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### BACKGROUND

Abnormal bleeding may result from defects in platelets, coagulation factors and/or blood vessels. Screening tests for coagulation factor abnormalities include the activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT) / International Normalized Ratio (INR). Thrombocytopenia is the most common platelet defect. Qualitative platelet defects may also occur and, in some cases, may be associated with thrombocytopenia. In patients with platelet defects, bleeding time and/or closure times using the platelet function analyzer (PFA-100/200™) may be prolonged. Vascular defects may be accompanied by joint hyperflexibility or skin laxity. Effective treatment of hemostatic disorders requires accurate diagnosis and special coagulation testing that may include coagulation factor assays, inhibitor assays, and platelet function tests. An algorithmic approach to diagnosis is beyond the scope of this review.

### CONGENITAL/INHERITED BLEEDING DISORDERS

Congenital/inherited bleeding disorders are relatively rare and their management can be complex. Management of these patients is best coordinated with regional comprehensive hemophilia/bleeding disorders programs and hematologist experts in the management of these disorders. In Canada, practically all patients with hemophilia are registered with one of the 25 hemophilia/bleeding disorders programs located across the country (for treatment centre contact information, see the Canadian Hemophilia Society [website](#)<sup>1</sup>). In addition, patients registered and seen in these clinics will have been issued a “Factor First” or “Treat First” card outlining the individual patient’s diagnosis, recommended initial emergency treatment for “major” and “minor” bleeds, as well as the patient’s clinic contact information. It is recommended that patients carry this card on their person at all times. After the initial emergency dose, the hemophilia/bleeding disorders clinics should be informed to secure recommendations for continuing care.

#### Congenital Coagulation Disorders

While the mainstay of therapy for bleeding is to increase the coagulation factor level with concentrates or pharmaceuticals, appropriate use of adjunctive agents including antifibrinolytics (tranexamic acid), fibrin glue, topical thrombin, gel foam and microporous polysaccharide particles are often effective for minor bleeds in specific sites. These adjunctive agents, together with clotting factor concentrates for more severe bleeding, can result in earlier hemostasis and less overall use of factor concentrates. Conservative measures, including local pressure and rest, ice, immobilization compression and elevation (RICE), should be applied where appropriate. Antifibrinolytic agents should, however, be avoided when using concentrates with thrombogenic potential, such as FEIBA (factor eight inhibitor bypassing activity) or prothrombin complex concentrates, and in patients with bleeding from the upper urinary tract and/or bleeding into the thoracic cavity. Antifibrinolytics are generally safe when used with recombinant factor VIIa (rFVIIa).

#### Hemophilia<sup>2</sup>

Hemophilia can be due to a deficiency of either factor VIII (FVIII) (hemophilia A, classic hemophilia) or factor IX (FIX) (hemophilia B, Christmas disease) with an overall incidence of about 1:5,000–7,000 male births. Hemophilia A is more common, comprising 80–85% of cases. The management of bleeding depends on the type and severity of hemophilia, as well as the site and severity of bleeding. Patients with severe hemophilia A or B have baseline clotting factor levels of <1 IU/dL (0.01 IU/ml or 1%) and those with clotting factor levels >5 IU/dL (0.05 IU/ml or 5%) are defined as mild hemophilia A or B. Moderate disease falls in between severe and mild.

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**Desmopressin (DDAVP):** In mild hemophilia A patients (baseline FVIII activity above 5%), minor bleeding or minor procedures can often be successfully managed with desmopressin (0.3 µg/kg body weight intravenous (IV) or subcutaneously (sc)). If possible, the patient should have had prior testing to assure an adequate response. Closely spaced repetitive dosing may result in tachyphylaxis, so that supplementation by factor concentrates is required for prolonged treatment. Patients on desmopressin may develop fluid retention and hyponatremia. This is particularly problematic in children younger than two years, the elderly, and patients with compromised cardiovascular systems. Attention to restricting fluid intake (usually 1500 cc or less for 24h after a dose for an adult, and weight-based maintenance volume for a child) and monitoring sodium levels are important with this therapy.

**Clotting Factor Concentrates:** The approach to FVIII or FIX replacement therapy is outlined in Table 1. The initial desired factor level for different types of bleeding and maintenance therapy for severe bleeding are described. A general formula for dosage calculation in IU/kg suitable for these concentrates (applicable also to other clotting factor concentrates) with known in vivo recoveries is in the footnote to Table 1. In general, if the dosing interval is identical to the  $T_{1/2}$  (half-life) of the clotting factor, the maintenance dose required to reach the original peak factor concentration is half the loading dose. Pharmacokinetic (PK) studies to measure the recovery and  $T_{1/2}$  are desirable to guide dose and dosing interval as these PK parameters vary between products and more significantly between individuals. This is particularly important in children, who may have a larger plasma volume and require larger doses to achieve the same factor levels compared with an adult patient. PK determination using as few as 2-4 samples is now possible using the population PK analysis technique offered by WAPPS-Hemo.<sup>3</sup>

Continuous infusion (CI) following a loading dose for severe bleeding and for surgery (see footnote to Table 1) has an advantage in that the in vivo factor level is more constant, without the peaks and troughs that result from bolus injections. CI may result in less overall use of concentrate. Infusion pumps capable of delivering small volumes are required, as the concentrates should not be diluted beyond manufacturer recommended dilutions. Careful monitoring of the pump and intravenous site/tubing is also necessary to ensure no interruptions in treatment occur.

For factor IX concentrate, it is advisable for newly diagnosed severe hemophilia B patients to receive approximately the first 20 infusions in a setting equipped for management of severe allergic reactions. This is because about 1-3% of severe hemophilia B patients may develop inhibitors (usually early on with FIX replacement therapy), often accompanied by severe allergic reactions including anaphylaxis.

**Table 1:** Recommended peak plasma factor level and duration of administration (please refer to Table 1, Chapter 5 of this [Guide](#) for details of available clotting factor concentrates)

Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired peak level (IU/dL)*	Duration (Days)	Desired peak level (IU/dL)*	Duration (Days)
<b>Joint</b>	40-60	1-2 may be longer if response is inadequate	40-60	1-2 may be longer if response is inadequate
<b>Muscle</b> (except iliopsoas)	40-60	2-3 sometimes longer if response is inadequate	40-60	2-3 sometimes longer if response is inadequate

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Type of hemorrhage	Hemophilia A		Hemophilia B	
	Desired peak level (IU/dL)*	Duration (Days)	Desired peak level (IU/dL)*	Duration (Days)
<b>Iliopsoas</b> - initial - maintenance	80-100 30-60	1-2 3-5 sometimes longer as secondary prophylaxis during physiotherapy	60-80 30-60	1-2 3-5 sometimes longer as secondary prophylaxis during physiotherapy
<b>CNS/head</b> - initial - maintenance	80-100 50	1-7 8-21	60-80 30	1-7 8-21
<b>Throat and neck</b> - initial - maintenance	80-100 50	1-7 8-14	60-80 30	1-7 8-14
<b>Gastrointestinal</b> - initial - maintenance	80-100 50	1-7 7-14	60-80 30	1-7 7-14
<b>Renal</b>	50	3-5	40	3-5
<b>Deep laceration</b>	50	5-7	40	5-7
<b>Surgery (major)</b> - Pre-op - Post-op	80-100 60-80 40-60 30-50	n/a 1-3 4-6 7-14	60-80 40-60 30-50 20-40	n/a 1-3 4-6 7-14
<b>Dental Extraction¶</b> Pre-op	30-50	n/a	30-50	n/a

Adapted from *Guidelines for the Management of Hemophilia*.<sup>2</sup>

\*1 IU/dL = 1% activity (= 0.01 IU/ml)

¶ plus oral antifibrinolytics (i.e. tranexamic acid 25 mg/kg every 8h) or local antifibrinolytics (i.e. 10 ml 5% tranexamic acid mouthwash rinse 4x per day) for 7-10 days.

Dosage calculation and maintenance does:

Note: while these are convenient dosing calculations using average recovery and  $T_{1/2}$  values, dosing is more accurate based on PK parameters of the particular product determined for the individual patient.

Dosage in IU/kg = (desired IU/dL factor activity - baseline IU/dL factor activity), IVR (where IVR = in vivo recovery in IU/dL activity rise per IU/kg body weight infused; see Table 1 in Chapter 5 of this Guide for average IVR of various FVIII and FIX products).

In the absence of an inhibitor activity in adults, the average *Recovery* per IU/kg infused is for rFVIII and pdFVIII, ~2 IU/dL; pdFIX, ~1 IU/dL; rFIX, ~0.8 IU/dL; glycopegylated rFIX, 2.0 IU/dL. Thus, using the dosage calculation formula, raising factor level from 10 IU/dL (baseline) to 100 IU/dL (desired) will need for rFVIII or pdFVIII: 45 IU/kg; for pdFIX: 90 IU/kg; for rFIX: 112.5 IU/kg; for glycopegylated rFIX 45 IU/kg.

The maintenance dose to reach the original peak factor concentration is half the original loading dose if the

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dosing interval is identical to the  $T_{1/2}$  for the clotting factor for the particular patient. Maintenance dose will vary if given at intervals different from the  $T_{1/2}$  for the clotting factor for the particular patient; see Table 1 in Chapter 5 of this Guide for average  $T_{1/2}$  of various FVIII and FIX products.

### Special considerations in children:

In children, the recovery is expected to be lower in all clotting factor preparations because of a higher plasma volume per unit body mass resulting in higher dosage requirements. For example, the recovery for rFIX for children  $\leq 15$  year can be as low as 0.65IU/dL activity rise per IU/kg infused.

### Continuous infusion:

Following the initial bolus infusion to achieve the desired peak level, continuous infusion can be given using a syringe pump at 2-4 IU/kg/hr for FVIII and 4-6 IU/kg/hr for FIX, with the dose adjusted to achieve the desired plasma clotting factor level based on frequent factor assays.

## Prevention of Bleeding<sup>2,4,5</sup>

### Factor concentrate infusion

Prophylaxis by factor concentrate infusion at regular intervals to prevent bleeding is now a standard of hemophilia care, with the goal to prevent musculoskeletal disability and improve patient quality-of-life.

**Primary Prophylaxis:** Regular continuous treatment started before the age of 3 years, before the second bleed into large joints (elbow, knee or ankle) and in the absence of osteochondral joint disease. Clinical trials have confirmed that primary prophylaxis is effective in preventing musculoskeletal disability.

- Full dose prophylaxis is defined as a dosage schedule of 25–40 IU/kg FVIII every other day for severe hemophilia A, and 25–40 IU/kg FIX every third day for severe hemophilia B, and is designed to maintain clotting factor level above 1 IU/dL at all times (i.e. converting a patient with severe to moderate disease).<sup>2,4</sup>
- The Canadian Hemophilia A Prophylaxis Study protocol starts with FVIII 50 IU/kg per week (step 1), with escalation to 40 IU/kg twice weekly (step 2) then to 25 IU/kg every other day (step 3) after achieving predefined bleeding symptoms while on the given dose schedule of FVIII. This protocol appears effective, is less onerous, and in many young patients can be started without the need for an implanted vascular access device (IVAD).<sup>5</sup>
- Other dosage and dose intervals have also been reported in the literature for various FVIII and FIX products, both with regular and extended half-life. Selection of product type (regular half-life vs. extended half-life), dosage, and dosing interval may be adjusted to optimize clinical (bleeding rates, joint status) and patient-desired outcomes (activity level, quality of life).
- Historically, maintaining trough levels greater than or equal to 1 IU/dL has been the primary goal of prophylaxis to prevent spontaneous joint bleeds and progressive arthropathy. However, many patients may require higher target trough levels to achieve the desired bleed prevention, depending on their level of physical activity and joint status.
- Extended half-life (EHL) products may allow for less frequent dosing while achieving desired trough levels, especially with FIX EHL products, where there may be a 2.5–4.8-fold increase in half-life.<sup>6,7</sup>

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- Dosage and dose intervals for any particular product to achieve a desired trough level may also be individualized based on the pharmacokinetic parameters obtained on particular product for the individual patient.

**Secondary Prophylaxis:** Regular continuous treatment started after two or more bleeds into larger joints, but before the onset of osteochondral joint disease.

**Tertiary Prophylaxis:** Regular continuous treatment started after the onset of joint disease.

**Intermittent Prophylaxis:** Treatment given to prevent bleeding for a period less than 45 weeks in a year.

Prophylaxis is advisable prior to activities and after a major bleed to prevent recurrences or after recurrent bleeding into a single joint (target joint) to interrupt the bleeding cycle.

### Exercise programs

Patients should be engaged in exercise programs appropriate for their musculoskeletal status to improve muscle tone, balance, and to achieve general physical conditioning for overall health as well as to help prevent injury and bleeding. Weight bearing exercise may also improve bone density and prevent osteopenia/osteoporosis that may predispose to fragility bone fractures.

## Hemophilia with inhibitors and acquired FVIII inhibitors<sup>8,9</sup>

Twenty to thirty percent of hemophilia A patients and one to three percent of hemophilia B patients develop inhibitors to the clotting factor protein for which they are deficient. This renders treatment with clotting factor concentrates difficult. Management of bleeding in these patients **must** be in consultation with a centre experienced in the management of inhibitor patients. All serious bleeds should be managed in these centres.

**Hemophilia A with FVIII inhibitors:** Patients with low inhibitor titers at time of treatment (<5 BU) may be treated with human factor concentrate at a sufficiently high dose to neutralize the inhibitors and leave excess factor activity available to stop the bleeding. Doses of 100 IU/kg can be initiated with monitoring of clinical response and clotting factor levels to allow for adjustment of dosage. Patients with an inhibitor level above 5–10 BU are unlikely to respond to FVIII concentrates. Alternative “bypassing” agents include rFVIIa (Niasase<sup>®</sup>) (~90–120 µg/kg every 2–3 hours) and FEIBA (50–100 U/kg FEIBA every 8–12 hours, limit < 200 U/kg/24 hours). A management algorithm has been developed by the Inhibitor Subcommittee of the Association of Hemophilia Clinic Directors of Canada.<sup>8</sup> Antifibrinolytics can be used concurrently with human FVIII and rFVIIa, but should be avoided with FEIBA. Switching between rFVIIa and FEIBA should allow for a time gap of 3–6 hours for rFVIIa→FEIBA and 6–12 hours for FEIBA→rFVIIa, in order to decrease the thrombogenic potential of this combination. There are anecdotal reports of successful use of the two agents together (with each at a lower dose).<sup>10</sup>

Refractory patients (with continuing severe bleeding) may require plasmapheresis or immunoglobulin G (IgG) column immunoabsorption (in selected centres only) to rapidly decrease inhibitor titer and allow effective use of FVIII containing concentrates. Recombinant porcine FVIII is another option for life-threatening bleeding (i.e. CNS) or if surgery is required in consultation with a centre experienced in the management of inhibitor patients.

Eradication of FVIII inhibitor can be attempted with immune tolerance induction (ITI) therapy by daily to every other day FVIII infusion.

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Prevention (prophylaxis) of bleeding in inhibitor patients can be attempted by prophylactic IV infusions of FEIBA (usually once every other day), rFVIIa (usually once daily). Emicizumab is a bispecific antibody to human IX/IXa and FX/Xa which can be administered subcutaneously in 1–4 week intervals. Clinical trials showed that emicizumab is superior to bypassing agents at preventing bleeding in FVIII inhibitor patients,<sup>11</sup> and as a result, emicizumab has recently been approved by the US FDA and by Health Canada (August 2, 2018).

**Hemophilia B with FIX inhibitors:** The management principle is similar to that of hemophilia A with inhibitors. It is important to recognize that about 50% of hemophilia B patients with inhibitors may have severe allergic responses (including anaphylaxis) to FIX-containing concentrates and to FEIBA. In such patients, rFVIIa can be used. Nephrotic syndrome is a potential complication in these allergic inhibitor patients undergoing immune tolerance induction therapy.

**Acquired FVIII inhibitors:** <sup>12, 13</sup>

Acquired FVIII inhibitor, also known as acquired hemophilia A, is a rare but potentially life-threatening acquired bleeding disorder caused by the development of autoantibodies (inhibitors) directed against FVIII. Management includes treatment of bleeding events and concurrent immunosuppression (prednisone 1 mg/kg/d and/or agents such as cyclophosphamide 1–1.5 mg/kg/day, rituximab 375 mg/m<sup>2</sup> weekly for four weeks) to eradicate the inhibitors. Identification and management of comorbid conditions associated with FVIII inhibitor formation should be considered.

Minor bleeding often can be managed successfully with desmopressin (0.3 µg/kg to 20 µg IV or sc) and/or conservative measures. Severe bleeding requires the use of rFVIIa (~90 µg/kg every 2–3 hours), FEIBA (50–100 U/kg every 8–12 hours, maximum 200 U/kg/day) with careful clinical monitoring. A management algorithm has been developed by the Inhibitor Subcommittee of the Association of Hemophilia Clinic Directors of Canada.<sup>8</sup> Recombinant porcine FVIII is now licensed and available for the treatment of life or limb threatening bleeding and for use during surgical procedures in these patients. Importantly, the use of this agent can be monitored with FVIII activity levels.<sup>14, 15</sup> The latter product should be used only in a centre experienced in the management of inhibitor patients.

### Emerging therapies and innovations in factor concentrates

Treatment and prevention of bleeding in hemophilia patients has, for many years, been limited by the short half-life of “native” clotting factor products and the need for frequent intravenous infusion. There are now extended half-life clotting factors available or in clinical development. The risk of developing inhibitors to clotting factors also prompted the investigation of new therapies.

Extended half-life (EHL) clotting concentrates<sup>6</sup>

EHL products were developed using either fusion technology to link a moiety (Fc or albumin) to the native recombinant clotting factor or through adding pegylation to the protein. Both strategies increase the time in which the clotting factor remains in circulation. For factor VIII, these fusion technologies extend the FVIII half-life by ~1.5 times, and for factor IX the half-life is extended by 2.5–4.8 times.<sup>7</sup> The improvements in half-life are product and patient-specific and determination of dose/dosing interval can be optimized by individual PK parameters. Potential benefits of EHLs may include less frequent dosing, higher trough levels, and improved adherence to prophylaxis. Further extension of clotting factor VIII half-life, including fusion with XTEN protein polymers and D'D3 VWF fragment,<sup>16</sup> is currently under clinical development.

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### Non-clotting factor therapies

Manipulating pathways to rebalance hemostasis or mimic FVIII activity is under rapid development in hemophilia. These technologies have the advantages of a subcutaneous route for administration, effective hemostasis in the presence or absence of factor inhibitor, and amelioration of the risk of clotting factor inhibitor development (although anti-drug antibodies may still occur). Emicizumab is a bi-specific antibody to FIX/FIXa discussed above. Fitusiran is a siRNA (small interfering RNA) that targets antithrombin synthesis. Fitusiran therefore decreases endogenous antithrombin levels, which improves thrombin generation and fibrin clot formation without the need for FVIII or FIX replacement.<sup>17</sup> This molecule is currently in Phase II/III clinical trials. Concizumab is one of several humanized monoclonal antibodies to tissue factor pathway inhibitor (TFPI) in development that result in increased thrombin generation and hemostasis in hemophilia A and B patients.<sup>18</sup>

### Gene therapy

There has been rapid progress in gene therapy for both hemophilia A and B. Long-term data available on the adeno-associated virus (AAV)-8 FIX gene therapy trial demonstrate sustained FIX levels (mean 5.1 IU/dL) for up to seven years.<sup>19</sup> Gene therapy with recombinant AAV vector (Spark-9001)-FIX Padua (a gain of function FIX variant Arg338Leu) resulted in a mean sustained FIX level of 33.7 IU/dL for 28–78 weeks.<sup>20</sup> An AAV-5 FVIII gene therapy trial is showing promising results, with sustained FVIII levels (mean 77 IU/dL) at 35 weeks.<sup>21</sup>

## Von Willebrand's disease (VWD)<sup>22</sup>

**Desmopressin (DDAVP):** Most patients with mild quantitative von Willebrand's factor (VWF) deficiency (type 1 VWD) and some patients with qualitative VWF defects (type 2A) respond to desmopressin (0.3 µg/kg body weight IV or sc, or intranasally at 150 µg for body weight less than or equal to 50 kg and 2 x 150 µg for weight above 50 kg). Testing to establish desmopressin responsiveness is desirable prior to use to confirm appropriate correction of VWF levels to treat minor and/or major bleeding episodes. Patients with type 3 disease (virtual absence of VWF) or type 2M disease, and some patients with type 2A disease do not respond to desmopressin. The use of desmopressin may result in thrombocytopenia in type 2B patients and is generally not recommended for these patients. In Vincenza type and type 2N VWD, the peak response may be normal, but  $T_{1/2}$  of the raised FVIII/VWF (for Vincenza type) and FVIII (for type 2N) is much shorter.

**Clotting Factor Concentrates:** Replacement therapy for desmopressin non-responsive patients and for severe bleeding or major procedures can be accomplished using pd FVIII/VWF (Humate-P<sup>®</sup>, Wilate<sup>®</sup>) or rVWF concentrate (Vonvendi<sup>®</sup>, registration under review by Health Canada). FVIII/VWF concentrate contains both FVIII and VWF at various ratios, depending on the product and rVWF concentrate does not contain FVIII (see Chapter 5 of this [Guide](#), Table 1). The usual dosage is 30–50 units/kg (in ristocetin cofactor units for Humate-P<sup>®</sup>, or FVIII units for Wilate<sup>®</sup>) for minor bleeding, and 50–80 units/kg for more severe bleeding. Types 2 and 3 patients should receive the higher dose within the range. The dose can be repeated every 12 hours depending on the clinical situation. In patients refractory to FVIII/VWF concentrates, desmopressin and/or platelets may be used in addition. Although VWF is necessary for initial cessation of mucosal bleeding, adequate FVIII levels are more important for soft tissue and surgical bleeding and for maintenance of hemostasis. When prolonged coverage with these concentrates is required, it is desirable to monitor the FVIII level and to maintain FVIII below 200 IU/dL (200% activity) to decrease potential thrombogenic effects. This is particularly important in surgical and immobilized medical patients. The rVWF concentrate is free of FVIII and therefore, a lag period for in vivo FVIII level to rise following rVWF infusion is expected. Thus, for surgical procedures in severe VWD (e.g. type 3 and severe type 1), either rFVIII will need to be given concurrently with the initial rVWF dose immediately prior to the procedure, or a loading rVWF dose should be given some hours before incision, to allow FVIII level to

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rise to the desired level before the procedure.

### Rare Congenital Coagulation Disorders<sup>23,24</sup>

Patients with rare congenital coagulation factor deficiencies with bleeding diatheses include those with FII, FV, FVII, FX, FXI, fibrinogen and FXIII deficiencies (each with an incidence of 1:500,000–1:2,000,000). Management of bleeding in patients with these factor deficiencies is summarized in Table 2. Characteristics of factor concentrates used to treat these deficiencies are summarized in Table 1, Chapter 5 of this [Guide](#).

**Table 2:** Management of a patient with a rare clotting factor deficiency (please refer to Table 1, Chapter 5 of this [Guide](#) for details of available clotting factor concentrates)

Deficiency	Plasma T <sub>1/2</sub>	In vivo recovery# (IU/dL‡ per IU/kg, except for fibrinogen)	Desired levels¶	Treatment options	Comments
Fibrinogen	2–4d	10 mg/kg infused increases circulating level by ~0.2 g/L	<ul style="list-style-type: none"> <li>• 0.5–1g/l for most bleeding</li> <li>• 1 g/l for major bleeding and surgery</li> <li>• 1.0 g/l during pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>• Fibrinogen concentrate 50–100 mg/kg</li> <li>• Cryoprecipitate (200–300 mg/bag): 1 bag /5 kg initially, then 1 bag/15 kg every 24h</li> </ul>	<ul style="list-style-type: none"> <li>• Paradoxical venous/arterial thromboses have been reported in patients with afibrinogenemia</li> <li>• Thrombosis may also be a complication of replacement therapy</li> </ul>
FII	2–3d	~1.0	<ul style="list-style-type: none"> <li>• 20–40 IU/dL for most bleeding and surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Plasmat<sup>†</sup> 15–20 ml/kg, then 3 ml/kg every 12–24h</li> <li>• PCC‡ – FII 20–30 IU/kg</li> </ul>	
FV	15–36h	~1.6	<ul style="list-style-type: none"> <li>• 15–20 IU/dL for most bleeds</li> <li>• 20–25 IU/dL for surgery/severe bleeds</li> </ul>	<ul style="list-style-type: none"> <li>• Apheresis fresh frozen plasma (AFFP) or Octaplasma<sup>®*</sup> 15–20 ml/kg, then 5–10 ml/kg every 12h</li> <li>• Platelet transfusion could be considered</li> </ul>	<ul style="list-style-type: none"> <li>• Factor concentrates are not available</li> <li>• FV is unstable so stored plasma should not be used (see the <a href="#">Circular of Information</a> for plasma components for more information)</li> </ul>
FVII	3–6h	~2.0	<ul style="list-style-type: none"> <li>• 15–25 IU/dL for most bleeds</li> <li>• 40–60 IU/dL for surgery/severe bleeds</li> </ul>	<ul style="list-style-type: none"> <li>• pdFVII concentrate 20–40 IU/kg every 6–12h</li> <li>• rFVIIa 15–30 microgram/kg every 4–6h</li> <li>• Plasmat<sup>†</sup> 15–20 ml/kg, then 4 ml/kg every 6h</li> </ul>	<ul style="list-style-type: none"> <li>• Variable bleeding diathesis inconsistent with FVII level, but likely to bleed with FVII &lt;3%</li> <li>• FVII level can vary with thromboplastin used in assay</li> </ul>
FX	20–40h	1–1.9	<ul style="list-style-type: none"> <li>• 10–20 IU/dL for minor bleeds</li> <li>• 20–40 IU/dL for major bleeds</li> <li>• 30–50 IU/dL for surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Plasmat<sup>†</sup> 15–20 ml/kg, then 3–6 ml every 12h</li> <li>• PCC‡ 20–30 FX IU/kg</li> </ul>	
FXI	35–60h	~1.8	<ul style="list-style-type: none"> <li>• 20–30 IU/dL</li> </ul>	<ul style="list-style-type: none"> <li>• Plasmat<sup>†</sup> 15–20 ml/kg then 3–6 ml every 12h</li> <li>• FXI concentrate 15–25 IU/kg</li> </ul>	<ul style="list-style-type: none"> <li>• Variable bleeding diathesis inconsistent with FXI level – correlated with family history of bleeding. When in doubt, patients with FXI activity &lt;10% should receive replacement therapy before surgery</li> <li>• FXI concentrate dose &gt;30 IU/kg may be associated with thromboembolism, particularly in the elderly</li> </ul>
FXIII	5–11d	1.0–2.0	<ul style="list-style-type: none"> <li>• 5–10% for most bleeds</li> <li>• 25–30 IU/dL for severe bleed/surgery</li> <li>• Pregnancy: &gt;10 IU/dL early gestation; 20–40 IU/dL later pregnancy and delivery</li> </ul>	<ul style="list-style-type: none"> <li>• Plasmat<sup>†</sup> 15–20 mL/kg</li> <li>• pdFXIII or rFXIII concentrate 20–40 IU/kg; cryoprecipitate 1 bag/10 kg</li> <li>• Prophylaxis: pdFXIII concentrate: 20–40 IU/kg every 4 weeks (every 2–3 weeks during pregnancy); rFXIII concentrate: 35 IU/kg every 4 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• rFXIII concentrate contains only FXIII-A subunits and should not be used for FXIII-B subunit deficiency as FXIII-A has a much shortened T<sub>1/2</sub> in the absence of FXIII-B subunit (which binds and stabilizes FXIII-A)</li> <li>• pdFXIII concentrate should contain both FXIII-A and FXIII-B subunits and can be used for deficiency of FXIII-A or FXIII-B deficiency</li> </ul>

**Table 2:** Management of a patient with a rare clotting factor deficiency (please refer to Table 1, Chapter 5 of this [Guide](#) for details of available clotting factor concentrates)

¶ 1 IU/dL = 1% activity (= 0.01 IU/ml).

# In vivo recovery (IVR) expected to vary between individuals.

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† Plasma: stored plasma, fresh frozen plasma or virus-inactivated plasma [e.g. Octaplasma<sup>®</sup> (Octapharma)]. If the desired level and hemostasis cannot be reached with plasma, may need plasmapheresis with plasma replacement.

\* If the desired level and hemostasis could not be reached with fresh frozen plasma or virus-inactivated plasma [e.g. Octaplasma<sup>®</sup> (Octapharma)], may need plasmapheresis with fresh frozen plasma replacement.

‡PCC: prothrombin complex concentrate. Thrombotic risk precaution – use minimal effective dose.

## CONGENITAL PLATELET DISORDERS<sup>25-27</sup>

There are many types of congenital platelet functional defects (the Association of Hemophilia Clinic Directors of Canada (AHCDC) has published a list of platelet functional disorders and their diagnostic criteria<sup>28</sup> and analysis algorithm<sup>29</sup>). These disorders include, among others, Glanzmann's thrombasthenia (platelet membrane GPIIb/IIIa deficiency or abnormality), Bernard-Soulier syndrome (platelet membrane GPIa/IX/V deficiency or abnormality) and storage pool diseases.

Most minor bleeding in these patients can be managed with conservative measures, including pressure, antifibrinolytics, and topical hemostatics including fibrin glue. Desmopressin may also be effective for minor/moderate bleeding, but response to this agent is variable.

Severe bleeding that does not respond to conservative treatments can be managed by platelet transfusions (preferably apheresis HLA (human leukocyte antigen)-matched). In transfused patients who have developed antibodies to HLA and/or the missing platelet glycoproteins and who are refractory to platelet transfusion, some case series suggest that rFVIIa can be useful. Experience with Glanzmann's thrombasthenia suggests that rFVIIa (at a dose of approximately 90 µg/kg every 2–2.5 hours for three doses or more, as appropriate), in conjunction with administration of antifibrinolytics, is effective in a high proportion of bleeding episodes and surgical procedures. Limited experience suggests that the continuous infusion (CI) of rFVIIa may not be as effective in stopping ongoing bleeding, although CI appears effective in surgical prophylaxis. Thrombotic complications have been reported with high dose CI for a prolonged period in surgical settings in persons with co-morbid risks for thrombosis. Desmopressin together with antifibrinolytics have variable efficacy.

## Collagen Vascular Disorders

Patients with collagen vascular disorders seldom have serious bleeding and most episodes can be managed with conservative measures. Desmopressin has been used successfully in some patients undergoing surgical procedures probably by improving platelet-endothelium interaction. For bleeding in mucosal surfaces, tranexamic acid can also be used. There is no evidence that blood products are indicated.

## ACQUIRED COAGULATION DISORDERS

### Liver Disease

With the exception of tissue factor, all clotting factors are synthesized in the liver with some (factors II, VII, IX, X) requiring vitamin K as a cofactor. In patients with liver disease the levels of clotting factors are often low. Fibrinogen and FVIII, which are acute phase reactants, are exceptions; their levels tend to increase in uncomplicated liver disease. Concomitant DIC should be considered if fibrinogen and FVIII levels are decreased.

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The aPTT and PT are usually prolonged in liver disease and are usually sufficient for monitoring therapy without the need for assays to determine clotting factor levels. Patients with liver disease may also have thrombocytopenia because of splenomegaly from portal hypertension or from underlying viral infection. Bleeding from coagulopathy related to liver disease is generally mild and can usually be treated adequately with an infusion of plasma, which contains all the clotting factors synthesized in the liver. PCC is thrombogenic in liver disease and is to be avoided for these patients.<sup>30</sup> Bleeding from structural lesions such as varices and ulcers may be severe in these patients and their management must include attempts to achieve hemostasis at the bleeding site in addition to treating the coagulopathy.

## Oral Anticoagulant Overdose

### Vitamin K antagonists (VKA)<sup>31,32</sup>

Vitamin K is required for the synthesis of functional factors II, VII, IX, and X (vitamin K dependent factors). Coumarin type drugs exert their anticoagulant action by competitively inhibiting vitamin K function. This results in a decrease in functional vitamin K dependent factors and an increase in INR (PT). Many drugs may interact with coumarin and may result in excessive anticoagulation with marked increases in INR. When the INR is moderately increased without bleeding, cessation of the anticoagulant drug may be sufficient. This is to allow the vitamin K dependent factors to increase slowly according to the intrinsic synthetic rate. In situations where the immediate increase of the clotting factor is required, as in acute bleeding or when emergency surgery is necessary, infusion of prothrombin complex concentrates (Octaplex<sup>®</sup>, Beriplex<sup>®</sup>; for dosage guidelines, see the NAC recommendations for the use of prothrombin complex concentrates<sup>30</sup>) with concurrent use of vitamin K for sustained response. For elective surgery, discontinuation of coumarin drugs (and substitution with low molecular heparin as appropriate) for a few days to allow INR to fall below 1.5 is generally sufficient. In patients bleeding while on VKA, bleeding source must be identified and definitively treated.

### Direct oral anticoagulants (DOAC, oral Xa and IIa inhibitors)<sup>31-33</sup>

Direct oral anticoagulants (DOAC) available in Canada include direct inhibitors of FIIa (dabigatran), and FXa (rivaroxaban, apixaban, edoxaban). All DOACs are partially dependent on renal elimination for clearance from circulation; dabigatran is the most dependent at 85% renally excreted. While taking these anticoagulants, renal function monitoring is important, as bioaccumulation can occur with renal insufficiency. The DOACs do not require routine laboratory coagulation monitoring or dose adjustment. However, in anticoagulated patients presenting with bleeding who require an urgent surgery or thrombolysis, assessing for the presence and/or concentration of DOAC is important.

**Dabigatran:** A normal thrombin time (TT) essentially excludes the presence of dabigatran. It should be noted that a prolonged TT does not differentiate between clinically important and insignificant levels of dabigatran (test is very sensitive), and that a normal aPTT does not exclude the presence of circulating dabigatran (test can be insensitive to dabigatran depending on test reagents used). Dilute thrombin time, best for accurate assessment of dabigatran anticoagulant activity is not widely available.

**Factor Xa inhibitors:** For the direct FXa inhibitors (rivaroxaban, apixaban, edoxaban), the PT is generally prolonged, but a normal PT does not exclude clinically relevant levels of a direct FXa inhibitor (test can be insensitive depending on the test reagents used). A normal anti-Xa activity excludes clinically relevant levels of a direct FXa inhibitor but is useful for quantification of plasma drug levels only when calibrated with the specific drug in question.

The management of bleeding in patients on DOACs is complex. Please refer to local treatment algorithms/pathways and/or published guidelines.<sup>31, 33</sup> General principles include:

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1. For mild bleeding, local therapy and/or withdrawal of next DOAC dose(s) may be all that is needed.
2. For clinically significant and life-threatening bleeding not responsive to local and general supportive measures (including transfusion), the following measures are suggested:
  - Consider oral administration of activated charcoal for known recent ingestion (2–4 hours).
  - Specific antidotes for the DOACs include idarucizumab (Praxbind®, a monoclonal antibody fragment, licensed in Canada) for dabigatran and andexanet alfa (AndexXa®, a recombinant modified human factor Xa decoy protein, FDA approved in the US but not yet licensed in Canada) for the FXa inhibitors.
  - For patients on dabigatran with life-threatening bleeding, with impaired renal function and/or excessively prolonged APTT (or dabigatran level >500 ng/ml) and in cases where idarucizumab is not available, hemodialysis to reduce circulating drug level may be considered. Hemodialysis is not appropriate for rivaroxaban and apixaban as these drugs are protein-bound and not dialysable.
  - Prospective cohort studies have also shown usefulness of activated prothrombin complex concentrate (APCC: FEIBA)<sup>34</sup> for dabigatran and regular prothrombin complex concentrates (PCC: Octaplex®, Beriplex®, 25–50 IU/kg) for direct FXa inhibitors.<sup>35</sup> Their clinical benefit and risk (e.g. thrombosis) will need further assessment by clinical trials.
  - Antifibrinolytics (tranexamic acid) may also be used in bleeding patients, but should not be used together with APCC or PCC (or with blood in the urine or chest cavity).
3. For perioperative management of emergency and elective surgery of patients on DOAC, consult references.<sup>31, 33</sup>

## Disseminated Intravascular Coagulation (DIC)

DIC can be triggered by a number of clinical situations, including massive tissue destruction, infection, obstetrical complications, and cancer, among others. Unregulated activation of the coagulation system will result in the activation and consumption of clotting factors and platelets. In addition, widespread secondary fibrinolytic activation will result in the destruction of clotting factors and generation of fibrin-fibrinogen degradation products that interfere with fibrin polymerization and platelet function.

Depending on the balance between coagulation and fibrinolysis, patients may have bleeding and/or thrombotic complications. Treatment to remove the stimulus that initiates DIC in a non-bleeding patient is often sufficient to reverse the process. When bleeding occurs, the patient can be stabilized by replacing the consumed factors. Therapy may include the use of frozen plasma, cryoprecipitate (for FVIII and fibrinogen) and platelet transfusion (for severe thrombocytopenia). PCC is thrombogenic in DIC and should be avoided.<sup>30</sup> Transfusion therapy is only an adjunct to treating the underlying clinical condition that initiates DIC. Replacement of clotting factors does not stop the DIC process.

Overwhelming bacterial sepsis with DIC and skin necrosis is associated with high morbidity and mortality and

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the potential place of natural protease inhibitors as therapeutic agents has been assessed. Phase III clinical trials initially suggest a survival benefit with the use of recombinant activated protein C (rAPC).<sup>37</sup> This finding was however not confirmed in subsequent studies, including a large placebo-controlled trial in patients with severe sepsis and septic shock.<sup>38</sup> A large Phase III trial on the use of antithrombin also did not show survival benefit<sup>39</sup> although a recent propensity-adjusted retrospective studies in Japan showed a significant advantage of anti-thrombin-treated severe sepsis patients with DIC.<sup>40</sup> The latter observations will need prospective validation. Another agent showing promise in a multicenter retrospective study is recombinant soluble thrombomodulin.<sup>41</sup>

## HEREDITARY ANGIOEDEMA<sup>42</sup>

Hereditary angioedema (HAE) is due to a quantitative or functional deficiency in C1-esterase inhibitor (C1-INH), a key regulator of the complement, intrinsic coagulation and fibrinolytic systems. The prevalence of HAE is approximately 1 in 50,000. It is associated with mutations of the *SERPING1* gene (previously known as *C1-INH*), located on chromosome 11, and is inherited in an autosomal dominant manner. Two main types of HAE have been described. Type I HAE is defined by a quantitative deficiency in circulating C1-INH antigen (85% of cases) while Type II HAE is associated with normal C1-INH antigen levels, but exhibits a functional deficiency (15% of cases).<sup>43</sup> A third type of HAE has also been described which is not associated with C1-INH deficiency, but the clinical symptoms are attributed to excessive bradykinin production.<sup>44</sup>

Patients with hereditary angioedema have episodic swellings, referred to as attacks, which can affect any part of the body. Commonly involved sites include the skin, face, upper respiratory tract, oropharynx, gastrointestinal tract, extremities and genitals; edema of the face and oropharynx remains the most concerning as it may be associated with life-threatening airway compromise. Edema of the gastrointestinal tract is frequently associated with severe pain, nausea, vomiting, diarrhea and temporary bowel obstruction that may lead to unnecessary surgical procedures. Common triggers which may result in swelling include stress, medications, trauma, infection or hormonal exposure.

Although frequently mistaken for allergic or anaphylactic angioedema, the lack of urticaria and slowly progressive nature of symptoms help to distinguish HAE from these conditions. An acute swelling episode is typically associated with progressive edema of the affected site over 24 hours with gradual resolution during the following 1 to 5 days if left untreated. However, the frequency, duration, and severity of attacks are variable within affected individuals. It should not be considered a benign disease as mortality rates reaching 30% have been described in individuals who have not been treated or appropriately diagnosed.<sup>45</sup>

The management of HAE generally consists of two strategies: treatment of acute swelling (on demand) and treatment used to prevent swelling episodes (prophylaxis). On demand treatment may consist of replacing C1-INH or by reducing the production or function of bradykinin. Therapeutic options for on demand treatment include:

- Plasma-derived C1-INH replacement therapy, such as Berinert 20 U/kg IV push
- Icatibant, a bradykinin B2 receptor antagonist, at a dose of 30 mg slow sc injection every 6 hours to a maximum of 3 doses in 24 hours
- Plasma at a dose of 10–15 ml/kg every 2–4 hours until clinical improvement

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Plasma-derived C1-INH replacement is the preferred prophylactic treatment (Berinert 20 U/kg IV twice weekly or Cinryze 1000 U IV twice weekly). However, for specific cases, oral tranexamic acid (25 mg/kg daily given in divided doses) or danazol (200–600 mg daily) may be considered. Emerging therapies for prophylaxis include subcutaneous C1-INH replacement and medications which inhibit kallikrein. Corticosteroids, epinephrine, and antihistamines are ineffective for the treatment of HAE.

## CONTINUING PROFESSIONAL DEVELOPMENT CREDITS

Fellows and health-care professionals who participate in the Canadian Royal College's Maintenance of Certification (MOC) Program can claim the reading of the Clinical Guide to Transfusion as a continuing professional development (CPD) activity under [Section 2: Self-learning credit](#). The reading of one chapter is equivalent to **two credits**.

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We're here to answer your questions about the Clinical Guide to Transfusion. We'd also appreciate your ideas on how to improve the Guide. Please contact us through the [Clinical Guide feedback form](#).

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## Chapter 17: Hemostatic Disorders and Hereditary Angioedema

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