

Chapter 8

INHIBITORS TO CLOTTING FACTOR

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INHIBITORS

Inhibitors are IgG alloantibodies to exogenous clotting factor VIII (FVIII) or factor IX (FIX) that neutralize the function of infused CFCs



Inhibitors are one of the most serious complications in hemophilia treatment



Inhibitors are more common in hemophilia A than in hemophilia B



Inhibitors are associated with higher disease burden: more serious bleeding and complications, more hospitalizations and higher mortality

SCREENING AND MONITORING FOR INHIBITORS

Inhibitors are detected and measured by the Bethesda assay or Nijmegen-modified Bethesda assay. Inhibitors are positive when Bethesda titer >0.6 BU for FVIII and ≥ 0.3 BU for FIX. Testing is critical to detect inhibitors early to ensure appropriate treatment.

Screening and monitoring for inhibitors

- ✓ After initial factor exposure, every 6-12 months and then annually
- ✓ Failure to respond to adequate CFC replacement therapy
- ✓ After intensive CFC exposure, e.g., daily exposure for more than 5 days and within 4 weeks of the last infusion
- ✓ Before major surgery and if suboptimal post operative response to CFC therapy
- ✓ Poor clinical response to CFC replacement therapy

There are 2 levels of inhibitors, based on the titers observed:

Low-responding inhibitor
 < 5.0 BU, typically transient

High-responding inhibitor
 ≥ 5.0 BU, typically persistent

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People with Hemophilia A and B can both develop inhibitors, but there are differences in management and response to treatment between the two.

MANAGEMENT OF ACUTE BLEEDS

Treatment should be based on type of hemophilia (A or B), inhibitor titer (high vs low), clinical response to the product, current treatment, previous infusion reactions, site and nature of the bleed, and product availability by country.

Management of bleeds in PWH with inhibitors				
	Hemophilia A		Hemophilia B	
	Low responding	High responding	Low responding	High responding
Agent	FVIII	rFVIIa* or aPCC or FVIII	FIX	rFVIIa or aPCC
Monitoring	FVIII activity (FVIII:C) assay	Thromboelastography or thrombin generation assay	FIX activity (FIX:C) assay	Thromboelastography or thrombin generation assay

aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; FVIII:C, FVIII activity; rFVIIa, recombinant activated factor VIIa

* for people with Hemophilia A and inhibitors receiving emicizumab prophylaxis, rFVIIa is preferred over aPCC due to thrombotic microangiopathy risk

ERADICATION OF INHIBITORS

Hemophilia A

Inhibitor eradication by immune tolerance induction (ITI) therapy is successful in 70%-80% of people with severe hemophilia A. ITI is considered a failure after a 2-3 year trial with no eradication of inhibitor.

Hemophilia B

Due to the low prevalence of inhibitors in people with hemophilia B, the evidence on ITI is limited, and therefore there is no recommendation on the use of ITI for hemophilia B.



- All people with hemophilia who have inhibitors should undergo a trial of ITI
- ITI should start immediately after detection of inhibitors, no matter the titer
- The optimal regimen is undefined, however, rFVIII 100 IU/kg/day preferred

SEE CHAPTER 8 OF THE TREATMENT GUIDELINES FOR FULL RECOMMENDATIONS.