and twice a week for those with hemophilia B.
• In patients with repeated bleeding, particularly into joints, short-term secondary prophylaxis for 4-8 weeks can be used to interrupt the bleeding cycle. Secondary prophylaxis reduces the number of joint bleeding episodes and increases use of FVIII (compared to therapy without secondary prophylaxis).
• Prophylaxis usually requires the insertion of a venous access catheter. The risks and morbidity associated with such devices in young children should be weighed against the advantages of starting prophylaxis early.

Surgery
• Surgical procedures should be performed in co-ordination with a team experienced in the management of hemophilia.
• Pre-operative assessment should include inhibitor screening.
• Surgery should be scheduled early in the week and early in the day for optimal laboratory and blood bank support, if needed.
• Availability of sufficient quantities of clotting factor concentrates should be ensured before undertaking major surgery for hemophilia.
• The dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed (see Table 5).

Inhibitors
About 10%-15% of hemophilia A patients and 1%-3% of hemophilia B patients may develop persistent inhibitors rendering treatments with factor concentrates difficult. These inhibitors are IgG antibodies, predominantly subtype 4.
• The majority of patients who develop inhibitors do so early – within the first 10-20 exposure days.
• Patients more likely to develop inhibitors are those with severe gene defects such as gene deletion or inversion, nonsense, and frameshift mutations. The location of missense mutation also influences inhibitor risk. Missense mutations affecting molecular sites that are critical for protein interactions convey a higher inhibitor risk than similar mutations in more neutral regions of the factor VIII molecule. Clinically relevant inhibitor formation is associated with (i) early FVIII exposure of high dose and duration; and (ii) surgery as the indication for first treatment. In contrast, early administration of lower-dose prophylaxis infusions of FVIII decreased inhibitor risk.
• Inhibitors may be transient despite continual specific factor replacement, usually when the titer is low (<5 Bethesda Units [BU]).
• Patients whose inhibitor titres are >5 BU (high responders) tend to have persistent inhibitors. If not treated for a long period, titer levels may fall but there will be a recurrent anamnestic response in 3-5 days when challenged again.
• For children, inhibitors should be screened once every 3-12 months or every 10-20 exposure days, whichever occurs first.
• Inhibitors should also be screened prior to surgery, and when clinical response to adequate treatment is sub-optimal.
• Very low titer inhibitors may not be detected by the Bethesda inhibitor assay, but by a poor recovery and/or shortened half-life following clotting factor infusions.
Inhibitors: Management of bleeding

- Management of bleeding in patients with inhibitors must be in consultation with a centre experienced in the management of such patients, and all serious bleeds should be managed in these centers.
- Choice of product should be based on titer of inhibitor, records of clinical response to product, and site and nature of bleed.
- Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralize the inhibitor with excess factor activity and stop bleeding.
- Patients with a history of a high responding inhibitor but with low titres may be treated similarly in an emergency, until an anamnestic response occurs, usually in 3-5 days, precluding further treatment with treatment products.
- With an inhibitor level >5 BU, the likelihood is low that specific factor replacement will be effective in overwhelming the inhibitor without high dose continuous infusion therapy.
- Alternative agents for hemophilia inhibitor patients include bypassing agents, such as recombinant factor VIIa and prothrombin complex concentrates, including the activated ones such as FEIBA® and Autoplex®. A recent multinational randomized crossover clinical trial demonstrated equivalence of an 85 U/kg dose of FEIBA and two 105 mcg/kg doses of rFVIIa. Response to both was judged to be effective in about 80% of cases at 6 hours.

Allergic reactions in hemophilia B patients with inhibitors

Hemophilia B patients with inhibitors have special features, in that up to 50% of cases may have severe allergic reactions, including anaphylaxis to FIX administration. Thus, newly diagnosed hemophilia B patients, particularly those with a family history and/or with genetic defects predisposed to inhibitor development, should be treated in a clinic/hospital setting capable of treating severe allergic reactions during the initial 10-20 treatments with FIX concentrates. Reactions can occur later but may be less severe.

Immune tolerance induction

- In patients with hemophilia A and inhibitors, eradication of inhibitors is often possible by immune tolerance induction (ITI) therapy. The primary ITI method is administration of repetitive doses of factor VIII with or without immunosuppressive therapy. Many responders have an initial rise in the antibody titer caused by the anamnestic response, followed by a progressive reduction to a low or undetectable titer. Immune tolerance can be long lasting but usually must be maintained by continued exposure to infused clotting factor.
- Experience with ITI for hemophilia B inhibitor patients is limited. The principles of treatment in these patients are similar to those mentioned above, but the success rate is much lower, especially in persons whose inhibitor is associated with an allergic diathesis. Furthermore, hemophilia B inhibitor patients with a history of severe allergic reactions to FIX may develop nephrotic syndrome during ITI, which is not always reversible upon cessation of ITI therapy.

Patients switching to new concentrates

For the vast majority of patients, switching products does not lead to the development of inhibitors. However, in rare instances inhibitors in previously treated patients have occurred with the introduction of new FVIII concentrates. In those patients, the inhibitor disappeared only after withdrawal of the offending product. Therefore, patients switching to a new factor concentrate should be monitored for inhibitor development.

Laboratory diagnosis

Coagulation screening tests

- In individuals with hemophilia:
  - The APTT is prolonged in severe and moderate hemophilia A or B.
  - Prolongations in APTT that correct on mixing with an equal volume of normal plasma indicate an intrinsic system clotting factor deficiency, including FVIII or FIX, without an inhibitor.
- The APTT may be normal or mildly prolonged in mild hemophilia A or B. Diagnosis of all cases of mild haemophilia requires both one-stage and two-stage clotting or chromogenic assays.

**Factor assay**

Factor assay is required in the following situations:

- **To determine diagnosis**
- **To monitor treatment**
  - The laboratory monitoring of clotting factor concentrates is possible by performing pre- and post-infusion clotting factor levels.
  - The actual amount of infused clotting factor given to the patient should predict the rise in blood levels. This approach is especially important when surgical procedures are to be performed. It is also useful for documenting dose-response relationship.
  - Lower than expected recovery may be an early indicator of the presence of inhibitors.

- **To detect carriers**
  - In the case of phenotypic analyses, a ratio of the factor VIII:C to von Willebrand factor antigen (VIII:C/VWF:Ag) is normally 1.0. A result of less than 0.7 gives an 80% chance of a female being a carrier.

**Genetic testing**

- Molecular genetic testing of F8, the gene encoding factor VIII, identifies disease-causing mutations in as many as 98% of individuals with hemophilia A.
- F9 is the only gene in which mutations are known to cause hemophilia B.

**Clotting factor concentrates**

**Purity**

Purity refers to the percentage of the desired ingredient (e.g., FVIII) in concentrates, relative to other ingredients present.

- Low purity is less than 10 IU per mg of protein.
- Intermediate purity is 10–100 IU per mg of protein.
- High purity is 100–1,000 IU per mg of protein.
- Very high purity is more than 1,000 IU per mg of protein.

Products with higher purity have a lower percentage of von Willebrand factor. The risk of thromboembolic complications is decreased with the high purity FIX products.

**Viral transmission**

Recombinant factor is the concentrate of choice. It is produced using mammalian cell culture systems and viral transmission has not been reported.

**Mode of administration**

Continuous infusion will help avoid peaks and troughs and is considered by many to be safer and more cost-effective. This will reduce significantly the total amount of factor concentrates used to treat bleeding or during prophylaxis after surgery. Dosage is adjusted based on frequent factor assays and calculation of clearance. FVIII and FIX concentrates of very high purity are stable in IV solutions for at least 24-48 hours at room temperature with less than 10% loss of potency. Recently, multiple approaches have been taken to increase the effective half-life of FVIII and FIX after infusion.

**Cryoprecipitate**

Cryoprecipitate contains significant quantities of FVIII (about 5 IU/ml), von Willebrand factor (vWF), fibrinogen, and FXIII (but not FIX or XI). It is not recommended for treatment of hemophilia.

**Other Pharmacological Options**

In addition to conventional coagulation factor concentrates, there are other agents that can be of great value in a significant proportion of cases. These include:

- Desmopressin;
- Antifibrinolytics (tranexamic acid; epsilon aminocaproic acid).

**Desmopressin (DDAVP)**
Desmopressin boosts the plasma levels of FVIII and VWF after administration.
- A single intravenous infusion at a dose of 0.3 micrograms/kg body weight can be expected to boost the level of FVIII three- to sixfold.
- The peak response is seen approximately 90 minutes after completion of the infusion.
- Closely spaced repetitive use of DDAVP may result in decreased response (tachyphylaxis) after 1-2 days so that factor concentrates may be needed when higher factor levels are required for a prolonged period.
- A concentrated nasal spray is available. Recommended dose is 300 micrograms for those over 50 kg and 150 micrograms for those up to 50 kg.
- Test the patient’s response as significant individual differences are possible.
- The compound is ineffective in patients with severe hemophilia A.
- Desmopressin does not affect FIX levels and is of no value in hemophilia B.
- The decision to use DDAVP must be based on both the baseline concentration of FVIII and on the nature of the procedure. It would not, for example, be feasible to perform gastrectomy in a patient with a baseline FVIII level of 10% or less. The expected postinfusion level of 30-40% would not be sufficient to ensure hemostasis and the responses to subsequent doses would be even less. On the other hand, the same patient might be able to have a dental extraction after an infusion.
- Desmopressin is particularly useful in the treatment of bleeding in female carriers of hemophilia.
- Obvious advantages of DDAVP over plasma products are the much lower cost and the absence of any risk of transmission of viral infections.
- Rapid infusion may result in tachycardia, flushing, tremor, and abdominal discomfort.
- Water retention and hyponatremia is a concern in children, especially if there concomitant administration of diuretic therapy. Children under two years old are at particular risk of hyponatremia that may provoke seizures.

**Tranexamic acid**
Tranexamic acid is an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin. It promotes clot stability and is useful as adjunctive therapy. Tranexamic acid alone is of no value in prevention of hemarthroses in hemophilia. However, it is certainly valuable in controlling bleeding from mucosal surfaces (e.g., oral bleeding, epistaxis, menorrhagia) in hemophilia A and B and is particularly valuable in the setting of dental surgery and may obviate the need for replacement therapy with concentrates.

**Tranexamic acid administration:**
- The usual dose for children is 25 mg/kg up to three times daily.
- The drug can be used as a mouthwash and may be of particular use in controlling oral bleeding associated with eruption of teeth.
- Gastrointestinal upset (nausea, vomiting and diarrhea) may rarely occur as a side effect, but these symptoms usually resolve if the dosage is reduced. It may also be given by intravenous injection, but it must be infused slowly as rapid injection may result in dizziness and hypotension.
- The kidneys excrete the drug and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.
- The use of tranexamic acid is contraindicated for the treatment of hematuria in severe hemophilia, as treatment may precipitate clot colic and even obstruction of the outflow from the renal pelvis.
- Similarly, the drug is contraindicated in the setting of thoracic surgery, where it may result in the development of insoluble hematomas.
- Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrates. Please note:
  - It should not be given to patients with inhibitory antibodies receiving activated prothrombin factor concentrates (APCCs) (such as FEIBA® or Autoplex®) as this may exacerbate the risk of thromboembolism.
  - If treatment with both agents is deemed necessary, it is recommended that at least 4–6
hours elapse between the last dose of APCC and the administration of tranexamic acid. By contrast, tranexamic acid may be usefully used in combination with recombinant factor VIIa to enhance hemostasis.

**Aminocaproic acid**

Epsilon aminocaproic acid (EACA) is an antifibrinolytic similar to tranexamic acid but has a shorter plasma half-life and is less potent.

**Administration:**
- The commonly used pediatric dosage is 50-100 mg/kg (maximum 5 gms) PO or IV every 6-8 hours.
- Myopathy is a rare adverse reaction specifically reported in association with EACA therapy. Full resolution may be expected once drug treatment is stopped.

**Treatment of Hemophilia A**

**FVIII concentrates**
- Each FVIII unit per kilogram of body weight infused intravenously will raise the plasma FVIII level approximately 2%. The half-life is approximately 8-12 hours.
- Infuse FVIII by slow IV push at <100 units per minute in children.

**Cryoprecipitate/fresh frozen plasma**
- Only use cryoprecipitate if factor concentrates are not available.
- FVIII content per bag of cryoprecipitate is 60-100 units (average = 80 units).
- Fresh frozen plasma may also be used if factor concentrates are not available. One ml of fresh frozen plasma contains 1 unit of factor activity.

**Desmopressin (DDAVP)**
- DDAVP is useful in the treatment of persons with mild hemophilia who have a 5% or greater FVIII level and who have been shown to be responsive in pre-tests.

**Treatment of Hemophilia B**

**Gene therapy**

Successful gene therapy was reported by Nathwani AC, et al. (N Engl J Med. 2011 Dec).

**FIX concentrates**

FIX concentrates fall into two classes:
- Pure coagulation FIX products (either plasma-derived FIX or recombinant FIX
- Prothrombin complex concentrates (PCCs).

The use of pure FIX concentrates is recommended. Purified FIX products are largely free of the risks of that could cause patients to develop thrombosis or disseminated intravascular coagulation (DIC), which may occur with large doses of intermediate purity PCCs.
- Each FIX unit per kilogram of body weight infused intravenously will raise the plasma FIX level approximately 1%. The half-life is about 18-24 hours.
- Recombinant FIX (rFIX; BeneFIX®, Wyeth) has a lower recovery, and each FIX unit per kg body weight infused will raise the FIX activity by approximately 0.8% in adults and 0.7% in children < 15 years of age. rFIX is derived from hamster ovary cells.
- Infuse FIX by slow IV push at a rate at <100 units per minute in children.

**Surgery**
- Once the coagulation defect is corrected by infusion with factor, operative and invasive procedures can be performed. A consultation with a hematologist who is familiar with surgery in hemophilia is necessary.
- Document the patient’s individual response to the replacement material prior to surgery. Rule out an inhibitor if the patient does not respond adequately.
- Immediately prior to the procedure, the factor level must be raised to the appropriate level required for hemostasis (see Table 5).
- An appropriate factor level should be maintained for 5–7 days or till wound healing after
minor surgery, and for 10–14 days after major surgery (see Table 5). After some orthopedic procedures, factor level may need to be maintained for a longer period of time.

**Minor invasive procedures**
- Infuse factor concentrates before invasive diagnostic procedures are performed. These procedures include lumbar puncture, arterial blood gas determination, bronchoscopy with brushings or biopsy, and gastrointestinal endoscopy with biopsy.

**Emergency surgery**
If a patient is known or suspected to have hemophilia and requires emergency surgery, the following approach is recommended:

**Hemophilia A without Inhibitor**
- The treatment of choice is rFVIII or else the patient’s product of choice.
- When bleeding is severe, the appropriate dose of factor VIII is 50 units/kg. This should result in a factor VIII level of 80-100%.

**Hemophilia B without Inhibitor**
- The treatment of choice is rFIX or else the patient’s product of choice.
- When bleeding is severe, the appropriate dose of factor IX is 100-120 units/kg. This should result in a factor IX level of 80-100%.

**Hemophilia A or B with Inhibitor**
- If an individual with an inhibitor presents in a life- or limb-threatening scenario, the safest immediate action is to prescribe rFVIIa at a dose of 90 mcg/kg or activated prothrombin complex concentrates (FEIBA) at 75-100 units/kg.
- In factor IX patients with a history of inhibitors and anaphylaxis, do not give factor IX-containing products unless the bleeding is life-threatening.

**Allergic reactions to factor replacement products**
- Use the filters included in factor packages to avoid the possibility of reaction.
- To prevent or reduce symptoms, use antihistamines.
- Changing the brand of clotting factor concentrate sometimes reduces symptoms.
Table 5: Recommended Plasma Factor Level and Duration of Administration

<table>
<thead>
<tr>
<th>Hemorrhage type</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Desired level</td>
<td>Duration (days)</td>
</tr>
<tr>
<td>Joint</td>
<td>40-60%</td>
<td>1-2, longer if poor response</td>
</tr>
<tr>
<td>Muscle (except iliopsoas)</td>
<td>40-60%</td>
<td>2-3, longer if poor response</td>
</tr>
<tr>
<td>Iliopsoas</td>
<td>80-100%</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>30-60%</td>
<td>3-5, sometimes longer as secondary prophylaxis during physiotherapy</td>
</tr>
<tr>
<td>CNS/head</td>
<td>80-100%</td>
<td>1-7</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>8-21</td>
</tr>
<tr>
<td>Throat &amp; neck</td>
<td>80-100%</td>
<td>1-7</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>8-14</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>80-100%</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>7-14</td>
</tr>
<tr>
<td>Renal</td>
<td>50%</td>
<td>3-5</td>
</tr>
<tr>
<td>Deep laceration</td>
<td>50%</td>
<td>5-7</td>
</tr>
<tr>
<td>Surgery (major)</td>
<td>80-100%</td>
<td>1-3</td>
</tr>
<tr>
<td>Pre-op</td>
<td>60-80%</td>
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</tr>
<tr>
<td></td>
<td>40-60%</td>
<td>7-14</td>
</tr>
<tr>
<td></td>
<td>30-50%</td>
<td></td>
</tr>
</tbody>
</table>

Acquired Hemophilia A

Acquired haemophilia A (AHA) is an auto-immune disease caused by an inhibitory antibody to factor VIII. AHA is associated with immune diseases such as rheumatoid arthritis, polymyalgia rheumatica and systemic lupus erythematosus; malignancy (occasionally occult); pregnancy and dermatological disorders such as pemphigoid. In about half of cases no underlying cause is found.

The pattern of bleeding is similar to inherited hemophilia A but with fewer joint bleeds. Patients remain at risk of life threatening bleeding until the inhibitor has been eradicated by immunosuppression. To treat bleeds recombinant factor VIIIa and activated prothrombin complex concentrate are equally efficacious and both are superior to factor VIII or desmopressin. Immunosuppression should be started as soon as the diagnosis is made. Commonly used regimens are steroids alone or combined with cytotoxic agents.

AHA in children is very uncommon, estimated at 0.045 per million year\(^{-1}\). Patients appeared to present with a bleeding pattern typical for AHA and response to immunosuppression appears to be similar to adults.

FXI deficiency (also called hemophilia C)

Genetics

Factor XI deficiency is an autosomal recessive bleeding disorder, which is common in Jews particularly of Ashkenazi origin. About 8% of Ashkenazi Jews are heterozygotes and 0.22%
individuals (1:450) have severe FXI deficiency. The prevalence in a general population is >1:1,000,000.

Homozygotes or compound heterozygotes have an FXI level of <15 U dL⁻¹ and heterozygotes have levels of 25–70 U dL⁻¹ or normal values. FXI activity is usually concordant with antigenicity, patients with dysfunctional FXI are uncommon.

**Bleeding**
The bleeding pattern differs from other types of hemophilia. Spontaneous bleeding, except for menorrhagia, is rare in patients with severe FXI deficiency. Bleeding is usually injury-related, particularly when it afflicts tissues containing activators of the fibrinolysis, such as oral cavity, nose, tonsils, and urinary tract. At other sites of trauma like during orthopedic surgery, appendicectomy, circumcision, or cuts in the skin, bleeding is less common. BLEEDING can occur at the time of injury and persists unless treated, or can begin several hours later. Some patients with very low level of FXI may not bleed at all following trauma. Bleeding can vary in the same patient over time even when provoked by similar hemostatic challenges.

**Coagulation tests**
All patients with severe FXI deficiency (activity of <15 U dL⁻¹) have a markedly prolonged APTT. Heterozygotes may have a slightly prolonged APTT or values within the normal range. Because severe FXI deficiency can remain asymptomatic until injury is inflicted, it is essential for all Ashkenazi Jews in need of surgery to be tested by an APTT assay. If a prolonged APTT is obtained, FXI activity should be measured by a specific assay.

**Therapy**
Therapy for prevention of bleeding during surgery in patients with severe FXI deficiency consists of plasma, factor XI concentrates, fibrin glue and antifibrinolytic agents.

Following exposure to blood products, inhibitors to FXI develop in one-third of patients with very severe FXI deficiency (usually those who are homozygous for null alleles). Such patients do not usually present with spontaneous bleeding. However, trauma or surgery can be accompanied by excessive bleeding that cannot be managed by FXI concentrate or plasma. rFVIIa is reported effective at low dose (15 mcg/kg), along with antifibrinolytic therapy.
Suggested reading

6. Blanchette VS. Prophylaxis in the haemophilia population Haemophilia 2010; 16 (Suppl. 5):181–188.