

# Congenital Hemophilia with Inhibitors

Disease background

October 2024

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Summary

# Characteristics of inhibitors

An antibody against FVIII or FIX <sup>1</sup>	Mechanism of action <sup>1</sup>
<ul style="list-style-type: none"> <li>• Can develop in response to exogenous FVIII/FIX<sup>1</sup></li> <li>• A serious treatment complication<sup>2</sup></li> <li>• Can be alloantibody or autoantibody*<sup>3</sup></li> <li>• Antibodies against FVIII/FIX are predominantly an IgG subclass 4<sup>4,5</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Neutralizing inhibitors bind to an active site and inhibit the ability of replacement factor to stop bleeding</li> </ul>
Associated with treatment challenges <sup>6,7</sup>	Increases morbidity and mortality <sup>8,9</sup>
<ul style="list-style-type: none"> <li>• FVIII or FIX replacement may not prevent or stop bleeding owing to neutralizing effect of inhibitors</li> <li>• Treatment of bleeding episodes in the presence of inhibitors is more challenging</li> </ul>	<ul style="list-style-type: none"> <li>• Historically, patients with inhibitors have reported higher rates of hospitalization, greater treatment cost, greater incidence of bleeding episodes, and higher mortality vs those without<sup>10</sup></li> <li>• Although rare, inhibitor formation in HB is associated with allergic reaction to FIX: anaphylaxis occurs in 50% of HB patients with inhibitors; HBwI patients with allergic reactions to FIX may develop nephrotic syndrome<sup>11,12</sup></li> </ul>
<ul style="list-style-type: none"> <li>• <b>Inhibitors occur in approximately 30% of previously untreated patients with HA, of which 79% occur within the first 20 EDs<sup>†</sup> and the remainder within the first 75 EDs<sup>13</sup></b></li> <li>• <b>Inhibitors in severe HB are less common (&lt;5%), with most occurring after a median of 9–11 EDs, and before 20 EDs<sup>14,15</sup></b></li> </ul>	

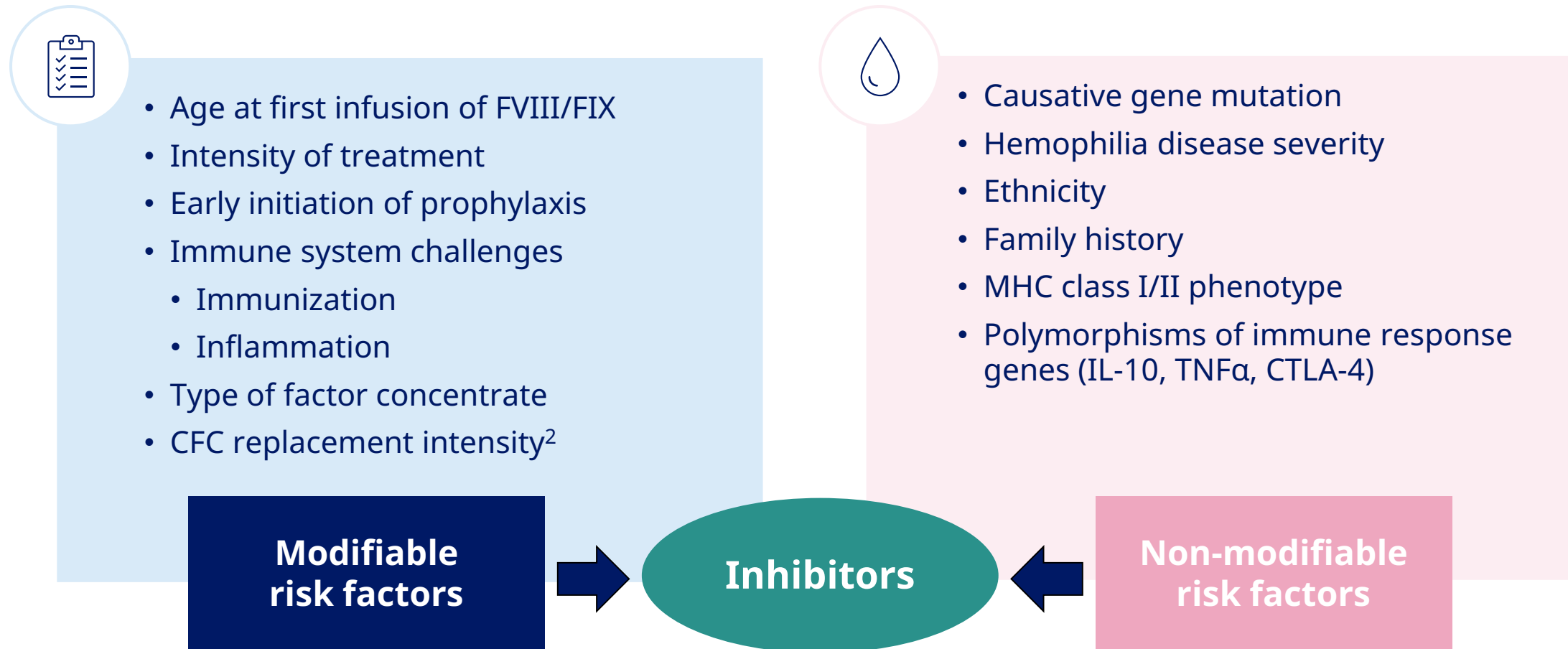
\*An alloantibody is an antibody formed in response to a non-self-antigen. An autoantibody is an antibody formed in response to a self-antigen.

†An ED is defined as any 24-hour period in which a FVIII/FIX-containing product is given.

ED, exposure day; FIX, factor IX; FVIII, factor VIII; HA, hemophilia A; HB, hemophilia B; HBwI, hemophilia B with inhibitors; IgG, immunoglobulin G.

1. DiMichele DM. Inhibitors in hemophilia: a primer. In: Treatment of Hemophilia, Monograph No. 7. World Federation of Hemophilia. April 2008; 2. Reding MT. Haemophilia 2006;12(Suppl 6):30–5; 3. Janbain M, Pipe S. Hematology Am Soc Hematol Educ Program 2016;2016:648–9; 4. Astermark J. Blood 2015;125:2045–51; 5. Franchini M, Mannucci PM. Br J Clin Pharmacol 2011;72:553–62; 6. DiMichele DM. Haemophilia 2006;12(Suppl 6):37–41; 7. Lillicrap D. Hematology Am Soc Hematol Educ Program 2006;1:421–5; 8. Morfini M et al. Haemophilia 2007;13:502–7; 9. Eckhardt CL et al. J Thromb Haemost 2015;13:1217–25; 10. Gringeri A et al. Blood 2003;102:2358–63; 11. Chitlur M et al. Haemophilia 2009;15:1027–31; 12. Male C et al. Haematologica 2021;106:123–9; 13. van den Berg HM et al. Blood 2019;134:317–20; 14. Carcao M, Goudemand J. Inhibitors in hemophilia: a primer. WFH 2018. Available at: <http://www1.wfh.org/publication/files/pdf-1122.pdf>. Accessed July 2024; 15. Fischer K et al. Thromb Haemost 2015;113:968–75.

# Risk factors for inhibitor development<sup>1</sup>



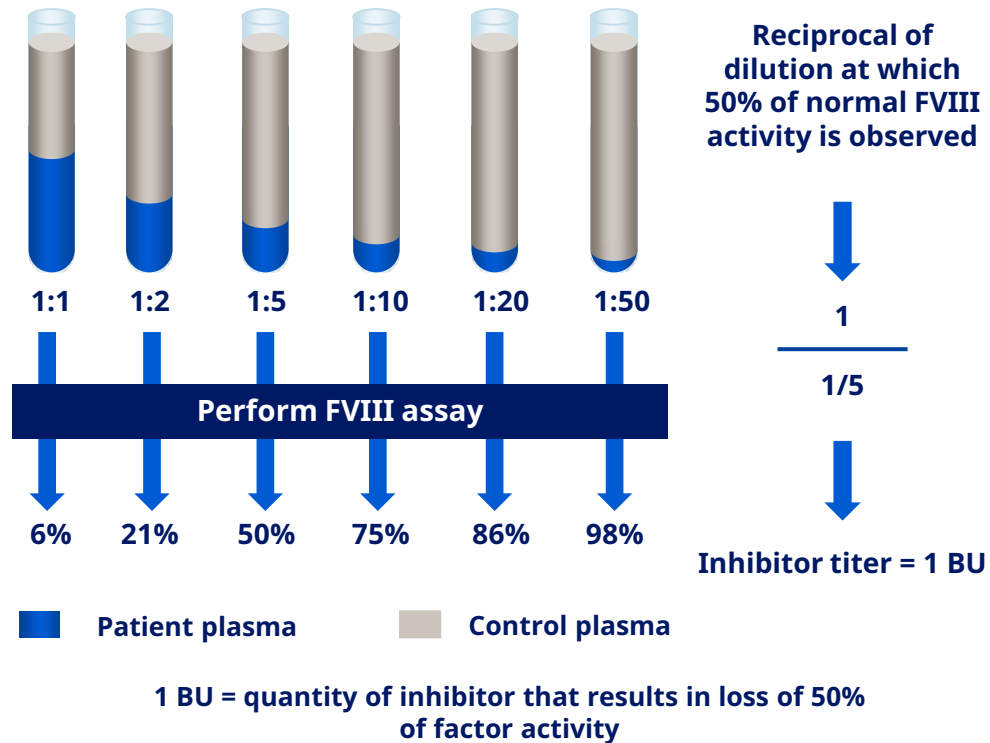
CFC, clotting factor concentrate; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FIX, factor IX; FVIII, factor VIII; IL-10, interleukin-10; MHC, major histocompatibility complex; TNFα, tumor necrosis factor alpha.

1. Carcao M, Goudemand J. Inhibitors in hemophilia: a primer. WFH 2018. Available at: <http://www1.wfh.org/publication/files/pdf-1122.pdf>. Accessed July 2024;

2. Srivastava A et al. Hemophilia 2020;26:1–158.

# Classification of inhibitors in hemophilia A and B<sup>1,2</sup>

## Inhibitor status can be measured in titer by the Bethesda assay<sup>1</sup>



### High titer $\geq 5$ BU<sup>1</sup>

- High-responding inhibitors are those in which inhibitor titers rise to  $\geq 5$  BU at any time

### Low titer $< 5$ BU<sup>1</sup>

- Low-responding inhibitors do not rise to  $\geq 5$  BU with repeated exposure to factor
- Some are transient and will disappear without treatment
- Others remain or progress to high titer following exposure to FVIII products

### Transient inhibitors<sup>1</sup>

- Transient inhibitors decrease within 6 months of initial documentation, despite continuing exposure to factor

BU, Bethesda unit; FVIII, factor VIII.

Image created from concepts described in the following: DiMichele DM. Haemophilia 2006;12(Suppl 6):37-41; Millner AH et al. Int J Lab Hematol 2016;38:639-47.

1. Garagiola I et al. Thromb Res 2018;168:20-7; 2. Carcao M, Goudemand J. Inhibitors in hemophilia: a primer. WFH 2018. Available at: <http://www1.wfh.org/publication/files/pdf-1122.pdf>. Accessed July 2024.

# Regular screening leads to earlier diagnosis of inhibitors and the potential for successful eradication<sup>1</sup>



## **Inhibitor testing should be performed:<sup>2</sup>**

- After initial factor exposure
- After intensive factor exposure (eg, daily exposure for >5 days)
- For recurrent bleeds or target joint bleeds, despite adequate CFC replacement therapy
- For failure to respond to adequate CFC replacement therapy
- For lower-than-expected factor recovery or half-life after CFC replacement therapy
- For suboptimal clinical or laboratory response to CFC replacement therapy
- Before surgery
- For suboptimal post-operative response to CFC replacement therapy



**Inhibitor screening is recommended at least every 6–12 months for patients with newly diagnosed HA, and then annually**

**Due to the severity of complications, patients with HB should be screened for inhibitors every 6–12 months after initiating CFC replacement therapy, and annually thereafter**

BA, Bethesda assay; CFC, clotting factor concentrate; HA, hemophilia A; HB, hemophilia B.  
1. Soucie JM et al. *Haemophilia* 2014;20:230–7; 2. Srivastava A et al. *Hemophilia* 2020;26:1–158.

# Current algorithm for the management of patients with hemophilia and inhibitors

## Treatment of acute bleeds<sup>1,2</sup>

- For patients with HAwI, FVIII concentrate is recommended for those with low-responding inhibitors, and a bypassing agent (rFVIIa or aPCC) is recommended for those with high-responding inhibitors
- In patients with severe HAwI with joint bleeding to be treated with rFVIIa, recent guidelines recommend treatment with either three doses of 90 µg/kg at 3-hour intervals or a single dose of 270 µg/kg
- For patients with HBwI, the use of a FIX-containing product is recommended in patients with low-responding inhibitors, if there is no allergic reaction to FIX; for high-responding inhibitors, rFVIIa is preferred over aPCC\*

## Prophylaxis<sup>1,2</sup>

- In patients with severe HAwI, prophylaxis is recommended over episodic treatment of bleeding events
- Prophylaxis with FVIII mimetics has been demonstrated as an effective treatment for prevention of bleeds in patients with HAwI
- In patients with severe HAwI, prophylaxis with FVIII mimetics is recommended over bypassing agents
- In patients with severe HAwI undergoing invasive procedures requiring treatment with bypassing agents, either rFVIIa or aPCC are recommended
- aPCC is approved for prophylaxis in HAwI/HBwI
- An anti-TFPI has been approved for prophylactic treatment in patients with HA and HB without inhibitors<sup>6</sup>

## Inhibitor eradication<sup>1,2</sup>

- Patients with inhibitors should undergo a trial of ITI, when possible, to eradicate the inhibitor<sup>4</sup>
- For patients with HA who develop persistent low-responding inhibitors, ITI should be considered; however, response to ITI may be less favorable in patients with moderate/mild HA
- In patients with severe HA and high-responding inhibitors who will start ITI, either low- or high-dose FVIII concentrates are recommended
- Experience with ITI in HB is limited because of low inhibitor prevalence; however, the success rate of ITI in HB is lower, and some patients with a history of severe allergic reactions may develop nephrotic syndrome
- In certain patient populations, FVIII mimetics have become a preferred first-line approach to prevent bleeds, as an alternative to ITI<sup>5</sup>

\*aPCC contains FIX and may cause or worsen an allergic or anaphylactic response.

aPCC, activated prothrombin complex concentrate; FIX, factor IX; HA/BwI, hemophilia A/B with inhibitors; ITI, immune tolerance induction; rFVIIa, recombinant activated factor VII; TFPI, tissue factor pathway inhibitor.

1. Srivastava A et al. *Hemophilia* 2020;26:1–158; 2. Rezende SM et al. *J Thromb Hemost* 2024;20:S1538-7836(24)00353-2; 3. Keam SJ. *Drugs* 2023;83:1053–9; 4. Ljung RCR. *Br J Haematol* 2018;180:501–10; 5. Holstein K et al. *Haemophilia* 2022;28:215–22; 6. Business Wire. U.S. FDA Approves Pfizer's HYMPAVZIT™ (marstacimab-hncq) for the Treatment of Adults and Adolescents with Hemophilia A or B Without Inhibitors. Accessed October 11, 2024.

Driving  
change | in rare  
disease

# Prophylaxis agents for patients with inhibitors

## BPAs

- Prophylaxis with BPAs has been shown to:<sup>1</sup>
  - Reduce bleeding events
  - Prevent or delay the development/progression of target joints and arthropathy
- Consideration should be balanced against inconvenience of administration, potential (low) risk of thrombosis, and cost<sup>1</sup>

## Novel treatments

Class	Indication	Characteristics	Approval status
FVIIIa mimetics <sup>2</sup>	HA and HAwI	Subcutaneous treatment, unaffected by FVIII/FIX inhibitors	Approved, first-line prophylactic treatment for patients with inhibitors <sup>3</sup>
Anti-TFPI <sup>4,5</sup>	HA, HAwI, HB, and HBwI	Subcutaneous treatment for all indications, unaffected by FVIII/FIX inhibitors	Approved for prophylactic treatment in patients with HA and HB without inhibitors <sup>6</sup>
siRNA knockdown of antithrombin <sup>7,8</sup>	HA, HAwI, HB, and HBwI	Subcutaneous treatment for all indications, unaffected by FVIII/FIX inhibitors	Under investigation for use in the US (phase 3)
APC inhibitors <sup>9,10</sup>	HA, HAwI, HB, and HBwI	Subcutaneous treatment for all indications, unaffected by FVIII/FIX inhibitors	Under investigation for use in the US (phase 1/2)

APC, activated protein C; BPA, bypassing agent; FIX, factor IX; FVIIIa, activated factor VIII; HA, hemophilia A; HB, hemophilia B; HAwI, hemophilia A/B with inhibitors; siRNA, small interfering ribonucleic acid; TFPI, tissue factor pathway inhibitor. 1. Ljung R et al. *Eur J Haematol* 2019;102:111–22; 2. Shima M et al. *N Engl J Med* 2016;374:2044–53; 3. Srivastava A et al. *Hemophilia* 2020;26:1–158; 4. Chowdary P. *Int J Hematol* 2020;111:42–50; 5. Matsushita T et al. *N Engl J Med* 2023;389:783–94; 6. Business Wire. U.S. FDA Approves Pfizer's HYMPAVZ™ (marstacimab-hncq) for the Treatment of Adults and Adolescents with Hemophilia A or B Without Inhibitors. Accessed October 11, 2024; 7. Sehgal A et al. *Nat Med* 2015;21:492–7; 8. Franchini M, Mannucci PM. *Blood Transfus* 2018;16:457–61; 9. Polderdijk SGI et al. *Curr Opin Hematol* 2017;24:446–52; 10. Young G et al. *Lancet* 2023;401:1427–37.



# Immune tolerance induction (ITI)

What is ITI?	How is ITI used?
<ul style="list-style-type: none"> <li>Regular infusions of factor administered frequently to eradicate immune response<sup>1-3</sup></li> <li>Currently the only effective modality to remove inhibitors and restore FVIII sensitivity<sup>2,3</sup></li> <li>Effective in 70–80% of cases in severe HA<sup>1,2</sup> <ul style="list-style-type: none"> <li>Successful HA ITI: persistently negative Bethesda titer, normal pharmacokinetics (including factor recovery &gt;66%), and half-life &gt;6 hours for SHL FVIII</li> <li>Failure of HA ITI: inability to achieve successful tolerance within 2–3 years of initiation</li> </ul> </li> <li>ITI success in HB is low; monitoring for allergic reactions or nephrotic syndrome is important<sup>1</sup></li> </ul>	<ul style="list-style-type: none"> <li>Various ITI protocols have been developed (Bonn,<sup>4</sup> Malmö,<sup>5</sup> and Van Creveld<sup>6</sup>)</li> <li>Ideal regimen and time to commence treatment have not yet been established<sup>2,3</sup></li> <li>Ideal treatment schedules may be patient-specific and should be individualized<sup>1-3</sup></li> <li>Considered a costly, long-term, demanding therapy<sup>1-3</sup></li> <li>Treating bleeds may require bypassing agents, especially if inhibitor titers are <math>\geq 5</math> BU/mL<sup>7-9</sup></li> <li>Currently there is no consensus on the use of immunosuppressive and immunomodulatory therapies in patients with inhibitors<sup>1</sup></li> </ul>

**Although usual recommendation is to delay ITI until inhibitor titer is <10 BU/mL (if possible, within 2 years of inhibitor onset), prompt ITI should be considered, regardless of current inhibitor titer, for those with frequent/or severe bleeds<sup>9</sup>**

BU, Bethesda unit; FVIII, factor VIII; HA, hemophilia A; HB, hemophilia B; ITI, immune tolerance induction; SHL, standard half-life.

1. Srivastava A et al. *Hemophilia* 2020;26:1–158; 2. Nakar C et al. *Haemophilia* 2015;21:365–73; 3. Kruse-Jarres R et al. *Expert Opin Biol Ther* 2008;8:1885–96; 4. Brackmann HH et al. *Vox Sang* 1996;70(Suppl 1):30–5; 5. Freiburghaus C et al. *Haemophilia* 1999;5:32–9; 6. Mauser-Bunschoten EP et al. *Blood* 1995;86:983–8; 7. Escobar MA et al. *Hemophilia A and Hemophilia B*. Williams Hematology. New York, NY: McGraw Hill. 2016; 8. Ryu JE et al. *Blood Res* 2015;50:248–53; 9. Ljung R et al. *Eur J Haematol* 2019;102:111–22.



# Summary

Inhibitors are antibodies against exogenous FVIII/FIX that neutralize the ability of factor replacement to stop bleeds<sup>1,2</sup>

Development of inhibitors poses a therapeutic challenge and increases morbidity in people with hemophilia<sup>1,2</sup>

ITI is an effective but demanding strategy to eradicate inhibitors in patients with hemophilia A<sup>3</sup>

Acute bleeds in patients unresponsive to ITI can be treated with on-demand therapy, such as bypassing agents<sup>3</sup>

Prophylaxis with bypassing agents or non-factor replacement therapies (such as FVIIIa mimetics and anti-TFPI therapies) may be an effective alternative to ITI (including patients with unsuccessful ITI)<sup>3,4</sup>

*FIX, factor IX; FVIIIa, activated factor VIII; ITI, immune tolerance induction; TFPI, tissue factor pathway inhibitor.*

*1. Morfini M et al. Haemophilia 2007;13:502–7; 2. Eckhardt CL et al. J Thromb Haemost 2015;13:1217–25; 3. Ljung R et al. Eur J Haematol 2019;102:111–22; 4. Okaygoun D et al. J Biomed Sci. 2021;28:64.*