Congenital Hemophilia with Inhibitors

Disease background

October 2024

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Characteristics of inhibitors

An antibody against FVIII or FIX[1]

- Can develop in response to exogenous FVIII/FIX[1]
- A serious treatment complication[2]
- Can be alloantibody or autoantibody*[3]
- Antibodies against FVIII/FIX are predominantly an IgG subclass 4[4,5]

Mechanism of action[1]

- Neutralizing inhibitors bind to an active site and inhibit the ability of replacement factor to stop bleeding

Associated with treatment challenges[6,7]

- FVIII or FIX replacement may not prevent or stop bleeding owing to neutralizing effect of inhibitors
- Treatment of bleeding episodes in the presence of inhibitors is more challenging

Increases morbidity and mortality[8,9]

- Historically, patients with inhibitors have reported higher rates of hospitalization, greater treatment cost, greater incidence of bleeding episodes, and higher mortality vs those without[10]
- 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[11,12]

- **Inhibitors occur in approximately 30% of previously untreated patients with HA, of which 79% occur within the first 20 EDs† and the remainder within the first 75 EDs[13]**
- **Inhibitors in severe HB are less common (<5%), with most occurring after a median of 9–11 EDs, and before 20 EDs[14,15]**

**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.

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Risk factors for inhibitor development[1]

- Age at first infusion of FVIII/FIX
- Intensity of treatment
- Early initiation of prophylaxis
- Immune system challenges
  - Immunization
  - Inflammation
- Type of factor concentrate
- CFC replacement intensity[2]

Modifiable risk factors

Inhibitors

Non-modifiable risk factors

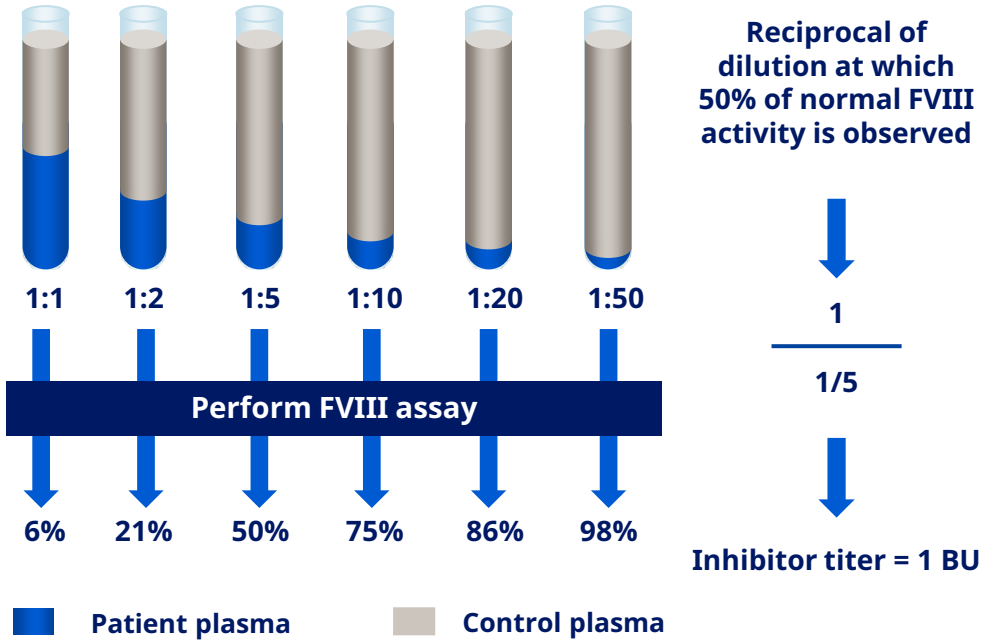
- Causative gene mutation
- Hemophilia disease severity
- Ethnicity
- Family history
- MHC class I/II phenotype
- Polymorphisms of immune response genes (IL-10, TNFα, CTLA-4)

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[1,2]

Inhibitor status can be measured in titer by the Bethesda assay[1]



1 BU = quantity of inhibitor that results in loss of 50% of factor activity

High titer ≥5 BU[1]

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

Low titer <5 BU[1]

- Low-responding inhibitors do not rise to ≥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[1]

- 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[1]

Inhibitor testing should be performed:[2]

- 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.

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Current algorithm for the management of patients with hemophilia and inhibitors

Treatment of acute bleeds[1,2]	• 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[1,2]	• 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[6]
Inhibitor eradication[1,2]	• Patients with inhibitors should undergo a trial of ITI, when possible, to eradicate the inhibitor[4] • 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[5]

**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 HYMPAVZI™ (marstacimab-hncq) for the Treatment of Adults and Adolescents with Hemophilia A or B Without Inhibitors. Accessed October 11, 2024.

Prophylaxis agents for patients with inhibitors

BPAs

- Prophylaxis with BPAs has been shown to:[1]
  - 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[1]

Novel treatments

Class	Indication	Characteristics	Approval status
FVIIIa mimetics[2]	HA and HAwI	Subcutaneous treatment, unaffected by FVIII/FIX inhibitors	Approved, first-line prophylactic treatment for patients with inhibitors[3]
Anti-TFPI[4,5]	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[6]
siRNA knockdown of antithrombin[7,8]	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[9,10]	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; HA/BwI, 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 HYMPAVZI™ (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?

• Regular infusions of factor administered frequently to eradicate immune response[1–3]
• Currently the only effective modality to remove inhibitors and restore FVIII sensitivity[2,3]
• Effective in 70–80% of cases in severe HA[1,2]
  • Successful HA ITI: persistently negative Bethesda titer, normal pharmacokinetics (including factor recovery >66%), and half-life >6 hours for SHL FVIII
  • Failure of HA ITI: inability to achieve successful tolerance within 2–3 years of initiation
• ITI success in HB is low; monitoring for allergic reactions or nephrotic syndrome is important[1]
	• Various ITI protocols have been developed (Bonn,[4] Malmö,[5] and Van Creveld[6])
	• Ideal regimen and time to commence treatment have not yet been established[2,3]
	• Ideal treatment schedules may be patient-specific and should be individualized[1–3]
	• Considered a costly, long-term, demanding therapy[1–3]
	• Treating bleeds may require bypassing agents, especially if inhibitor titers are ≥5 BU/mL[7–9]
	• Currently there is no consensus on the use of immunosuppressive and immunomodulatory therapies in patients with inhibitors[1]

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[9]

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[1,2]

Development of inhibitors poses a therapeutic challenge and increases morbidity in people with hemophilia[1,2]

ITI is an effective but demanding strategy to eradicate inhibitors in patients with hemophilia A[3]

Acute bleeds in patients unresponsive to ITI can be treated with on-demand therapy, such as bypassing agents[3]

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)[3,4]

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.