Bleeding Between the Lines: Hemophilia Updates

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Disclosures

The following faculty speakers and/or planning committee members have disclosed the following:

Faculty Name	Name of Ineligible Companies	Nature of Relationship
Chris (Paul) Parish, PharmD	Hema Biologics	Advisory Board, SEVENFACT®

The other and speakers have indicated that there are no relevant financial relationships with any ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

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Learning Objectives

At the end of this session, learners should be able to:

- Recognize pathophysiology, clinical features, and similarities and differences between hemophilia A and B including severity classification
- Compare on-demand and prophylaxis treatment approaches and options for hemophilia
- Identify factor repletion strategies for patients with hemophilia
- Outline novel therapies used for hemophilia, including gene therapy and nonfactor replacement therapies

Outline

- Epidemiology and pathophysiology
- Clinical presentation
- On-demand and prophylaxis treatment options
- Factor repletion strategies
- Gene therapy
- Nonfactor replacement therapies

Abbreviation Key

ABR – Annualized bleeding rate

ADE – Adverse event

aPCC – Activated prothrombin complex concentrate

aPTT – Activated partial thromboplastin time

BBW – Black box warning

BU – Bethesda Unit

CFC – Coagulation factor concentrates

FIX – Factor IX

FVIII – Factor VIII

FX – Factor X

MOA – Mechanism of action

PT – Prothrombin time

rFVIIa – Recombinant activated factor VII

TPFI – Tissue pathway factor inhibitor

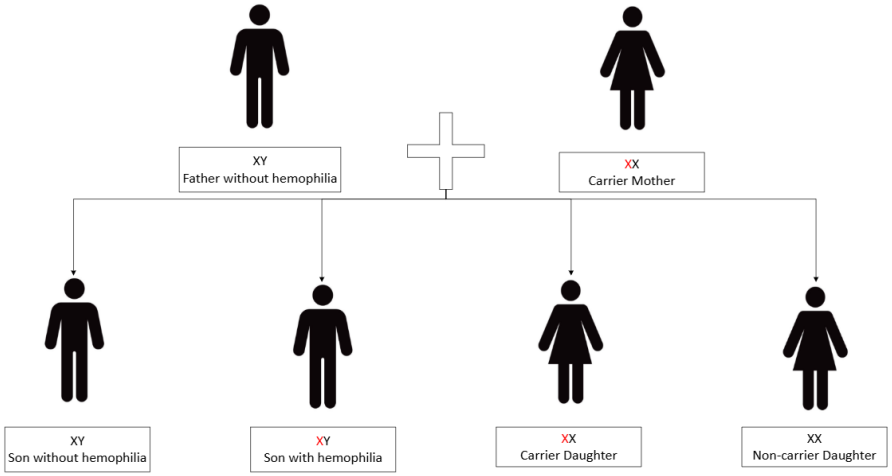
URTI – Upper respiratory tract infection

WFH – World Federation of Hemophilia

Epidemiology

Hemophilia

- Rare, genetic, X-linked, recessive bleeding disorder caused by a deficiency in clotting factors
- Affecting over 1 million people worldwide and 30,000 people in the US
  - Most common in males
- Two most common types:
  - Hemophilia A (more common)
  - Hemophilia B



Srivastava, et al. *Haemophilia*. 2020.
Rezende, et al. J Thromb Haemost. 2024.

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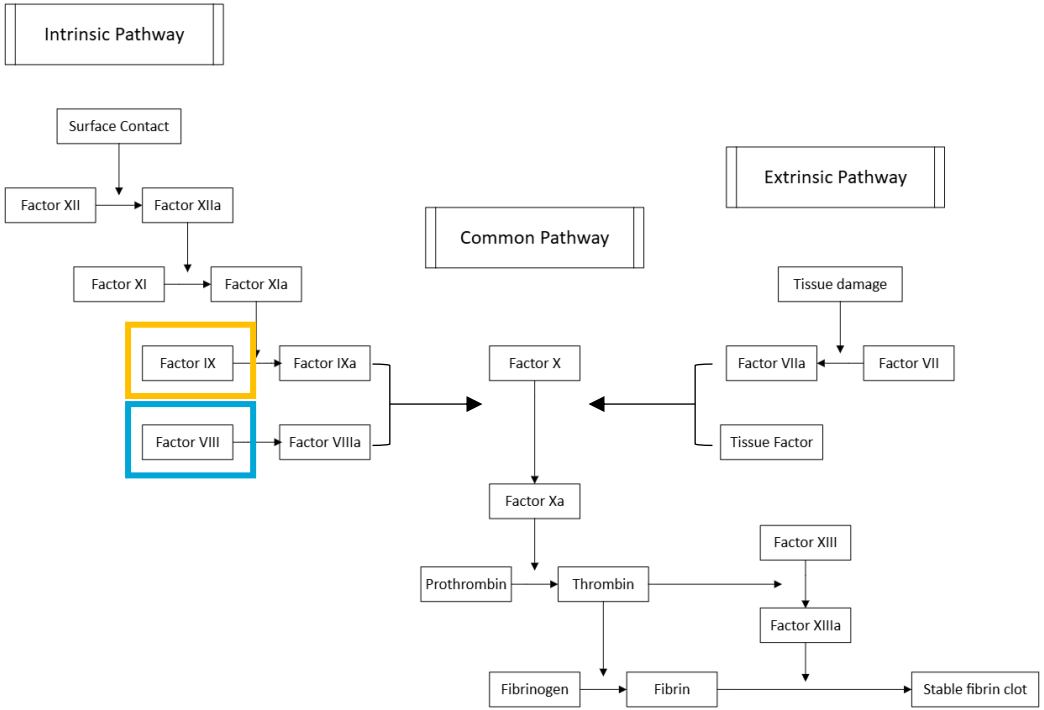
Pathophysiology

Coagulation Cascade

Hemophilia B

Hemophilia A



Park, et al. *Blood Res.* 2024

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Clinical Presentation

Clinical Presentation

Hemophilia A and B are clinically indistinguishable

- Hemophilia A tends to be more severe

Signs and symptoms:

- Hemarthrosis (most common)
- Mucocutaneous bleeding
- Spontaneous severe bleeding (uncommon)
- Severe trauma related bleeds

Hemophilia is diagnosed if factor activity is <40%

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Srivastava, et al. *Haemophilia*. 2020.

Diagnosis

1. Clinical features
2. Screening tests
   - aPTT – prolonged (> 35 seconds)
   - PT - normal (11-13.5 seconds)
   - Platelet counts – normal (150,000– 450,000/uL)
3. Factor activity assays
   - Determine hemophilia type and severity

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Srivastava, et al. *Haemophilia*. 2020.

Severity Classification

Severity	Clotting factor level	Bleeding episodes
Mild	>5-40% of normal (>5-40 IU/dL)	Rare spontaneous bleeding Severe bleeding with major trauma or surgery
Moderate	1-5% of normal (1-5 IU/dL)	Occasional spontaneous bleeding Prolonged bleeding with minor trauma or surgery
Severe	< 1% of normal (<1 IU/dL)	Spontaneous bleeding

- Factor levels generally remain stable over a patient's lifetime

Srivastava, et al. *Haemophilia*. 2020.
Rezende, et al. J Thromb Haemost. 2024.

Inhibitors

Inhibitors – IgG antibodies which neutralize exogenous factor VIII or factor IX

Measured by Bethesda assay in Bethesda Units (BU)

- > 0.6 BU for FVIII
- ≥ 0.3 BU for FIX

Inhibitors should be suspected in patients who fail to respond to coagulation factor concentrate (CFC) replacement therapy especially if previously responsive

Poses a greater challenge in controlling bleeds

Srivastava, et al. *Haemophilia*. 2020.
Rezende, et al. J Thromb Haemost. 2024.

Risk Factors for Inhibitors

- Hemophilia A, especially if inversions in F8 gene
- First 50-75 exposure days in hemophilia A
- Severe hemophilia
- Age
- Race and family history
- CFC intensity and type

Inhibitors in hemophilia B are rare, often occur early, and can present like an allergic reaction

Srivastava, et al. *Haemophilia*. 2020.
Garagiola, et al. *Thromb Res.* 2018.
Hermans, et al. *J Thromb Haemost.* 2012.

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Assessment Question #1

Which of the following laboratory findings is most consistent with a diagnosis of hemophilia A or B?

A. Prolonged PT, normal aPTT, low platelet count
B. Normal PT, prolonged aPTT, normal platelet count
C. Prolonged PT and aPTT with low platelet count
D. Normal PT and aPTT with low platelet count

Treatment Approaches

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Definitions

- **On-demand/episodic treatment:**
  - Treating active bleeding and/or hemostatic challenges
- **Prophylaxis:**
  - Regularly scheduled treatment to prevent bleeding episodes
- **Factor products:**
  - Purified, pharmaceutical-grade preparations of specific clotting factors to prevent or treat bleeding episodes
    - Direct factor repletion: supply the exact missing coagulation factor (ie. FVIII or FIX)
    - Bypassing agents: bypass the need for FVIII or FIX
- **Nonfactor products:**
  - Agents that prevent bleeding without directly replacing missing factor
- **Inhibitor status (+/-):**
  - If positive, the patient's immune system has developed antibodies against factor products

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Srivastava, et al. *Haemophilia*. 2020.

Treatment Modalities

On-demand therapies

- Direct factor repletion
- Bypassing agents

Prophylaxis therapies

- Factor products
- Gene therapies
- Nonfactor products

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On-Demand Factor Repletion Strategies

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On-Demand Factor Repletion Agents:

Agent	Direct vs. Bypassing	On-Demand vs. Prophylaxis	Inhibitor Considerations
Factor VIII Concentrates	Direct	Both	Avoid in patients with high titer inhibitors
Factor IX Concentrates	Direct	Both	Avoid in patients with high titer inhibitors
Recombinant Activated Factor VII (rFVIIa)	Bypassing agent	Both	Preferred in patients with high titer inhibitors
Activated Prothrombin Complex Concentrate (aPCC)	Bypassing agent	Both	Used in hemophilia A, typically in patients with high titer inhibitors

Srivastava, et al. *Haemophilia*. 2020.

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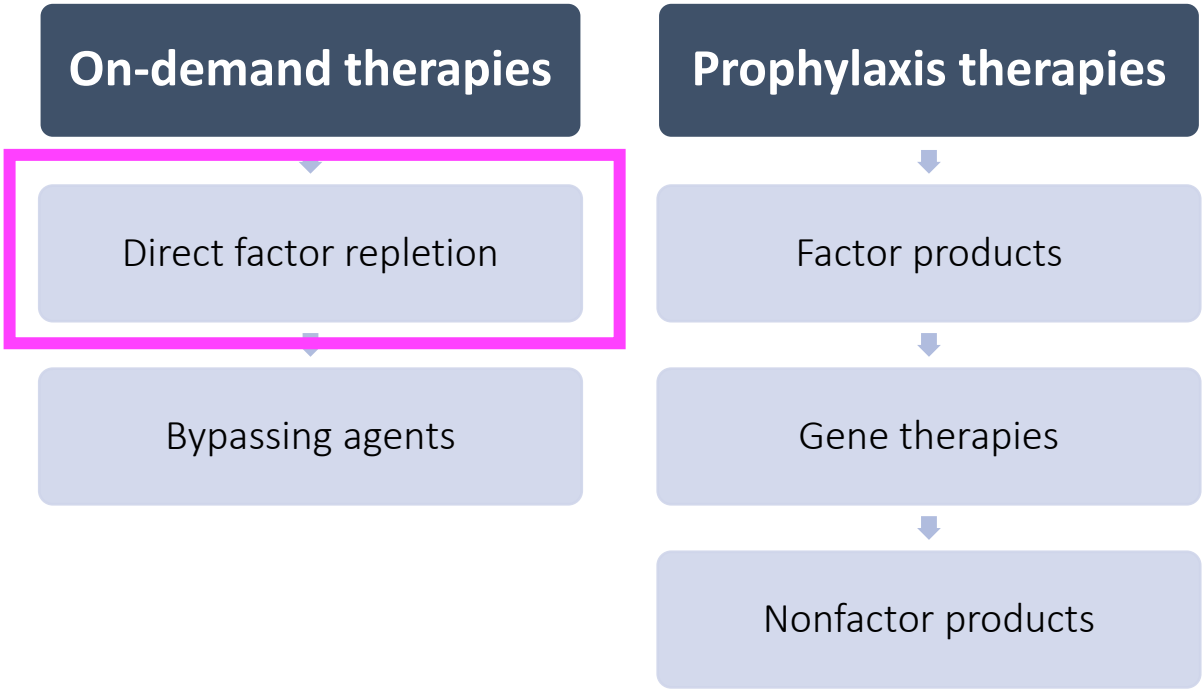
Treatment Modalities



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Factor VIII Concentrates

Standard half-life products

- Half-life: 6-10 hours
- On-demand dosing frequency: every 8-12 hours
- Product: Recombinant Antihemophilic Factor

Extended half-life products

- Half-life: 12-18h
- Mechanism: PEGylation reduces binding affinity to receptors responsible for the clearance of FVIII
- On-demand dosing frequency: every 24-36 hours
- Product: Pegylated Recombinant Antihemophilic Factor

Ultra-long half-life products

- Half-life: ~40 hours
- Mechanism: fusion technologies protect the FVIII molecule from premature clearance and degradation
- On-demand dosing frequency: every 72 hours
- Product: Recombinant Antihemophilic Factor Fc-VWF-XTEN Fusion Protein

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Srivastava, et al. *Haemophilia*. 2020.

Dosing of Factor VIII Concentrates

Factor VIII Dosing:

- 1 unit/kg of body weight raises FVIII plasma level by ~2 IU/dL

Calculation:

- Patient's weight (kg) x FVIII level desired x 0.5

General goal:

- Increase the factor VIII level > 40% for on-demand therapy

Srivastava, et al. *Haemophilia*. 2020.

Factor IX Concentrates

Standard half-life products

- Half-life: 16-18 hours
- On-demand dosing frequency: every 24 hours
- Product: Recombinant Factor IX

Extended half-life products

- Half-life: 25-30 hours
- Mechanism: fusion technology delays lysosomal degradation prolonging circulation of FIX
- On-demand dosing frequency: every 48 hours
- Product: Recombinant Factor IX Fc Fusion Protein

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Srivastava, et al. *Haemophilia*. 2020.

Dosing of Factor IX Concentrates

Factor IX Dosing:

- 1 unit/kg of body weight raises FIX plasma level by ~1 IU/dL

Calculation:

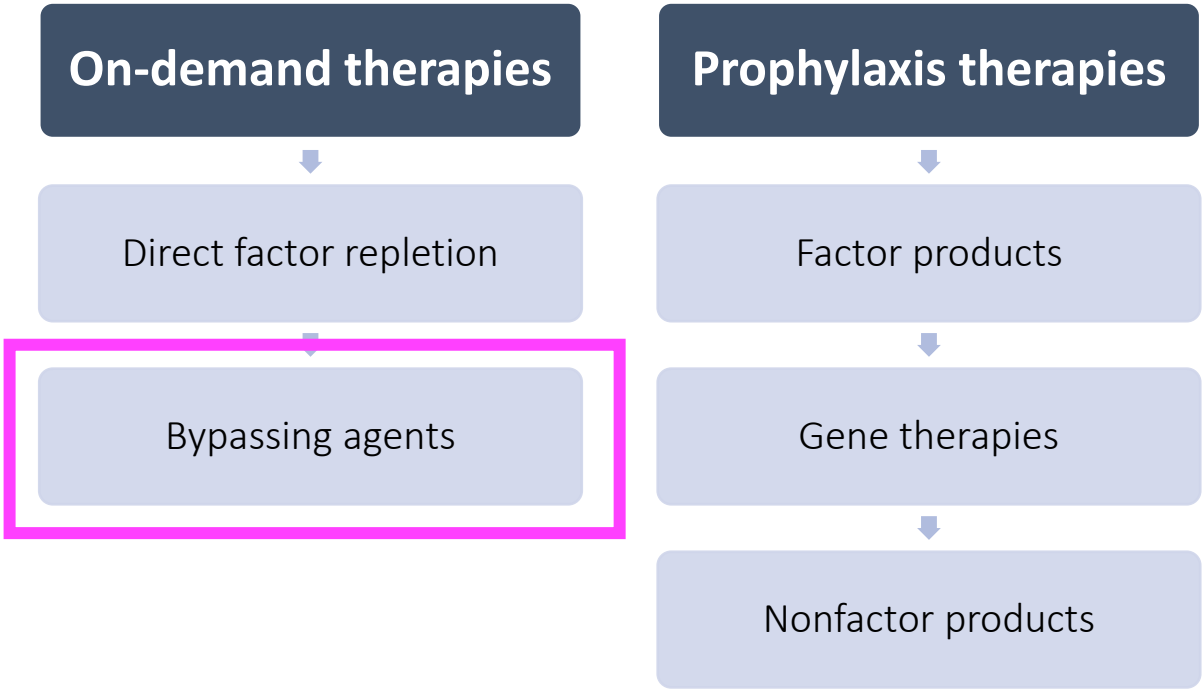
- Patient's weight (kg) x FIX level desired

General goal:

- Increase the factor IX level > 40% for on-demand therapy

Srivastava, et al. *Haemophilia*. 2020.

Treatment Modalities



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Bypassing Agents

Recombinant Activated Factor VII

- On-demand dosing: 90 mcg/kg/dose every 2 hours until hemostasis is achieved
- Mechanism: binds to tissue factor activating FX continuing the coagulation cascade

Activated Prothrombin Complex Concentrate

- On-demand dosing: 50-100 units/kg every 6-12 hours
  - Max: 200 units/kg/day
- Mechanism: provides activated clotting factors such as prothrombin, FIX, FX and FVIIa

Srivastava, et al. *Haemophilia*. 2020.
Novo Nordisk. NovoSeven RT package insert. FDA; 2014.
FEIBA package insert. Takeda Pharmaceuticals America, Inc.; 2025.

On-Demand Treatment with Inhibitors

Low Titer Inhibitors

- CFC replacement therapy preferred
- [body weight (kg) × 80 × [(1 − hematocrit) × antibody titer (BU)]
- An additional 50 IU/kg above the calculated loading dose is added to achieve a measurable FVIII activity

High Titer Inhibitors

- Bypass agent therapy with rFVIIa or aPCC

Hemophilia B: rFVIIa preferred over aPCC

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Srivastava, et al. *Haemophilia*. 2020.

Assessment Question #2

A 28-year-old man with hemophilia A presents with a moderate joint bleed. He weighs 72 kg. Your goal is to raise his Factor VIII level by approximately 50 IU/dL. Calculate the correct on-demand replacement dose needed for this patient if we were to use recombinant factor VIII product.

A. 1,800 units
B. 3,600 units
C. 900 units
D. 72 units

Prophylaxis Strategies

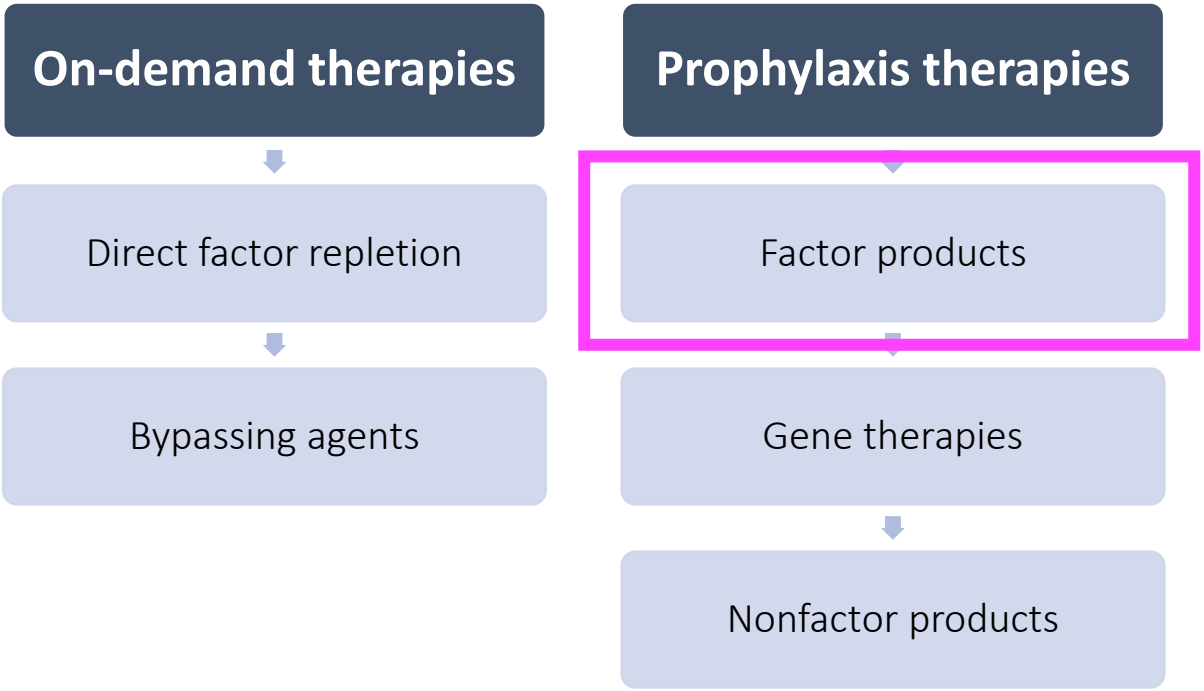
Prophylaxis Agents:

Agent	Factor/Nonfactor	On-demand vs. Prophylaxis	Inhibitor Considerations
Factor VIII Concentrates	Factor (Direct)	Both	Avoid in patients with high titer inhibitors
Factor IX Concentrates	Factor (Direct)	Both	Avoid in patients with high titer inhibitors
Etranacogene dexaparvovec	Gene Therapy	Prophylaxis	Avoid in patients with inhibitors
Valoctogene roxaparvovec	Gene Therapy	Prophylaxis	Can use in presence of inhibitors
Emicizumab	Nonfactor	Prophylaxis	Can use in presence of inhibitors
Concizumab	Nonfactor	Prophylaxis	Can use in presence of inhibitors
Marstacimab	Nonfactor	Prophylaxis	*Can use in presence of inhibitors
Fitusiran	Nonfactor	Prophylaxis	Can use in presence of inhibitors

*Marstacimab is FDA approved for prophylaxis in patients without inhibitors but is being studied in patients with inhibitors

Srivastava, et al. *Haemophilia*. 2020.

Treatment Modalities



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Coagulation Factor Concentrates

Factor VIII Concentrates

- Prophylaxis dosing frequency
  - Standard half-life: 3-4x per week
  - Extended half-life: 2x per week or every 3 days
  - Ultra-long half-life: once weekly
- Goal: Generally maintaining factor VIII levels > 1%

Factor IX Concentrates

- Prophylaxis dosing frequency
  - Standard half-life: 1-2x per week
  - Extended half-life: every 7-10 days
- Goal: Generally maintaining factor IX levels > 1%

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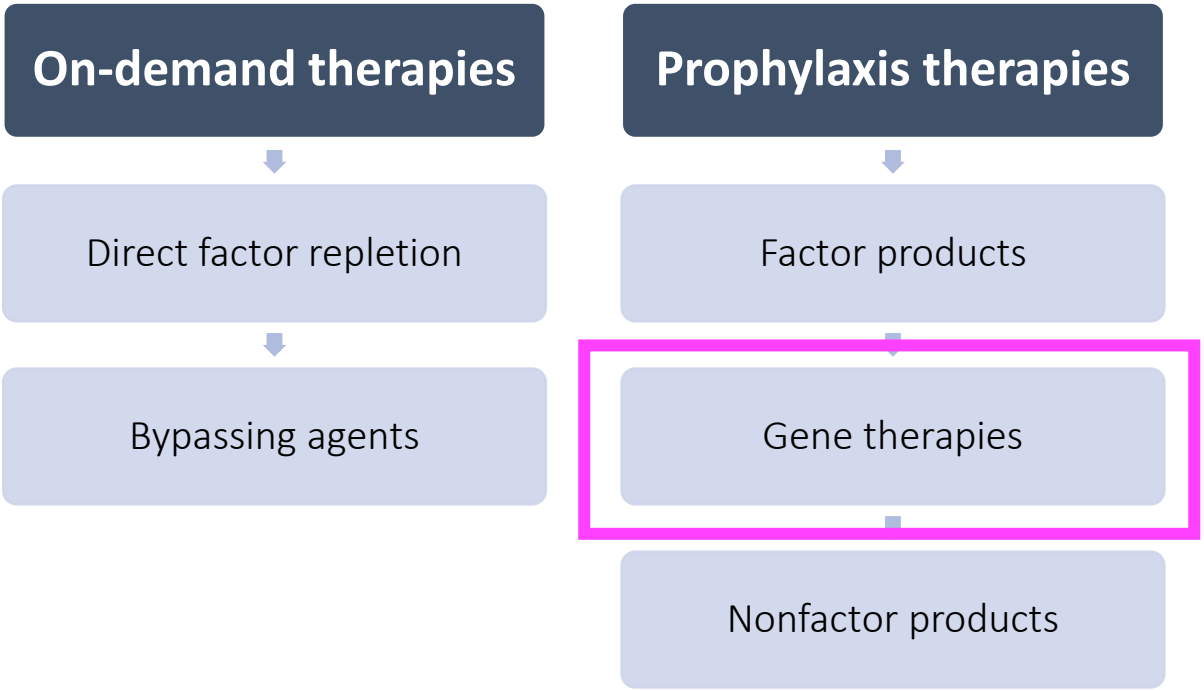
Srivastava, et al. *Haemophilia*. 2020.

Treatment Modalities



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Gene Therapies

Deliver functional genes via AAV5 viral vector to hepatocytes and enable homogenous factor production

Etranacogene Dezaparvovec	Valoctocogene Roxaparvovec
Factor 9 Replacement	Factor 8 Replacement
Administered IV	Administered IV
No reduction of effect seen over time	Can lose effect over time
Better tolerated	Associated with infusion reactions
90% of patients are able to eliminate prophylaxis long term	Requires closer monitoring

Pang X, et al. *Clin Appl Thromb Hemost*. 2025

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Assessment Question #3

Which of the following statements correctly describes the use of hemophilia treatment modalities for on-demand versus prophylaxis therapy?

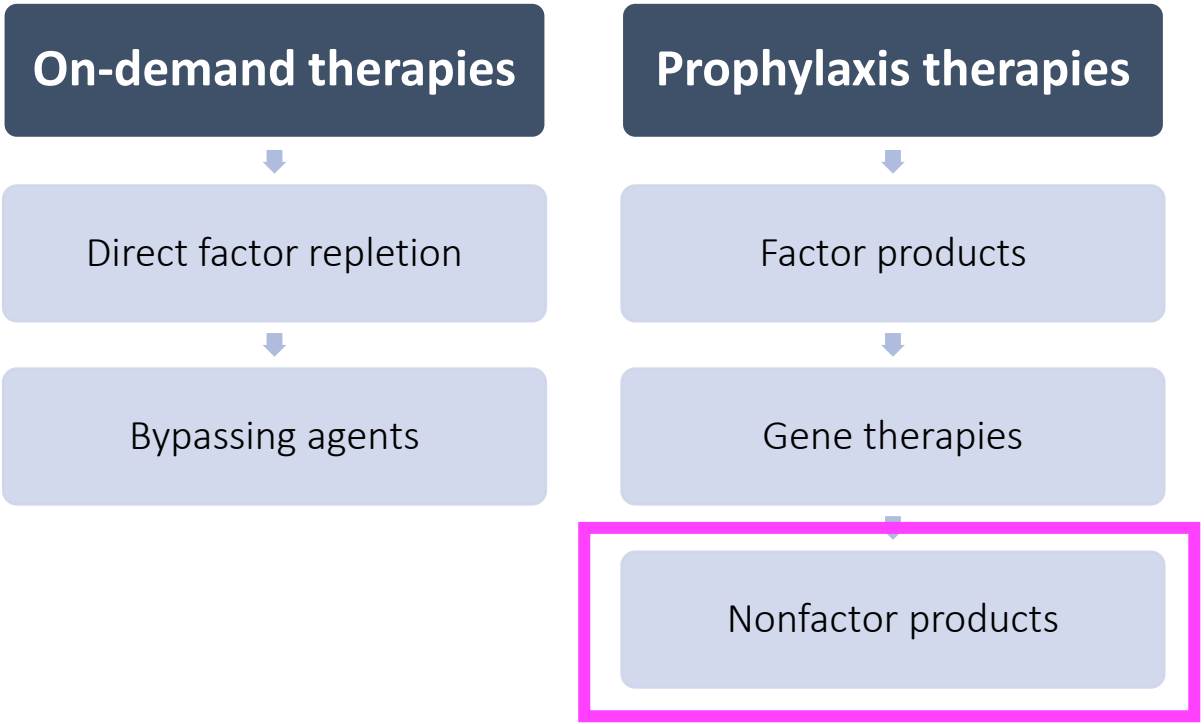
A. Factor VIII and Factor IX concentrates are restricted to prophylaxis and cannot be used for acute bleeding episodes

B. Bypassing agents such as rFVIIa and aPCC cannot be used to treat acute bleeding episodes

C. Etranacogene Dezaparvovec is indicated for the treatment of acute bleeding episodes in addition to routine prophylaxis

D. Factor concentrates may be used for both on-demand treatment and prophylaxis

Treatment Modalities



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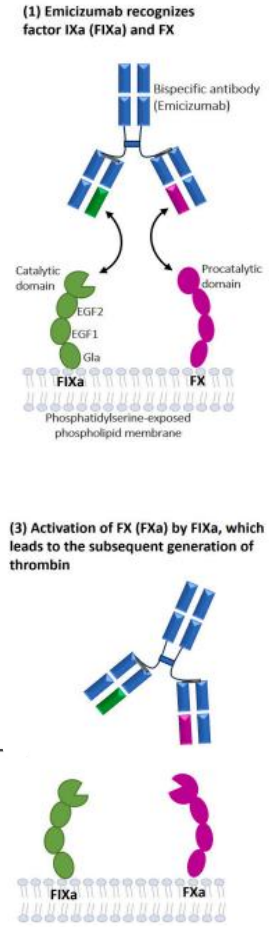
Emicizumab



- MOA: an antibody which acts as a FVIII mimic and binds both human FIX/FIXa and FX/FXa
- Route: subcutaneous
- Half-life: 27.8 days
- Dosing: 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly
- Recommended in hemophilia A with or without inhibitors

Anmed, et al. *Blood Rev.* 2024.

Srivastava, et al. *Haemophilia*. 2020.
Rezende, et al. J Thromb Haemost. 2024.
Hemlibra (emicizumab-kxwh) injection. [package insert]. Genentech, Inc; 2024.

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Emicizumab

Must use CFCs or bypassing agents for acute bleeds

Drug interactions: Hypercoagulability with concomitant use of aPCC, rFVIIa, or FVIII

BBW: increased risk of thrombotic events when >100 units/kg/24 hours of aPCC was administered to patients receiving emicizumab

Srivastava, et al. *Haemophilia*. 2020.
Hemlibra (emicizumab-kxwh) injection. [package insert]. Genentech, Inc; 2024.

New Non-Factor Therapies

	Concizumab	Marstacimab	Fitusiran
MOA	Monoclonal antibody targeting and inhibiting tissue factor pathway inhibitor (TFPI), increasing thrombin generation and supporting hemostasis		Small interfering RNA (siRNA) that targets antithrombin in the liver, reducing production and increasing thrombin generation
Approved Indications	Prophylaxis in hemophilia A or B with or without inhibitors	Prophylaxis in hemophilia A or B WITHOUT inhibitors	Prophylaxis in hemophilia A or B regardless of inhibitors
Dosing	Loading dose of 1 mg/kg followed by once daily subcutaneous injection of 0.2 mg/kg until individualization of maintenance dose	300 mg loading dose, then 150 mg weekly subcutaneous injection	50 mg subcutaneous injection every two months
Side effects	Injection site reactions, hives, hypersensitivity symptoms, mild gastrointestinal reactions, thrombotic events	Injection site reactions (less common), headache	Hepatic injury Boxed warnings for thrombotic events and acute/recurrent gallbladder disease

Gupta N, et al. J Assoc Physicians India. 2025; Lu DR, et al. Drug Discov Ther. 2025.
Alhemo package insert. Novo Nordisk; 2025; HYMPAVZI package insert. Pfizer; 2024.

Assessment Question #4

Which of the following hemophilia therapies carries an FDA black box warning (BBW) for thrombotic events?

A. Etranacogene dezaparvovec
B. Emicizumab 3 mg/kg weekly
C. Emicizumab 1.5 mg/kg weekly + aPCC >100U/kg/day
D. Recombinant factor VIII at doses >90 mcg/kg/dose

Explorer8 Trial (2024)

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Explorer8 Trial: Background

Design: Prospective, multicenter, open-label, randomized phase 3a trial

Purpose: To evaluate concizumab prophylaxis in people with hemophilia without inhibitors

Population: Males >12 years with moderate to severe hemophilia without inhibitors

Chowdary, et al. *Lancet Haematol*. 2024.

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Explorer8 Trial: Intervention

Loading dose: 1 mg/kg subcutaneously

Maintenance dose: 0.2 mg/kg subcutaneously daily

After 4 weeks, dose was changed to one of the following

- decreased to 0.15 mg/kg
- increased to 0.25 mg/kg
- maintained at 0.20 mg/kg

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Martino, et al. *Blood.* 2025.

Explorer8 Trial: Results

148 patients were included in the intention-to-treat analysis

Hemophilia A:

- **ABR reduction = 86%**
- **Mean ABR**:
  - Concizumab: **2.7** (95% CI 1.6–4.6)
  - No prophylaxis: **19.3** (95% CI 11.3–33.0)
- **ABR ratio: 0.14** (95% CI 0.07–0.29), **P <0.001**

Hemophilia B:

- **ABR reduction = 79%**
- **Mean ABR:**
- Concizumab: **3.1** (95% CI 1.9–5.0)
  - No prophylaxis: **14.8** (95% CI 8.1–26.9)
- **ABR ratio: 0.21** (95% CI 0.10–0.45), **P <0.001**

Safety

- Common adverse events:
  - COVID-19 (13%)
  - Increased D-dimer (8%)
  - Upper respiratory tract infection (7%)

ABR: Annualized bleeding rate

Martino, et al. *Blood.* 2025.

Explorer8 Trial: Conclusions

Strengths/Limitations

- Strengths: Evaluated safety and efficacy in hemophilia A and B; introduced the first subcutaneous prophylaxis option for hemophilia B patients without inhibitors
- Limitations: Open-label design; trial paused due to thrombotic events; uneven participants in control and treatment groups

Conclusion

- Concizumab prophylaxis significantly reduced bleeding rates compared with no prophylaxis in people with hemophilia A or B without inhibitors

Clinical Implications

- Expands prophylaxis options beyond factor replacement and emicizumab
- Benefits include subcutaneous once-daily therapy and reduced venous access burden

BASIS Trial (2025)

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BASIS Trial: Background

Design: Open label, 1-way crossover, multicenter phase 3 trial

Purpose: To evaluate the safety and efficacy of marstacimab

Population: Males aged 12-74 with moderate to severe hemophilia without inhibitors

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Martino, et al. *Blood.* 2025.

BASIS Trial: Intervention

Loading dose: 300 mg subcutaneously

Maintenance dose: 150 mg subcutaneously weekly

- Increased after 6 months of treatment to 300 mg if > 50 kg and experiencing > 2 breakthrough bleeds

6-month observational phase

- Patients were split into two cohorts:
  - Patients receiving on-demand treatment
  - Patients receiving routine prophylaxis with factor replacement or bypassing agents

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Martino, et al. *Blood.* 2025.

BASIS Trial: Results

116 participants received marstacimab during the active treatment phase

Prior On-demand Therapy

- **Mean ABR:**
  - Observational period: **39.86** (95% CI 33.05–48.07)
  - Marstacimab: **3.20** (95% CI 2.10–4.88)

Relative reduction: ~92%
ABR ratio: 0.080 (95% CI 0.057–0.113); **P < 0.0001**

Prior Routine Prophylaxis

- **Mean ABR:**
  - Observational period: **7.90** (95% CI 5.14–10.66)
  - Marstacimab: **5.09** (95% CI 3.40–6.78)

Absolute difference: –2.81 (95% CI -5.42 to -0.20); **P = 0.0349**

Safety

- Adverse events during active treatment phase
  - 36.4% on-demand group
  - 74.7% routine prophylaxis group
- Most common adverse events:
  - COVID-19–related, pruritus, upper respiratory tract infection, decreased range of joint motion

ABR: Annualized bleeding rate

Martino, et al. *Blood.* 2025.

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BASIS Trial: Conclusions

Strengths/Limitations

- Strengths: Comparison of marstacimab to standard of care therapies; inclusion of hemophilia A and B patients
- Limitations: High baseline bleeding rates in the standard of care groups; lack of separation between standard of care therapies

Conclusions

- Once-weekly subcutaneous marstacimab significantly reduced bleeding rates in people with hemophilia A or B without inhibitors especially in patients transitioning from on-demand therapy

Clinical Implications

- Provides a nonfactor, once-weekly subcutaneous option for patients without inhibitors, reducing reliance on IV factor infusions

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Martino, et al. *Blood.* 2025.

ATLAS-A/B Trial (2023)

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ATLAS-A/B Trial: Background

Design: Multicenter, open-label, randomized phase 3 trial

Purpose: Evaluate the efficacy and safety of fitusiran prophylaxis in people with severe hemophilia A or B without inhibitors

Population: Males aged ≥12 years with severe hemophilia A or B without inhibitors previously treated with on-demand therapy with CFCs

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Srivastava, et al. *Lancet Haematol*. 2023.

ATLAS-A/B Trial: Intervention

Fitusiran group

Fitusiran 80 mg subcutaneously once per month

On-demand group

On-demand CFCs for the treatment of bleeding episodes, no prophylaxis

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Srivastava, et al. *Lancet Haematol*. 2023.

ATLAS-A/B Trial: Results

120 participants included in the intention-to-treat analysis

Primary Outcome

- **Mean ABR:**
  - Fitusiran: **3.1** (95% CI 2.3–4.3)
  - On-demand: **31.0** (95% CI 21.1–45.5)
- **Rate ratio: 0.101** (95% CI 0.064–0.159); **P < 0.0001**

Safety

- 79% of fitusiran group experienced any adverse event compared to 45% of on-demand group
- Most common adverse events were increased AST/ALT, URTI, nasopharyngitis and abdominal pain
- 2 patients experienced a severe adverse event
- 2 patients discontinued fitusiran due to an adverse event

Srivastava, et al. *Lancet Haematol*. 2023

AST: aspartate aminotransferase; ALT: alanine aminotransferase; URTI: upper respiratory tract infection; ABR: annualized bleeding rate

ATLAS-A/B Trial: Conclusions

Strengths/Limitations

- Strengths: Clinically meaningful endpoints and well-characterized patient population
- Limitations: Comparator arm and short follow-up

Conclusion

- Monthly fitusiran prophylaxis led to a reduction in bleeding compared with on-demand factor therapy in severe hemophilia A or B without inhibitors with half of treated patients experiencing zero treated bleeds

Clinical Implications

- Fitusiran may be a viable option for factor-independent, once-monthly prophylaxis in severe hemophilia A and B without inhibitors
- Key advantage is subcutaneous monthly dosing and may be beneficial in patients previously managed with on-demand therapy and a high bleed burden

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Srivastava, et al. *Lancet Haematol*. 2023.

Summary/Conclusion

- Hemophilia is a rare, genetic blood disorder that poses many challenges as management is complex and multifaceted
- Treatment strategies include on-demand therapy for acute bleeding episodes and prophylaxis to prevent spontaneous bleeding and long-term joint damage
- Factor repletion remains foundational for hemophilia management, utilizing standard half-life or extended half-life recombinant FVIII or FIX products with dosing individualized based on bleed severity, pharmacokinetics, inhibitor status, and patient-specific factors
- Nonfactor replacement therapies are new and emerging, providing effective prophylaxis by restoring hemostatic balance, offering advantages in administration frequency and use in patients with inhibitors

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Questions?

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