

Hemophilia Patient Cases: Managing the Challenges of Inhibitors

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Case 1

3-month-old boy, diagnosed with Hemophilia A and a family history of severe hemophilia, including a brother with a high titer inhibitor. His mother was nervous about her second child developing an inhibitor, as well. She has lots of questions about treatment option and if there was anything she could do to prevent an inhibitor from forming.

Risk Factors for Inhibitor Development in Hemophilia A

- Severity of disease (severe >>>mild/moderate)
- In severe disease
 - Genetic or patient related variables
 - Environmental or treatment related risk factors

Genetic or Patient-related Variables

- FVIII mutation
- Race/ethnicity
 - African Americans 2x more likely to develop inhibitors
 - Reports of increased incidence in Hispanic patients
- Family history of inhibitors
- Other immune response related genes (MHC, IL-10, TNF-alpha, CTLA-4)

Gill JC. *Thromb Haemost.* 1999;82:500-504.

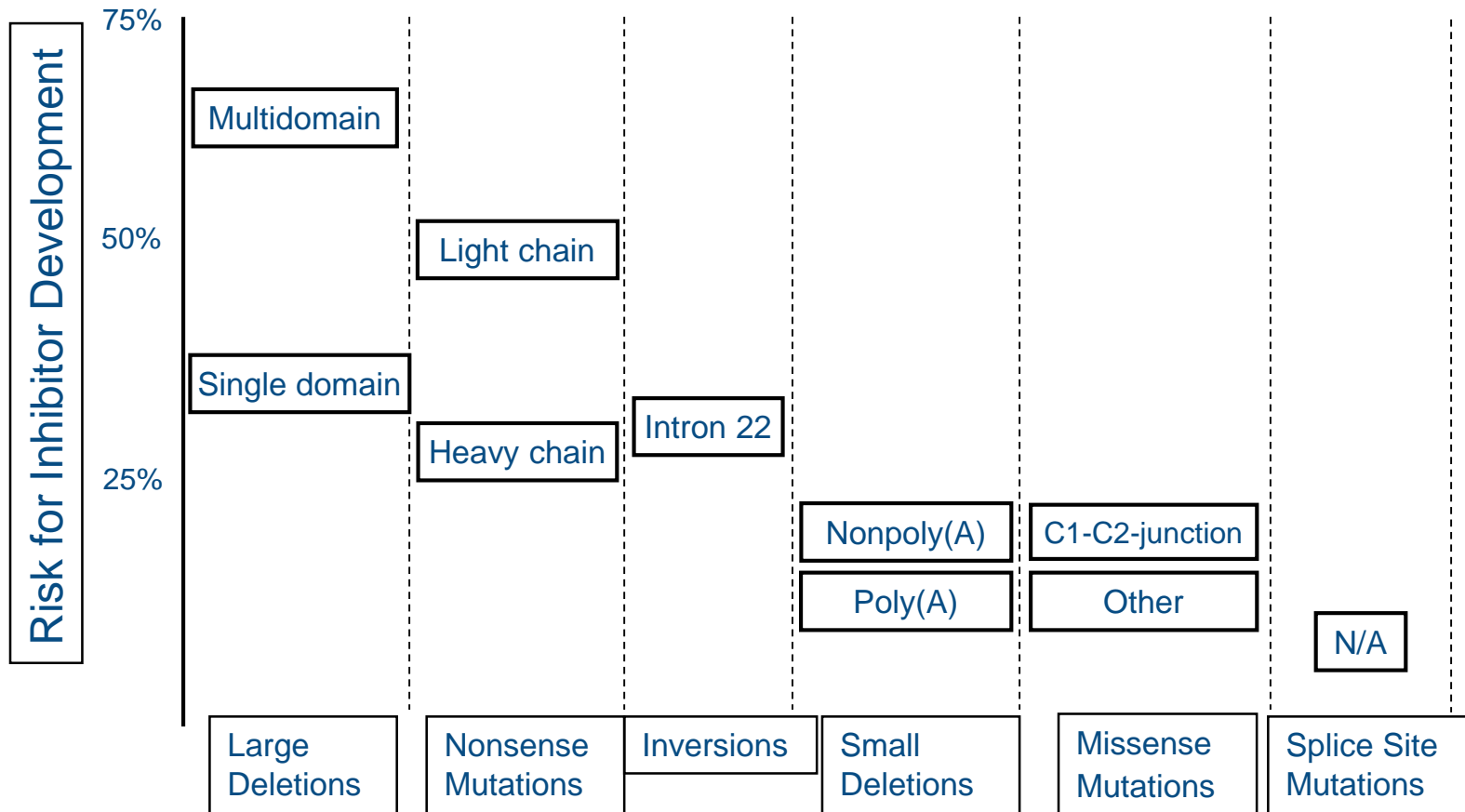
Astermark J et al. *Haemophilia.* 2001;7:267-272.

Hay C, et al. *Thromb Haemost.* 1997.

Astermark J et al. *Blood* 2006.

Astermark J, et al. *J Thromb Haemost* 2007.

Risk Factors for Inhibitor Development by Mutation Type



N/A = not applicable
(i.e., risk unknown)

Environmental or Treatment Related Risk Factors

- Early intense FVIII exposure
- Immune stimulation at time of factor exposure

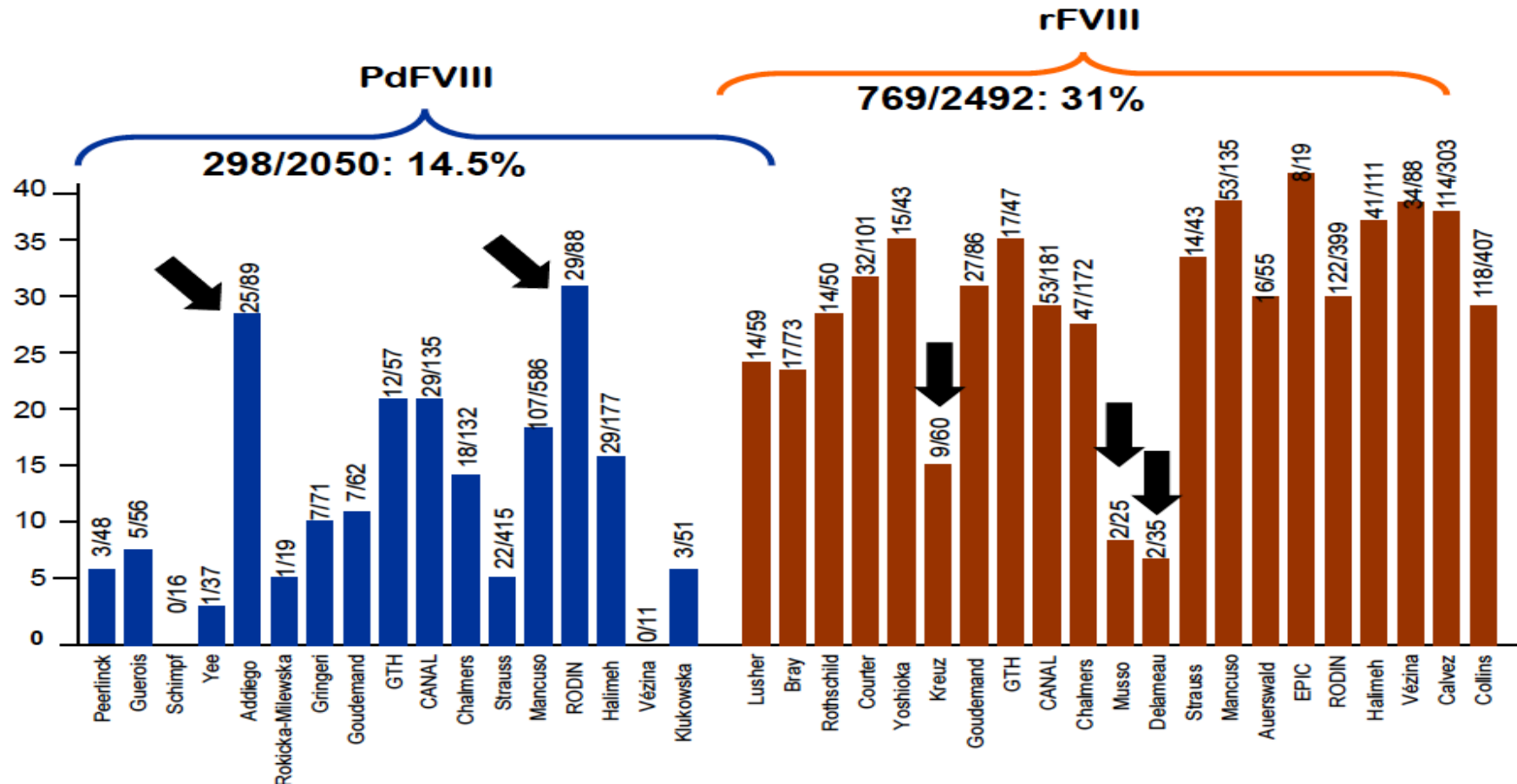
Factor VIII may be recognized as “dangerous” if encountered during periods of heightened immune responsiveness

- Frequency of monitoring
- Type of FVIII product
 - Recombinant vs. plasma derived
 - RODIN study and SIPPET trial

Types of FVIII Concentrates

- Plasma-derived
 - Variable purity and VWF content
- Recombinant
 - Produced in mammalian cell culture
 - High purity
 - No VWF
 - First, second, third generation products
 - Vary in cell culture media components, stabilizing molecule

Historical Data of Inhibitor Development



Potential Reasons for a Difference in Immunogenicity Between Products

- Different screening protocols over time
- VWF presence and affinity of FVIII for VWF
- Differences in FVIII structure
- Post-translational modifications
 - Cell line specific
 - Crucial for protein function

Rodin Study

- Multicenter cohort study (Europe, Israel, Canada)
- Prospective, observational
- 574 PUPs with severe hemophilia A born between 2000-2010
- Median age 4.6 (3.5-6.5)
- pdFVIII or rFVIII infusions up to 75 EDs or until inhibitor development

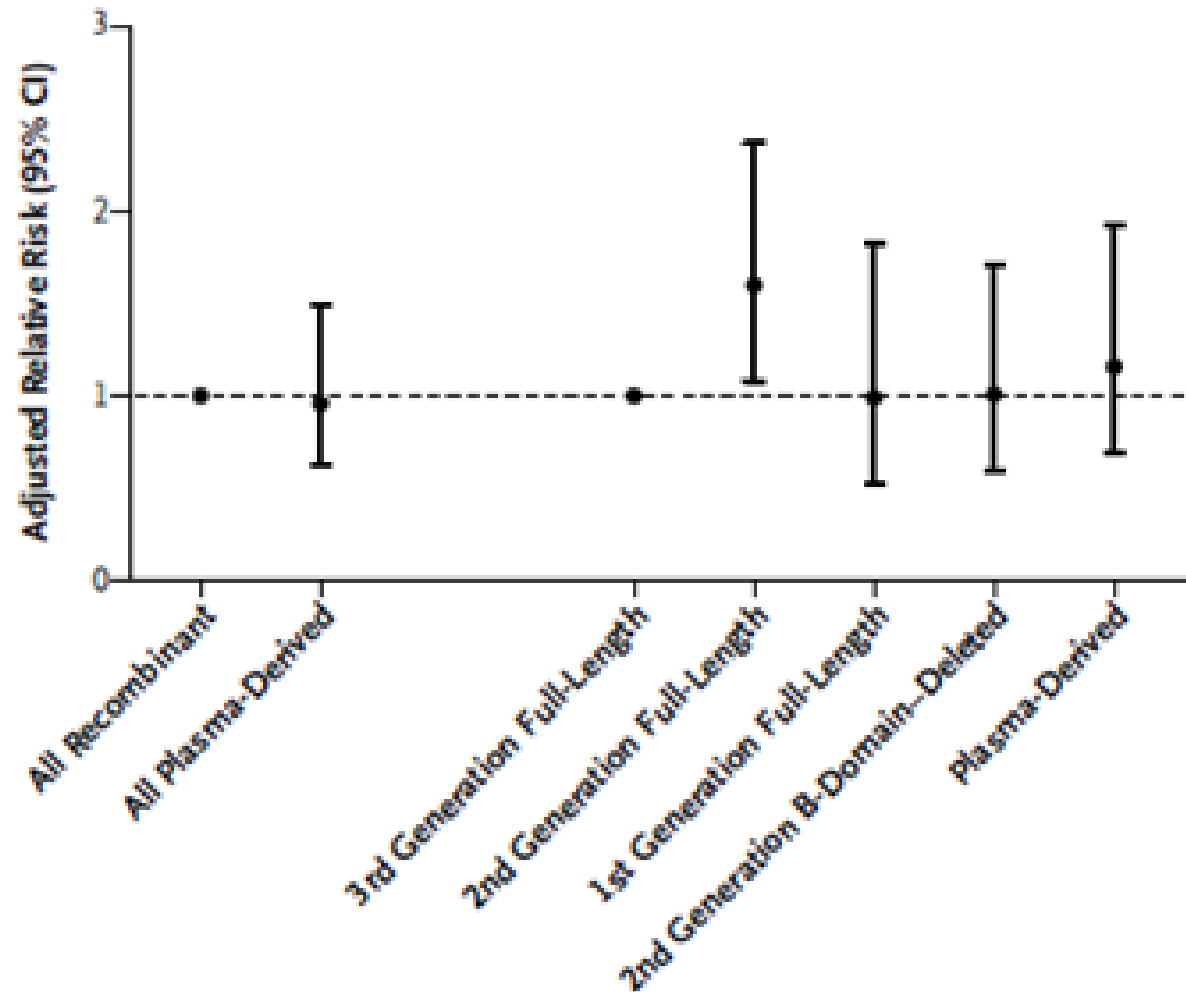
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Factor VIII Products and Inhibitor Development in Severe Hemophilia A

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Comparison of Adjusted Relative Risk Between Factor Products



Limitation of RODIN—Frequently Debated

- Comparison between generations of recombinant products not part of original design
- Choice of product was decided by provider
 - Not randomized
 - Center bias
- 72 patients enrolled not analyzed

SIPPET Trial

- Multicenter, international, randomized, controlled, open label trial
- Comparison of plasma-derived factor products and recombinant factor products
- Primary end point: Frequency of inhibitor development

Results

rFVIII	Number	Cumulative Incidence (%) with (95% CI)
All	47	44.5 (34.7-54.3)
High titer	30	28.4 (19.6-37.2)

pdFVIII	Number	Cumulative Incidence (%) with (95% CI)
All	29	26.7 (18.3-35.1)
High titer	20	18.6 (12.1-26.9)

SIPPET Results

- rFVIII was associated with an 87% higher incidence of inhibitors than pdFVIII (hazard ratio (HR) 1.87, CI95 1.18-2.97)
- For high-titre inhibitors the rate was 70% increased (HR 1.70, CI95 0.96-2.99)
- Subsequent analysis showed no differences in inhibitor rates on second generation products

Limitations to SIPPET

- Minimally treated patients were recruited along with previously untreated patients
- High rates of inhibitor development in both groups
- Although international in design the majority of patients enrolled were from 2 countries
- Did not investigate any of the newer extended half-life factor products

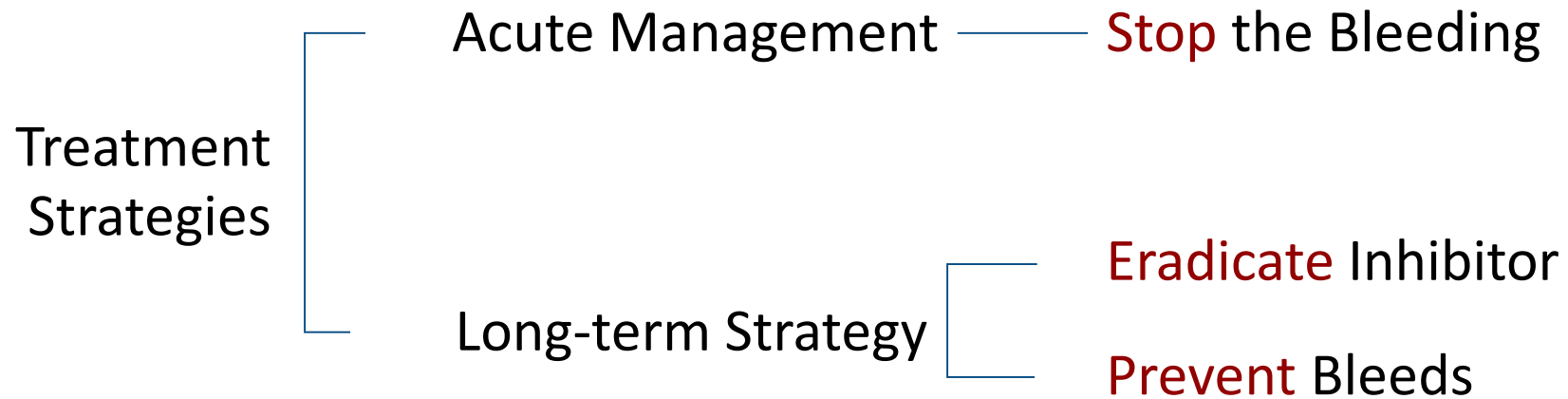
Summary

- Inhibitor risk is multifactorial with genetic and environmental risk factors
- This patient has a large gene deletion and a family history of inhibitor development making him also at very high risk for inhibitor development

Case 2

13-year-old boy with severe hemophilia A and a high titer inhibitor comes to clinic having failed standard immune tolerance. He's been on bypassing agent prophylaxis for many years but continues to have regular break through bleeding. His activities are limited. His parents have a lots of questions about immune tolerance induction and other new products available.

Treatment Strategies for Patients with Inhibitors



Treatment of Bleeding

- Goal: Replace what is missing i.e., FVIII
- For patients with inhibitors that do not respond to FVIII the mainstay of treatment is bypassing agents
 - Recombinant factor VIIa (rFVIIa, NovoSeven)
 - Activated prothrombin complex concentrates (aPCC, FEIBA)

Bypassing Therapy for Treatment of Bleeds—aPCCs

- Pros

- Half-life 8-12 hours
- 1-2x per day dosing adequate for most bleeding
- 3x per week for prophylaxis

- Cons

- Large volume
- Plasma product

Bypassing Therapy for Treatment of Bleeds—rFVIIa

- Pros
 - Small volume
 - Recombinant
- Cons
 - Half-life 2-4 hours
 - Every 2-4 hour dosing for major bleeds
 - Daily for prophylaxis

2 Bypassing Agents: Which Is Better?

- ~80% efficacy for bleeding events
- FENOC study
 - Prospective randomized crossover study of aPCC compared to rFVIIa to treat joint bleeds
 - Primary endpoint control of bleeding at 6 hrs
 - Results showed similar efficacy
 - *More discordance than anticipated indicating individual variability in response to bypassing agents*

Prophylaxis in Hemophilia with Inhibitors

- FEIBA (Hem A only)
 - Randomized, prospective, cross-over design
 - 85 U/kg 3 non-consecutive days per week
 - Both total bleeds and joint bleeds reduced
- rFVIIa 90 vs. 270 mcg/kg/day
 - Randomized, prospective
 - Similar decreased in bleeds in both prophylaxis groups

Prophylaxis in Hemophilia with Inhibitors

- Emicizumab (Hemlibra)
 - Bispecific antibody that binds to factor IXa and X
 - Once a week SQ injection
 - FDA approved for prophylaxis in adults and kids with inhibitors
 - Studies on-going in non-inhibitor patients as well

HAVEN 1: Adults with Inhibitors

	A: Emicizumab Prophylaxis (n=35)	B: No Prophylaxis (n=18)	C: Emicizumab Prophylaxis (n=49)
Duration of efficacy period (weeks), median (min–max)	29.29 (0.1–48.9)	24.14 (23.0–26.0)	19.14 (6.9–45.3)
Treated bleeds (with BPAs) ABR [†] (95% CI)	2.9 (1.69, 5.02)	23.3 (12.33, 43.89)	5.1 (2.28, 11.22)
% reduction (risk ratio), <i>P</i> value	87% (0.13), <i>P</i><0.0001		--
Median ABR, calculated (IQR)	0.0 (0.0–3.7)	18.8 (13.0–35.1)	0.0 (0.0–1.7)

*Group D was not included due to the short follow-up at the time of data cutoff (October 25, 2016);

[†]negative binomial regression model.

BPA=by-passing agent; ABR=annualized bleeding rate; CI=confidence interval; IQR=interquartile range.

Rationale for Eradication of Inhibitors

- Morbidity
 - Bypass therapy is effective but not as effective as factor VIII
 - More difficult to perform elective surgical procedures
 - Prevention of bleeding is more challenging with bypassing agents
- Increased cost
 - Wide range of utilization and global costs can be driven by several patients
- Mortality
 - In 1983, reported to be increased in all patients with inhibitors
 - More recently, difference in mortality in patients with inhibitors not consistently found

Immune Tolerance Induction (ITI)

- Regular infusions of FVIII (classically recombinant or plasma derived)
 - Low dose: 50 U/kg TIW
 - High dose: 200 U/kg/d
 - International ITI study compared the 2 regimens
 - Stopped early because of more bleeding in the low dose arm
- ITI requires
 - Very compliant patient/family
 - May need indwelling line for venous access
- 60-70% of patients will respond to ITI

Options if Initial ITI Attempts Fail

- ITI with extended half-life products
 - Modification may help tolerize FVIII
 - Case series of ITI with FVIII-Fc (Eloctate)
- Continue non-factor VIII therapy
 - Bypassing agents or emicizumab
 - Treatment of bleeds: Bypassing agents
- ITI with the addition of immunosuppressive agents
 - Utility in patients with good bleeding control with bypassing agents or emicizumab

rFVIII Fc For ITI: a Retrospective Analysis

- Chart review; n = 19 pts; 10 sites in the US & Canada [July 2014- June 2017]
 - 7 first time ITI
 - 12 ITI rescue
 - At the time of analysis, 16 of 19 pts remained on rFVIII Fc prophylaxis treatment or ITI, no reported adverse events.
- Rapid time to tolerization in high-risk first-time ITI patients
 - 6/7 \geq 1 high-risk feature for ITI failure
 - 4/7 were tolerized; ~7.8 months
- Therapeutic benefit in ITI rescue
 - 7/12 with Bethesda titre \leq 0.6; ~3.3 months
 - 2 were transitioned to other factors due to recurrence
 - 1/12 decreases in Bethesda titre
 - 1/12 switched to bypass therapy; 3/12 continued on rFVIII Fc