

Chapter 8: Inhibitors to Clotting Factor

Margaret V. Ragni, Erik Berntorp, Manuel Carcao, Carmen Escuriola Ettingshausen, Augustas Nedzinskas, Margaret C. Ozelo, Enrique D. Preza Hernández, Andrew Selvaggi, H. Marijke van den Berg, Glenn F. Pierce, Alok Srivastava

RECOMMENDATIONS

8.2 | Inhibitor screening

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.

•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}

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8.3 | Hemophilia A and FVIII inhibitors

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}

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. ^{CB}

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, 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}

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}

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.

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•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}

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}

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}

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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}

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. ^{CB}

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. ^{CB}

8.4 | Hemophilia B and FIX inhibitors

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}

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}

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. ^{CB}

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. ^{CB}

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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. ^{CB}

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}

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}

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}

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}

CB: Consensus based; aPCC, activated prothrombin complex concentrate; STEMI, ST-segment elevation myocardial infarction; ITI, immune tolerance induction.

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