



Original Research Article

Moderate Hemophilia (A)

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Name of Author:

Sharma K.K. and Sahu G.

Corresponding Author:

Sharma K.K.

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Abstract: Moderate Hemophilia A is an inherited bleeding disorder caused by partial deficiency of coagulation factor VIII, resulting in a variable but generally significant bleeding tendency. Defined by residual plasma factor VIII levels of 1–5%, this condition is intermediate between mild and severe forms of hemophilia. This article reviews the genetic and physiologic underpinnings, clinical manifestations, diagnostic approach, modern management strategies—including novel therapies, prophylaxis protocols, and the impact of personalized treatment algorithms—and summarizes outcomes and future perspectives. Recent recommendations emphasize individualized assessment beyond factor level alone, the role of joint health monitoring, and increasing use of new long-acting agents.

Keywords: Moderate Hemophilia A, Factor VIII Deficiency, Personalized Treatment, Prophylaxis Strategies, Long-Acting Therapies.

INTRODUCTION

Hemophilia A is the most frequent X-linked inherited bleeding disorder affecting primarily males, due to mutations in the F8 gene leading to factor VIII deficiency. Based on factor VIII clotting activity (FVIII:C), hemophilia is classified as:

- **Mild:** 6–40% normal FVIII.
- **Moderate:** 1–5% normal FVIII.
- **Severe:** <1% normal FVIII^{[1][2]}.

Moderate hemophilia accounts for approximately 15% of hemophilia A cases^{[2][3]}, often resulting in bleeding with mild trauma, challenging perioperative hemostasis, and occasionally spontaneous joint or muscle bleeding.

Pathophysiology and Genetics

F8 gene mutations lead to decreased or dysfunctional factor VIII, disrupting the intrinsic coagulation cascade^[4]. Bleeding risk directly correlates with the residual FVIII activity:

- <1%: frequent spontaneous bleeds;
- 1–5%: less spontaneous, more trauma-induced bleeds;
- 5%: usually bleeding only after significant trauma or surgery^{[5][2]}.

Clinical Manifestations

Patients with moderate hemophilia:

- Rarely experience spontaneous bleeds, but suffer prolonged bleeding after minor injuries, dental procedures, or surgeries.
- May present with joint (hemarthrosis) and muscle bleeds after mild trauma.

- Early signs: easy bruising, epistaxis, excessive bleeding after tooth extraction.
- Risk of joint damage increases if bleeding is not effectively prevented^{[5][2][6]}.

The mean annual bleeding rate typically ranges between that of mild and severe phenotypes—median 2.0 bleeds/year, with variability depending on bleeding history and activities^[7].

Diagnosis

Diagnosis is confirmed by:

- Clinical suspicion (personal or family history of bleeding).
- Laboratory assays showing FVIII:C between 1% and 5% of normal.
- Exclusion of acquired causes and other coagulopathies^{[5][8]}.

MANAGEMENT

1. Factor VIII Replacement Therapy

Factor VIII concentrate administration is the cornerstone of acute and perioperative bleed management. Both plasma-derived and recombinant concentrates are available^{[9][10]}.

- On-demand: Used for trauma, bleeding events, and surgical procedures in most moderate patients^{[11][9][12]}.
- Prophylaxis: Increasingly recommended for those with a severe bleeding phenotype (e.g., recurrent joint bleeding), high-risk activities, or poor joint health at diagnosis—approximately 30% of moderate patients may benefit from this^{[5][13][7][14]}.

2. Extended Half-life and Non-factor Therapies

- **Extended half-life (EHL) FVIII:** Allows less frequent dosing.
- **Emicizumab:** A subcutaneous, bispecific monoclonal antibody mimicking FVIII; used in moderate patients with frequent bleeding or poor venous access, and for those with inhibitors^{[15][16]}.

3. Multidisciplinary Care

Comprehensive care includes:

- Regular joint health monitoring (e.g., Haemophilia Joint Health Score).
- Physiotherapy to maintain mobility.
- Management of oral health and prompt dental care^{[4][17]}.
- Patient education on injury prevention and self-infusion techniques.

Table: Comparison of Hemophilia A Severity and Clinical Features ^{[2][6]}		
Severity	Factor VIII Activity	Bleeding Phenotype
Mild	6–40%	Bleeding after serious trauma/surgery
Moderate	1–5%	Bleeding after minor trauma, infrequent spontaneous
Severe	<1%	Frequent spontaneous bleeds, often into joints/muscles

Prophylaxis Recommendations

Indication in Moderate Hemophilia A ^{[13][7][14]}	Recommendation
High frequency of bleeds	Regular prophylaxis (FVIII/EHL/emicizumab)
Early joint damage	Prophylactic intervention
Perioperative or dental procedure	Factor VIII replacement
Routine activity, low risk	On-demand therapy

Outcomes

- Most moderate patients have good long-term outcomes, especially with early and individualized management.
- Subset with early joint bleeds or frequent bleeding benefit substantially from prophylaxis.

- Quality of life is improved by minimizing joint damage and functional limitations^{[7][16]}.
[image:1]

Figure 1: Frequency of annual bleeding events (ABR) and proportion of moderate patients experiencing joint damage (as measured by joint health score). Patients with earlier onset joint bleeds require more intensive management.

Advances and Future Directions

- Gene therapy and innovative non-factor therapeutics (e.g., anti-TFPI, siRNA against antithrombin) are in advanced clinical development and may reduce treatment burden in the future^{[15][16]}.
- Comprehensive, phenotype-based care algorithms optimize resource use and outcomes^[13].
- Treatment should factor in bleeding history, joint health, genetic profile, and patient preferences.

CONCLUSION

Moderate Hemophilia A remains a distinct clinical entity with variable bleeding risks and needs. While most patients live healthy lives with minimal intervention, a substantial subset requires individualized prophylaxis and careful joint monitoring to prevent long-term morbidity. Advances in therapy, multidisciplinary care, and patient-centered protocols have significantly improved prognosis and quality of life for these patients.

[image:1]

Figure legend: Flow diagram shows diagnostic approach and management algorithm for moderate hemophilia A: initial presentation, factor VIII assay, bleeding phenotype assessment, decision for on-demand vs. prophylactic therapy, and regular joint surveillance.

All information is substantiated by current clinical guidelines, expert consensus, and recent reviews.^{[1][11][5][2][9][13][7][15][16][8]}

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