

INHIBITORS TO CLOTTING FACTOR

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All statements identified as recommendations are consensus based, as denoted by .

This chapter describes inhibitor formation, one of the most serious complications in hemophilia treatment, and provides key definitions and guidance on inhibitor screening, testing, and treatment. The management of hemophilia A inhibitors and hemophilia B inhibitors is discussed separately given the differences in inhibitor incidence and treatment.

All recommendations on product use in this chapter are made under the assumption that a specific product is available in a particular country, region, or healthcare system.

8.1 | Introduction

- “Inhibitors” in hemophilia are IgG alloantibodies to exogenous clotting factor VIII (FVIII) or factor IX (FIX) that neutralize the function of infused clotting factor concentrates (CFCs).¹ Inhibitors are detected and quantified by the Nijmegen-modified Bethesda assay.
- The presence of a new inhibitor should be suspected in any patient with hemophilia who fails to respond clinically to CFC replacement therapy, particularly in previously responsive patients. (See 8.2 Inhibitor screening, below.)
- Inhibitors are more frequently encountered in patients with severe disease than in those with moderate or mild hemophilia, and more commonly in patients with hemophilia A than in those with hemophilia B. Controlling

bleeds is a greater challenge in hemophilia patients with inhibitors than in those without inhibitors. Inhibitors to FVIII or FIX are associated with a higher disease burden, including increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges, all of which may impact a patient’s physical functioning, capacity for physical activities, and quality of life.

- In addition, the immune response to FVIII and FIX products is poorly understood and, in the absence of evidence, there remain areas of evolving and sometimes ambiguous or conflicting information on inhibitor management.
- Furthermore, while new therapies and strategies for inhibitor treatment and eradication are emerging that may offer benefits, the long-term clinical outcomes remain unknown.
- Significant differences exist between hemophilia A and hemophilia B regarding inhibitor incidence, management, and response to immune tolerance induction (ITI) and alternative hemostatic agents. Therefore, in this chapter, hemophilia A inhibitors and hemophilia B inhibitors are discussed separately.

Patient/caregiver education

- Ongoing patient and family caregiver education and psychosocial support are essential components of the management of hemophilia patients with inhibitors given the complexity and challenges of this serious complication. It is vital for clinicians, patients, caregivers, and the hemophilia treatment centre team to maintain good communication through a well-coordinated plan of care.

8.2 | Inhibitor screening

- Inhibitors are measured by the Bethesda assay or the Nijmegen-modified Bethesda assay.^{2,3}
- The definition of a positive inhibitor is a Bethesda titer of >0.6 Bethesda units (BU) for FVIII and ≥0.3 BU for FIX.^{1,4}
- Inhibitor measurement may be performed during replacement therapy by assays utilizing heat treatment techniques.⁵ (See Chapter 3: Laboratory Diagnosis and Monitoring – Coagulation laboratory testing – Inhibitor testing.)
- A low-responding inhibitor is an inhibitor <5.0 BU, whereas a high-responding inhibitor is an inhibitor ≥5.0 BU.
- Low-responding inhibitors tend to be transient; a transient inhibitor is defined as a positive inhibitor that drops below the definition threshold within 6 months of initial documentation without any change in treatment regimen and despite antigenic challenge with CFCs.¹ A suspected inhibitor should be confirmed by repeat laboratory testing, documenting poor factor recovery and/or shortened half-life ($t_{1/2}$) of less than 6 hours in hemophilia A (in the case of standard half-life FVIII CFCs⁶) and 9 hours in hemophilia B (in the case of standard half-life FIX CFCs).⁷
- High-responding inhibitors tend to be persistent and may fall or become undetectable after a long period without CFC exposure; however, they increase 3–5 days after re-challenge with CFCs (anamnesic response).⁸
- It is critical to detect inhibitors early to ensure appropriate treatment. At least half of inhibitor cases are detected

TABLE 8-1 Indications for inhibitor testing

- After initial factor exposure
- After intensive factor exposure, e.g., daily exposure for more than 5 days^{7,15}
- For recurrent bleeds or target joint bleeds, despite adequate CFC replacement therapy^{7,12-14}
- For failure to respond to adequate CFC replacement therapy^{7,12,14}
- For lower than expected factor recovery or half-life after CFC replacement therapy^{7,12-14}
- For suboptimal clinical or laboratory response to CFC replacement therapy⁹
- Before surgery^{1,7,11}
- For suboptimal post-operative response to CFC replacement therapy^{7,12-14}

Abbreviation: CFC, clotting factor concentrate.

by routine inhibitor screening after initial exposures to CFCs, while the rest are detected after there is poor clinical response to CFC replacement therapy (i.e., when factor recovery and/or half-life are not as expected) when treating or preventing a bleed.⁹

- Inhibitor testing should be performed before major surgery and if there is suboptimal response to CFC replacement therapy in the post-operative period^{7,10,11}; and in any patient who fails to respond to adequate CFC replacement therapy after past responsiveness.^{7,12-14} (See Table 8-1.)
- It is particularly important to perform routine inhibitor screening during the time of greatest risk for inhibitor development, at least every 6–12 months after CFC replacement therapy is initiated, and annually thereafter. While some advocate more frequent screening,⁸ this remains controversial with few data to support the benefit of this approach.
- Screening should be performed in any patient, regardless of age or disease severity, who is intensively treated (i.e., for more than 5 consecutive days)^{7,15} and within 4 weeks of the last infusion.
- See also 8.3 Hemophilia A and FVIII inhibitors – Inhibitor incidence and 8.4 Hemophilia B and FIX inhibitors – Inhibitor incidence, below; and Chapter 3: Laboratory Diagnosis and Monitoring – Coagulation laboratory testing – Inhibitor testing.

RECOMMENDATION 8.2.1:

- **For patients with newly diagnosed hemophilia A, the WFH recommends regular inhibitor screening at least every 6–12 months, and then annually.**
- **REMARK: In general, more frequent screening should be considered for recurrent bleeds or target joints that occur despite standard factor replacement.**
- **REMARK: This recommendation places greater value on early inhibitor diagnosis in patients with severe hemophilia and late diagnosis in adulthood in patients with less severe disease, such as after intensive exposure to clotting factor concentrate, for example after surgery.**
- **REMARK: The requirement for frequent blood draws was considered in relationship to the potential morbidity of uncontrolled or life-threatening bleeds. CB**

RECOMMENDATION 8.2.2:

- **For patients with hemophilia A who receive clotting factor concentrate for more than 5 consecutive days, the WFH suggests inhibitor screening within 4 weeks of the last infusion. CB**

RECOMMENDATION 8.2.3:

- For patients with hemophilia A who have poor or no response to adequate clotting factor replacement therapy, or who have lower than expected factor recovery or half-life, the WFH suggests inhibitor screening. **CB**

RECOMMENDATION 8.2.4:

- For patients with hemophilia A who undergo surgery, the WFH suggests inhibitor screening preoperatively in order to determine if an inhibitor is present which, if present, may require non-FVIII-containing therapy. **CB**

RECOMMENDATION 8.2.5:

- For patients with newly diagnosed hemophilia B, the WFH recommends regular inhibitor screening at least every 6-12 months, and then annually.
- **REMARK:** In general, more frequent inhibitor screening should be considered when recurrent bleeds or target joints occur despite adequate factor replacement.
- **REMARK:** Because inhibitor incidence is much lower in hemophilia B than in hemophilia A, experience and evidence are limited.
- **REMARK:** This recommendation places greater value on early inhibitor diagnosis to avoid uncontrolled bleeds and bleeding complications. The requirement for frequent blood draws was considered in relationship to the potential morbidity of uncontrolled or life-threatening bleeds. **CB**

RECOMMENDATION 8.2.6:

- For patients with hemophilia B who are treated with clotting factor concentrate for more than 5 consecutive days, the WFH suggests inhibitor screening within 4 weeks of the last infusion. **CB**

RECOMMENDATION 8.2.7:

- For patients with hemophilia B who fail to respond to adequate clotting factor replacement therapy or who have lower than expected factor recovery or half-life, the WFH suggests inhibitor screening. **CB**

RECOMMENDATION 8.2.8:

- For patients with hemophilia B who develop an allergic reaction to FIX therapy, including anaphylaxis or nephrotic syndrome, the WFH suggests inhibitor screening to determine if an inhibitor is present. **CB**

RECOMMENDATION 8.2.9:

- For patients with severe hemophilia B who undergo major surgery, the WFH suggests preoperative inhibitor screening. **CB**

8.3 | Hemophilia A and FVIII inhibitors**Genetic and environmental risk factors**

- Inhibitors are more frequently encountered in persons with severe hemophilia A than in those with moderate or mild forms of the disease.
- Other risk factors for inhibitor formation in hemophilia A include family history of inhibitors, black African ancestry, Hispanic ancestry, genetic variants such as type of mutation and polymorphic immune regulatory genes, and high-intensity factor exposure (e.g., intensive CFC replacement therapy for a severe early bleed, central nervous system bleed, surgery, or trauma).^{6,9,10,12,14-20} (See Table 8-2.)
- Product type (i.e., plasma-derived FVIII CFCs with or without von Willebrand factor or recombinant FVIII CFCs) may contribute to inhibitor risk in hemophilia A patients; however, this is not well understood and remains controversial.^{6,16,21}

Inhibitor incidence

- Inhibitory antibodies develop with a cumulative incidence of approximately 30% among previously untreated patients with hemophilia A,^{16,22} of which 79% occur within the first 20 exposures and the remainder, 21%, within the first 75 exposures.²² An exposure is defined as any 24-hour period in which a FVIII/FIX-containing product is given.^{1,22}
- Inhibitor rates vary by study and may be underestimated in studies in which not all subjects are previously untreated patients (PUPs) and in whom follow-up is incomplete.⁶

TABLE 8-2 Potential risk factors for inhibitors

- Race^{9,10,15}
- Family history^{9,10,15}
- Genotype, immune regulatory genes^{9,16,17,20,25}
- Hemophilia severity^{9,10,12,14,19,25}
- CFC replacement intensity^{9,12,14-16,18,20}
- CFC type^{6,16,21}

Abbreviation: CFC, clotting factor concentrate.

- The incidence of inhibitors in mild and moderate hemophilia A patients is 5%-10%, lower than in those with severe hemophilia. These inhibitors typically occur at an older age and often after intensive FVIII exposure, e.g., for surgery or severe bleeds.^{12,23} In most cases, these are low-responding inhibitors; high-responding inhibitors are less common in such patients.²⁴
- Most cases of mild and moderate hemophilia A are caused by missense mutations, which in general are associated with a low rate of inhibitor development, although there are a few exceptions.²⁵

Disease burden

- Children and adults with persistent FVIII inhibitors typically have higher rates of hospitalization,²⁵ greater treatment costs,¹⁹ and higher mortality rates than those without inhibitors.²⁶ Development of new non-factor replacement therapies may reduce this burden in the future.
- Bleeding manifestations in mild and moderate hemophilia A patients with inhibitors are predominantly mucocutaneous, urogenital, and gastrointestinal bleeding, reminiscent of bleeding symptoms in patients with acquired hemophilia A (due to autoantibodies to FVIII).¹⁹ Consequently, the risk of severe complications or even death from serious bleeding may still be significant in these patients. The mortality rate among mild and moderate hemophilia A patients with inhibitors is reported to be five times greater than among those without inhibitors.²⁶
- Despite the availability of non-factor replacement therapies for hemophilia patients who develop inhibitors, there has been a consensus that patients with inhibitors should undergo a trial of ITI, when possible, in order to eradicate the inhibitor.²⁷
- The availability of non-factor replacement therapies (e.g., emicizumab) that are effective in bleed prevention in

patients with FVIII inhibitors has raised questions about whether such agents should be used before, during, after, or in place of ITI. This remains controversial, however, as there are insufficient data to resolve this question.

Management of bleeding

- Management of bleeding in hemophilia patients with inhibitors must be carried out in consultation with a hemophilia treatment centre and staff experienced in inhibitor treatment.^{7,28} (See Table 8-3.)
- Choice of treatment product should be based on inhibitor titer, clinical response to the product, site and nature of the bleed,^{7,29} and product availability by country.

RECOMMENDATION 8.3.1:

- **For patients with hemophilia A and FVIII inhibitors who develop an acute bleed, the WFH recommends that treatment be based on whether the inhibitor is low-responding or high-responding. CB**

Therapeutic options for FVIII inhibitor patients

CFC replacement therapy

- For low-responding inhibitors, FVIII CFC replacement therapy is preferred for acute bleeds if measurable factor levels are achieved.^{7,29,30} Careful monitoring for clinical efficacy is needed, as higher doses may be required to achieve hemostasis.
- In the absence of a rational and validated dosing algorithm, the following formula is used to estimate the amount of FVIII needed as a loading dose to neutralize the inhibitor³¹:
 - $[\text{body weight (kg)} \times 80 \times [(1 - \text{hematocrit}) \times \text{antibody titer (BU)}]]$
- An additional 50 IU/kg above the calculated loading dose is added to achieve a measurable FVIII activity.³¹

TABLE 8-3 Treatment of acute bleeds in hemophilia A patients with inhibitors

Hemophilia A	Low-responding inhibitors	High-responding inhibitors
Agent	• FVIII ^{31,a}	• rFVIIa or aPCC ^{33,40,47,b} or FVIII ^{39,c}
Monitoring	• FVIII activity (FVIII:C) assay	• Thromboelastography or thrombin generation assay ^{46,d}

Abbreviations: aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; FVIII:C, FVIII activity; rFVIIa, recombinant activated factor VIIa.

^aWill require higher, more frequent dosing if half-life is shortened.

^bIn patients on emicizumab prophylaxis, aPCC should be avoided or used with caution at lower doses because of the thrombotic microangiopathy risk (black box warning). Caution is also urged when rFVIIa is used in patients on emicizumab who have risk factors for thrombosis because of risk of myocardial infarction or pulmonary embolism.

^cIn patients with high-responding inhibitors with a currently low inhibitor titer, FVIII may be considered, with close monitoring for an anamnestic response.

^dThe thrombin generation assay is not state-of-the-art monitoring and is unavailable in most laboratories, but increasingly being used to assess response.

- FVIII levels should be measured 15 minutes after completion of the bolus, and adjustment to reach target levels is necessary because there is substantial individual variation.³¹
- For high-responding inhibitors, bypass agent therapy (recombinant activated factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) or porcine FVIII should be used to treat bleeds.

RECOMMENDATION 8.3.2:

- **For patients with hemophilia A and inhibitors who have acute bleeds, the WFH recommends FVIII concentrate for those with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors.**
- **REMARK: In those receiving non-factor therapy for prophylaxis (e.g., emicizumab), the WFH prefers rFVIIa over aPCC because of the risk of thrombotic microangiopathy when aPCC is used with emicizumab.**
- **REMARK: In patients receiving emicizumab who receive FVIII concentrate, the WFH recommends bovine reagent chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels.**
- **REMARK: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-ST segment elevation myocardial infarction (non-STEMI) and pulmonary embolism. **
- For patients with high-responding inhibitors whose titers have fallen to undetectable or low levels, standard FVIII CFC replacement may be used in an emergency for up to 3-5 days, at more frequent dosing due to the shorter half-life, until an anamnestic response occurs. When the latter occurs, further treatment with FVIII CFCs is typically no longer effective,^{7,29} and bypass agent therapy is needed. This underscores the need for close FVIII monitoring.
- The factor substitution therapy, emicizumab, is increasingly used to prevent hemorrhage in FVIII inhibitor patients.^{32,33} This agent is effective for *preventing* bleeds (prophylaxis) in hemophilia A inhibitor patients but is not indicated for *treating* bleeds. Thus, breakthrough bleeds require treatment with FVIII CFCs (for low-responding inhibitors) as described above, or hemostatic bypassing agents (for high-responding inhibitors), as described below. Conventional bypassing agents include rFVIIa and aPCC,

which have been shown to be effective as prophylaxis^{34,35} and for treatment of bleeds.

Conventional hemostatic bypassing agents

- Treatment with bypassing agents typically consists of one dose of aPCC or two doses of rFVIIa. The efficacy of two doses of rFVIIa (90-270 µg/kg) or one dose of aPCC (75-85 unit/kg) is comparable in the management of joint bleeding.³⁶ Notably, however, some patients may respond better to one agent than the other, highlighting the need to individualize therapy.^{30,36} (See Table 8-3.)
- However, if hemostasis is unsatisfactory with rFVIIa or aPCC as single agents, each may be alternated every 6 hours.^{37,38} (See Table 8-4.)
- Combination/sequential bypass agent treatment should be used only in treatment centres with extensive experience in managing hemophilia patients with inhibitors; close monitoring for thrombosis and disseminated intravascular coagulation is required.
- It is estimated that aPCC leads to an anamnestic response in approximately 30% of patients with FVIII inhibitors due to the presence of FVIII in aPCC.³⁹
- While rFVIIa or aPCC may be used to treat bleeds in both hemophilia A and B patients with inhibitors, there has been concern about using aPCC, which contains FIX, in patients with FIX inhibitors who manifest anaphylaxis to FIX. This, however, is not an issue for patients with FVIII inhibitors.
- **Caution:** Thrombosis or thrombotic microangiopathy may occur in patients receiving emicizumab who are also receiving aPCC.^{33,40} Thus, aPCC should be avoided in patients on emicizumab except in patients unresponsive to rFVIIa or when rFVIIa is unavailable, and with aPCC dosing not above 50 IU/kg and no more than 100 IU/kg total per day.

RECOMMENDATION 8.3.3:

- **For patients with hemophilia A and low-responding inhibitors who develop an acute bleed, the WFH recommends a FVIII-containing product or, if the hemostatic response is poor, the WFH recommends rFVIIa or aPCC. For those receiving emicizumab prophylaxis who develop an acute bleed, the WFH prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.**
- **REMARK: Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity,**

TABLE 8-4 Sequential bypass agent therapy alternating rFVIIa and aPCC³⁷

6:00 AM	90 µg/kg rFVIIa
9:00 AM	50 U/kg aPCC
12:00 PM	90 µg/kg rFVIIa
3:00 PM	50 U/kg aPCC
6:00 PM	90 µg/kg rFVIIa
9:00 PM	50 U/kg aPCC
12:00 AM	90 µg/kg rFVIIa
3:00 AM	50 U/kg aPCC
6:00 AM	90 µg/kg rFVIIa

Abbreviations: aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant factor VIIa.

smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism.

- **REMARK:** The WFH recommends bovine reagent-based chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels. **CB**

RECOMMENDATION 8.3.4:

- For patients with hemophilia A and high-responding FVIII inhibitors receiving emicizumab who develop an acute bleed, the WFH prefers rFVIIa over aPCC to avoid the risk of thrombotic microangiopathy.
- **REMARK:** Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of arterial thromboembolism, e.g., acute non-STEMI and pulmonary embolism.
- **REMARK:** The WFH recommends bovine reagent-based chromogenic FVIII assays (bovine FX in kit reagent) to measure plasma FVIII:C activity and inhibitor titer levels. **CB**

Emicizumab

- The factor substitution therapy, emicizumab, a bispecific monoclonal antibody and FVIII mimic, has been licensed for bleed prevention in patients with hemophilia A with and without inhibitors. Patients on emicizumab who experience breakthrough bleeds require episodic treatment with FVIII CFCs or with hemostatic bypassing agents, as described above.

- Several phase 3 clinical trials and post-marketing experience have shown that emicizumab is effective prophylaxis in adults and children with inhibitors.^{33,41-43} As emicizumab is injected subcutaneously every 1, 2, or 4 weeks, the burden of prophylaxis is much less than with bypassing agents. Emicizumab reduces morbidity, complications, and hospitalization, and is cost-effective.⁴¹
- Prophylaxis dosing with emicizumab consists of an induction period of 3.0 mg/kg/week for 4 weeks by subcutaneous injection. This is followed thereafter by 1.5 mg/kg/week or alternative dosing schedules including 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks.⁴¹⁻⁴⁴
- As emicizumab interferes with the measurement of FVIII:C and FVIII inhibitors using the one-stage FVIII assay, a specific chromogenic assay using bovine reagents is used to detect inhibitors to FVIII.^{45,46}

RECOMMENDATION 8.3.5:

- For patients with hemophilia A and inhibitors who receive emicizumab, the WFH recommends bovine chromogenic assays (bovine FX in kit reagent) to monitor inhibitor levels. **CB**
- Close monitoring of clinical response to emicizumab and laboratory monitoring of inhibitor titer level is advised with a chromogenic Bethesda assay using bovine reagents.
- In patients receiving emicizumab who have risk factors for thrombosis, e.g., past venous thromboembolism, obesity, smoking, chronic infection, or inflammation, rFVIIa should be used with caution due to the potential risk of acute non-STEMI and pulmonary embolism.⁴⁷

RECOMMENDATION 8.3.6:

- For patients with hemophilia A and inhibitors receiving emicizumab, the WFH recommends close clinical monitoring for thrombosis, adverse reactions, and thrombotic microangiopathy.
- **REMARK:** Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. **CB**

RECOMMENDATION 8.3.7:

- As emicizumab is used to prevent, but not treat, acute bleeds in patients with hemophilia A and inhibitors, the WFH recommends clotting factor replacement therapy for acute bleeds. **CB**

RECOMMENDATION 8.3.8:

- For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH recommends clotting factor replacement therapy including FVIII for those with low-responding inhibitors; the WFH prefers rFVIIa over aPCC for those with high-responding FVIII inhibitors due to the risk of thrombotic microangiopathy.
- **REMARK:** Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. **CB**

RECOMMENDATION 8.3.9:

- For patients with hemophilia A and inhibitors receiving emicizumab who have an acute bleed, the WFH prefers rFVIIa over aPCC, because of the risk of thrombotic microangiopathy.
- **REMARK:** The WFH suggests following black box warnings for emicizumab and maintaining vigilance as new evidence develops.
- **REMARK:** Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. Thrombotic risks may last for up to 6 months during which plasma levels of emicizumab may persist. **CB**

Therapies in clinical trials

- Extended half-life rFVIIa may have a role in the management of bleeds in hemophilia patients with inhibitors, although investigations have been in vitro and early-phase clinical trials.^{48,49}
- Non-factor therapies such as fitusiran, an investigational RNA interference agent that targets antithrombin (siRNA-AT),⁵⁰ and tissue factor pathway inhibitors (anti-TFPI),⁵¹ are in clinical trials on bleed prevention in patients with inhibitors. These are not expected to be effective in episodic treatment of bleeds.

Surgery and invasive procedures

- Inhibitor testing of patients with hemophilia of all types of severity is advised prior to surgery and invasive procedures. Special precautions must be taken in hemophilia patients with inhibitors undergoing surgery: factor coverage, bypass

agent treatment, and follow-up must be determined and planned in advance.

- Close monitoring of clinical response to bypass agent therapy is required, specifically monitoring for safety, i.e., thrombosis or consumptive coagulopathy.
- Once hemostasis is achieved and maintained on a selected regimen for 3-5 days, these agents may be tapered over 1-3 weeks. However, it is recognized that the dose and taper schedule must be individualized for each patient, as variability exists in individual response to bypass agent therapy.
- Adjusted-dose continuous infusion is another option in surgery and invasive procedures, for which clearance should be calculated every day with dose adjustment accordingly.⁵²
- Combination/sequential bypass agent treatment should be considered in those with poor response to one bypassing agent. Sequential use (i.e., alternating rFVIIa and aPCC every 3 hours) has been shown to improve efficacy over single bypass agent therapy and allows for lower total daily dose of aPCC,^{37,38} potentially reducing thrombotic risk. Sequential regimens should be used only in treatment centres with extensive experience in managing hemophilia patients with inhibitors, with close monitoring for thrombosis and disseminated intravascular coagulation. (See Table 8-4.)

RECOMMENDATION 8.3.10:

- For patients with hemophilia A and low-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH suggests higher, more frequent FVIII product dosing than usual due to the short half-life of FVIII.
- **REMARK:** The WFH also recognizes adjusted-dose FVIII continuous infusion as an option. **CB**

RECOMMENDATION 8.3.11:

- For patients with hemophilia A and high-responding FVIII inhibitors who undergo surgery or an invasive procedure, the WFH recommends bypass agent therapy (rFVIIa or aPCC) at the discretion of the clinician. If single-agent bypass fails, sequential bypass agent treatment, i.e., rFVIIa alternating with aPCC, is another therapeutic approach. The WFH also recommends close clinical monitoring for thrombosis. **CB**

RECOMMENDATION 8.3.12:

- For patients with hemophilia A and inhibitors receiving emicizumab who undergo major surgery or an invasive

procedure, the WFH recommends a FVIII-containing product for those with low-responding inhibitors. The WFH prefers rFVIIa over aPCC for those with high-responding inhibitors due to the risk of thrombotic microangiopathy. The WFH makes no recommendations on specific dose, frequency, or duration as there are insufficient data.

- **REMARK:** Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. **CB**

RECOMMENDATION 8.3.13:

- For patients with hemophilia A and inhibitors receiving emicizumab who undergo minor surgery or an invasive procedure, the WFH recommends either low-dose or no clotting factor replacement therapy.
- **REMARK:** Caution is urged when rFVIIa is used in patients receiving emicizumab who have risk factors for thrombosis (e.g., past venous thromboembolism, obesity, smoking, chronic infection, inflammation) due to the risk of acute non-STEMI and pulmonary embolism. **CB**

RECOMMENDATION 8.3.14:

- For patients with hemophilia A and inhibitors receiving emicizumab who undergo major surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis, consumptive coagulopathy, or thrombotic microangiopathy. **CB**

RECOMMENDATION 8.3.15:

- For patients with hemophilia A and inhibitors who use bypass agent therapy, the WFH recommends clinical monitoring and consideration for laboratory monitoring with thrombin generation and other coagulation tests, but more data are needed to recommend the latter. **CB**

Immune tolerance induction

- Inhibitor eradication by immune tolerance induction therapy is successful in 70%-80% of patients with severe hemophilia A.⁵³⁻⁵⁵
- Response to ITI may be less favourable in patients with moderate/ mild hemophilia A.^{7,17}

RECOMMENDATION 8.3.16:

- For patients with hemophilia A who develop persistent low-responding inhibitors, the WFH suggests that immune tolerance induction (ITI) be considered. **CB**
- Successful ITI is defined as a persistently negative Bethesda titer, accompanied by normal pharmacokinetics, including factor recovery >66% and half-life >6 hours for standard FVIII CFCs. Once successful ITI is achieved, FVIII prophylaxis may be initiated or resumed.
- There is general consensus that failure of ITI is the inability to achieve successful tolerance within 2-3 years of initiation of an ITI regimen.²⁷

RECOMMENDATION 8.3.17:

- For patients with hemophilia A and persistent inhibitors who fail immune tolerance induction (ITI) or never underwent ITI, the WFH recommends emicizumab prophylaxis over bypass agent prophylaxis (rFVIIa or aPCC), as emicizumab is more effective in bleed prevention and simpler to administer, as it is given weekly and subcutaneously. **CB**
- When to initiate ITI has been a topic of debate. Registry data from the 1990s and 2000s showed success was highest when ITI was begun in patients with low inhibitor titers (<10 BU). Thus, clinicians adopted a policy of waiting to start ITI until inhibitor titers had fallen to <10 BU; however, more recently, clinicians have begun to initiate ITI immediately after inhibitor detection no matter the titer, with good response.⁵⁶
- The optimal regimen (product or dose) for ITI remains to be defined. In the International ITI Trial, there was no difference in efficacy between a low-dose/low-frequency regimen (50 IU/kg FVIII 3 times weekly) and a high-dose/high-frequency regimen (200 IU/kg daily), but the low-dose/low-frequency regimen required a longer time to achieve tolerance and more bleeds occurred during that period, particularly in the first 3-6 months of ITI. For this reason, the trial was stopped early,⁵⁷ with subsequent clinician preference for the high-dose/high-frequency regimen.
- While on ITI, if patients experience frequent bleeding, bypass agent prophylaxis (rFVIIa, aPCC) or emicizumab prophylaxis may be instituted. Emicizumab prophylaxis has been associated with a significantly greater reduction in bleeding rates than bypass agent prophylaxis.³³
- It may be possible to delay or avoid ITI altogether with emicizumab prophylaxis, given the very low bleeding rates seen with this agent, but controversy continues and data

are scarce. (See “Therapeutic options for FVIII inhibitor patients – Emicizumab” above.)

- Few data exist on the use of extended half-life factor therapies or ancillary non-factor therapies for ITI. Preliminary data from small case series and observational studies have shown that extended half-life CFCs are effective in some patients with inhibitors, including those with high-responding inhibitors and those who have previously failed ITI with standard half-life CFCs or were never tolerized, and may shorten duration of ITI.^{17,59,60} Data from a small case series found FVIII 100 IU/kg three times weekly plus emicizumab prophylaxis is safe and associated with a decline in inhibitor titer.⁶¹ Larger, randomized studies are needed to confirm these findings.
- Because ITI requires frequent infusions (up to once daily), it generally requires good venous access. In young children with small veins and/or poor access, a central venous access device (CVAD) is usually required for ITI. However, CVAD use is associated with complications such as infection and/or thrombosis. For this reason, emicizumab, which is administered subcutaneously and requires no IV access, has been considered a simpler option than standard ITI and, it may allow for lower dose/lower frequency FVIII CFC infusions when used with ITI or instead of ITI, although this is unproven. This remains controversial as there are no data regarding inhibitor risk if episodic CFC replacement therapy is required for breakthrough bleeds during emicizumab prophylaxis.
- Whether emicizumab should be initiated before, during, after, or instead of ITI is unknown,⁶² and answering this question will require clinical trials. As emicizumab differs biochemically from FVIII, many questions remain regarding its long-term impact on joint pathology, immunogenicity, and cost-effectiveness in non-inhibitor patients.
- Although there has been interest in the use of immunosuppressive and immunomodulatory therapies in hemophilia patients with inhibitors, the role of these agents is not yet defined, and as there is no consensus regarding these agents in the management of inhibitor patients, clinical trials are needed.

FVIII prophylaxis after immune tolerance induction

- After successful ITI in hemophilia A patients with inhibitors, FVIII prophylaxis with close monitoring of clinical response should be initiated.
- At least one extended half-life CFC, rFVIIIFc, has been evaluated for its tolerogenic potential in the prevention of inhibitor formation and in the induction of immune

tolerance. At this time, data on the impact of extended half-life therapies are limited.^{58,60,63}

Product switching

- While there is controversy regarding inhibitor development in those switching CFC products, including rare case reports, data from large studies indicate there is no evidence supporting increased risk.⁶⁴⁻⁶⁶

RECOMMENDATION 8.3.18:

- **For patients with hemophilia A who switch to another type or brand of factor product, the WFH has no preference for the choice of specific type of therapy, as current evidence indicates product switching does not increase risk of inhibitor development.**
- **REMARK: The WFH encourages product choice based on potential advantages, such as simpler administration, safety, efficacy, and personal preferences.**
- **REMARK: The WFH supports prospective data collection on inhibitor formation by product, particularly before and after switching products. **

RECOMMENDATION 8.3.19:

- **For patients with severe hemophilia A and inhibitors, the WFH recommends emicizumab over bypass agent prophylaxis to reduce bleeding episodes, as emicizumab appears to be superior to bypass prophylaxis. **

8.4 | Hemophilia B and FIX inhibitors

Genetic and environmental risk factors

- FIX inhibitors are almost exclusively seen in patients with severe hemophilia B and very rarely in the milder forms.⁶⁷
- Inhibitors in patients with severe hemophilia B are rare and occur most commonly in those with null variants, in which no endogenous clotting factor is produced, in most cases due to large deletion, frame-shift, and nonsense variants.^{67,68} There is no known ancestral predilection to inhibitor development in hemophilia B.
- Inhibitor formation in hemophilia B is not thought to be related to type of FIX CFC, and it has been reported in those receiving plasma-derived and recombinant FIX CFCs alike.

Inhibitor incidence

- Inhibitor formation in patients with hemophilia B occurs infrequently, with a cumulative incidence of up to 5%.^{69,70}

- The development of an FIX inhibitor is considered the most serious complication in patients with hemophilia B,⁹ due not only to loss of response to FIX replacement, but also to the associated risks of anaphylaxis and nephrotic syndrome.⁶⁷
- Inhibitor detection in hemophilia B is similar to that in hemophilia A, with most inhibitors occurring after a median of 9-11 exposures, and before 20 exposures, typically before 2 years of age.¹⁸
- Treatment strategies for FIX inhibitors are similar to those for FVIII inhibitors; specifically, they focus on controlling hemostasis and eradicating the inhibitor.
- It is recommended that because of the severity of complications, patients with hemophilia B should be followed closely and screened for inhibitors every 6-12 months after initiating CFC replacement therapy, and annually thereafter.

Disease burden

Anaphylaxis to FIX

- Inhibitor formation in patients with hemophilia B is overall associated with a similar disease burden as in hemophilia A but may also be associated with allergic reaction to FIX CFCs. Anaphylaxis occurs in 50% of hemophilia B patients with inhibitors,²⁰ and more frequently in those with null mutations. Such reactions may be the first symptom of FIX inhibitor development.⁶⁷
- Newly diagnosed severe hemophilia B patients, particularly those with a family history of severe hemophilia B with inhibitors and/ or with genetic variants predisposing to inhibitor development, should be treated in a clinic or hospital setting capable of managing severe allergic reactions for the initial 10-20 exposures to FIX CFCs, with emergency equipment available to treat anaphylaxis.⁶⁷ Reactions may also occur later but may be less severe.^{20,71}

RECOMMENDATION 8.4.1:

- For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for an inhibitor to FIX, as an allergic reaction may be the first sign of inhibitor development. **CB**

RECOMMENDATION 8.4.2:

- For patients with hemophilia B and a family history of inhibitors or risk factors for inhibitor development, the WFH recommends monitoring initial infusions in a clinic or hospital setting capable of managing severe allergic reactions. **CB**

RECOMMENDATION 8.4.3:

- For patients with hemophilia B who develop anaphylaxis to FIX therapy, the WFH recommends screening for nephrotic syndrome, as it is more common in FIX inhibitor patients with allergic reactions to FIX. **CB**

RECOMMENDATION 8.4.4:

- For patients with hemophilia B and inhibitors and an allergic reaction/anaphylaxis to FIX therapy, the WFH recommends rFVIIa to treat acute bleeds but is against use of aPCC as it contains FIX and may cause or worsen an allergic reaction.
- **REMARK:** For patients with hemophilia B and inhibitors and allergic reaction to FIX therapy, the WFH indicates there are insufficient data to recommend desensitization by small, repeated doses of FIX, intravenously or subcutaneously, and recognizes that in some, this approach may worsen an allergic reaction or cause anaphylaxis. If undertaken, FIX desensitization should be performed with caution and under close supervision by experts only. **CB**

RECOMMENDATION 8.4.5:

- For patients with hemophilia B and inhibitors who develop anaphylaxis to FIX therapy, the WFH recommends bypass therapy with rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. **CB**

Management of bleeding

- Management of bleeding in hemophilia patients with inhibitors must be carried out in consultation with a hemophilia treatment centre and staff experienced in inhibitor treatment.^{7,28}
- Treatment of bleeding in hemophilia B patients with inhibitors should be individualized.⁶⁷ Choice of treatment product should be based on inhibitor titer, clinical response to the product, previous infusion reactions, site and nature of the bleed,^{7,29} and product availability by country.

RECOMMENDATION 8.4.6:

- For patients with hemophilia B and inhibitors who develop an acute bleed, the WFH recommends treatment based on whether the inhibitor is low-responding or high-responding and whether there is a history of allergic reactions. **CB**

Therapeutic options for patients with FIX inhibitors

CFC replacement therapy

- For those with low-responding inhibitors, specific FIX CFC replacement therapy may be used if there is adequate inhibitor neutralization to control bleeding. Because allergic reactions and anaphylaxis may occur in up to 50% of hemophilia B patients with inhibitors,²⁰ close monitoring is essential.

RECOMMENDATION 8.4.7:

- **For patients with hemophilia B and low-responding FIX inhibitors, the WFH recommends use of a FIX-containing product to treat acute bleeds, as long as there is no allergic reaction to FIX. **CE****
- For hemophilia B patients with high-responding inhibitors or those with low-responding inhibitors who develop allergic reactions or anaphylaxis, the bypassing agent rFVIIa may be used to control bleeding. As aPCC contains FIX, it may trigger or worsen an allergic or anaphylactic response; for that reason, aPCC should be avoided in hemophilia B patients. However, in the absence of such a reaction, aPCC has shown similar efficacy in controlling acute bleeding.²⁷

RECOMMENDATION 8.4.8:

- **For patients with hemophilia B and high-responding FIX inhibitors, the WFH prefers rFVIIa over aPCC to treat acute bleeds, as aPCC contains FIX and may cause or worsen an allergic reaction. **CE****

Conventional hemostatic bypassing agents

- Alternative hemostatic agents for prevention of spontaneous or traumatic bleeds (prophylaxis) in hemophilia B inhibitor patients include rFVIIa, or, in the absence of an allergic/anaphylactic reaction to FIX, aPCC.^{34,47,60,72,73}
- Bypass agent prophylaxis in inhibitor patients is not as effective nor as convenient as standard factor prophylaxis is in patients without inhibitors.⁷²
- For hemostasis, bypass agent therapy with rFVIIa constitutes the standard approach. In general, aPCC may increase risk of anaphylaxis because of FIX content and should be avoided in those with hemophilia B inhibitors (see above). Both agents are effective in treating 90% of musculoskeletal bleeds and can be used in major and minor prophylaxis.^{34,72} (See Table 8-5.)

- As there are no reliable laboratory assays to monitor bypass agent therapy, careful monitoring of hemoglobin levels, blood loss, wound healing, and clinical response to treatment is advised, including patient-reported outcomes and subjective patient feedback.

RECOMMENDATION 8.4.9:

- **For patients with hemophilia B and inhibitors who use bypass agent therapy, the WFH recommends clinical monitoring and consideration for laboratory monitoring with thrombin generation and other coagulation tests, although more data are needed to recommend the latter. **CE****

Therapies in clinical trials

- Several emerging non-factor therapies are in clinical trials for bleed prevention in hemophilia B patients with inhibitors, including fitusiran (siRNA-AT3)⁵⁰ and anti-TFPI.^{51,74} These therapies may provide a less invasive route and/or lower frequency of dosing and, if safe and effective, may be adopted into use.
- An extended half-life rFVIIa with in vitro hemostasis⁴⁸ is in early clinical trials for bleed prevention in patients with hemophilia B and inhibitors.⁴⁹ This therapy may reduce the frequency of dosing and, if safe and effective, may be adopted into use.⁴⁹

Immune tolerance induction

- Because inhibitor prevalence is low in hemophilia B, experience with ITI is limited. The principles of treatment are similar to those in hemophilia A, but the success rate is lower, especially in patients with an allergic reaction to FIX. The latter may require FIX desensitization before attempting ITI, although few data are available regarding the efficacy or safety of this approach.
- Hemophilia B inhibitor patients with a history of severe allergic reactions to FIX may develop nephrotic syndrome, which may be irreversible. In some patients undergoing ITI, nephrotic syndrome may develop; close monitoring is required even after ITI is completed, as nephrotic syndrome may persist.
- There is little evidence regarding when or whether to initiate ITI in hemophilia B patients after inhibitor detection; however, some have initiated a high-dose/high-frequency FIX regimen until tolerance is achieved, i.e., the inhibitor titer is persistently negative and factor recovery and half-life return to normal. However, there is no supporting evidence, and this approach is based on experience with hemophilia A inhibitor management. Clinical and laboratory monitoring

is important, especially for development of allergic reactions or nephrotic syndrome.

- Little is known about the role of immunosuppressive agents in hemophilia B patients with inhibitors, as few data are available; thus, there is no consensus regarding their use in these patients.

RECOMMENDATION 8.4.10:

- **For patients with hemophilia B and inhibitors, the WFH is unable to make a recommendation on the use of immune tolerance induction, as experience with ITI in hemophilia B is limited.**
- **REMARK: In patients with hemophilia B and inhibitors in whom ITI is attempted, high-dose factor replacement protocols should be followed similar to what is recommended for hemophilia A, with strong consideration for the use of immunosuppression. It should be noted the risk of nephrotic syndrome may increase with high-dose ITI. **CB****

FIX prophylaxis after immune tolerance induction

- After successful immune tolerization in hemophilia B patients with inhibitors (defined as the return to a persistently negative inhibitor titer), FIX prophylaxis with close monitoring of clinical response should be initiated.⁷

Surgery and invasive procedures

- Inhibitor testing is advised in patients with hemophilia B prior to surgery and invasive procedures. Special precautions, as noted above in the “Management of bleeding” section, must be taken in hemophilia B patients with inhibitors, including monitoring for allergic reactions and nephrotic syndrome.
- In those with low-responding inhibitors, standard FIX CFC coverage may be considered if high enough levels

are achieved. In those with high-responding inhibitors or in those with a history of allergic reactions to FIX CFCs, treatment with the bypassing agent rFVIIa is advised, recognizing the risk of an allergic reaction or worsening of such a reaction in those who experience allergic reactions to FIX when treated with aPCC due to its FIX content.

- If hemostasis is unsatisfactory with rFVIIa or aPCC used as single agents, these agents may be alternated,³⁷ recognizing this is based on a small observational study and also recognizing the risk for allergic reaction or worsening of an allergic reaction with aPCC due to FIX content.
- Close perioperative monitoring of clinical response to bypass agent therapy is required, particularly for thrombosis or consumptive coagulopathy. (See Recommendation 8.4.9 on clinical monitoring of bypass agent therapy, above.)
- Once hemostasis is achieved and maintained on a bypass agent regimen for 3-5 days, use of these agents may be tapered over a week or more.

RECOMMENDATION 8.4.11:

- **For patients with hemophilia B and low-responding FIX inhibitors who undergo surgery, the WFH has no preference for type of FIX products, but recommends more frequent dosing due to the short FIX half-life. **CB****

RECOMMENDATION 8.4.12:

- **For patients with hemophilia B and FIX inhibitors who undergo surgery, the WFH recommends rFVIIa over aPCC, as aPCC contains FIX and may cause or worsen an allergic reaction. **CB****

RECOMMENDATION 8.4.13:

- **For patients with hemophilia B and inhibitors and an allergic reaction to FIX who undergo surgery, the WFH prefers rFVIIa over aPCC as aPCC contains FIX and may cause or worsen an allergic reaction. **CB****

TABLE 8-5 Treatment of acute bleeds in hemophilia B patients with inhibitors

Hemophilia B	Low-responding inhibitors	High-responding inhibitors
Agent	• FIX ^{20,a}	• rFVIIa or aPCC ^{27,b}
Monitoring	• FIX activity (FIX:C) assay	• Thromboelastography or thrombin generation assay ^{46,c}

Abbreviations: aPCC, activated prothrombin complex concentrate; FIX, factor IX; FVIII, factor VIII; rFVIIa, recombinant activated factor VIIa.

^aWill require higher, more frequent dosing if half-life is shortened.

^bIn patients with FIX inhibitors, there is high risk for allergic reaction and nephrotic syndrome with FIX-containing products, e.g., aPCC, and caution is urged; however, in those with an allergic reaction or nephrotic syndrome with FIX-containing products, aPCC should be avoided since it contains FIX.

^cThe thrombin generation assay is not state-of-the-art monitoring and is unavailable in most laboratories, but increasingly being used to assess response.

RECOMMENDATION 8.4.14:

- For patients with hemophilia B and inhibitors who undergo surgery or an invasive procedure, the WFH recommends close clinical monitoring for thrombosis or consumptive coagulopathy. **CB**

Product switching

- While there is controversy regarding risk of inhibitor development in patients with hemophilia B switching FIX CFC products, including rare case reports, there is a lack of evidence supporting this risk.⁶⁴

RECOMMENDATION 8.4.15:

- For patients with hemophilia B who switch to another type or brand of factor product, the WFH has no preference in the choice of specific type of therapy, as current evidence indicates product switching does not increase the risk of inhibitor development, but rigorous controlled trials are lacking. **CB**

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.