


MISSION
The Hemophilia Federation of America (HFA) is a national nonprofit organization that assists and advocates for the bleeding disorders community.




**Past, Present & Future of
Inhibitor Prevention &
Treatment: Panel Discussion**

HFA Symposium – Inhibitor Track
March 26, 2015

Panelists:
Chris Walsh, MD
Shannon Meeks, MD
Mike Soucie, PhD
Dave Robinson, PhD
Sue Geraghty, RN
Kyme Groller, RN
Debbie Porter

Discussion Questions

- How many people with hemophilia get inhibitors and why?
- What testing is being done to determine inhibitor status?
- What is being done to learn more about inhibitors and how to decrease the number of people affected by an inhibitor?




How many people with hemophilia get inhibitors?

	1974 Jones, Peter	1987 Lusher, Jeanne	1993 Hathaway, W Goodnight, S	2001 Hathaway, W Goodnight, S	2008 D'Allicchiele, Donna	2015
% of hemophiliacs with inhibitors	A 5-10% B rare	A 10-15% B 1-2%	A at least 15% B 3%	A 21-33% B 1-6%	A 20-33% B 1-6%	?
Products used when inhibitors developed	FFP, Cryo, Early factor concentrates	Plasma concentrates	Plasma concentrates, early recombinant VIII	Plasma and recombinant VIII and IX	Plasma and recombinant VIII, and IX	
Testing	"new" Oxford	Bethesda titer (1975 in US)	Bethesda titer	Bethesda titer	Bethesda titer, Nijmegen modification	
Treatment	Withhold unless life threatening; then tx with massive doses of factor VIII	PCC's 1972 APCC's Autoplex 1980, Feba 1982 Porcine VIII 1986 Immunosuppression alone, Immune tolerance	PCC's, APCC's, Porcine VIII, Immune tolerance	PCC's, APCC's, Porcine VIII, Novoseven (1999) Immune tolerance	PCC's, APCC's, Novoseven RT Immune tolerance, Prophylaxis with bypassing agents	

How many people with hemophilia get inhibitors?

CDC Inhibitor Surveillance


- No data systematically collected in the U.S.
- "Community Counts" begun December 2013 in the federally-supported HTC Network
- Standardized protocol specifying patients to be tested and testing intervals
- Inhibitor surveillance protocol
 - Standardized, centralized testing at CDC
 - Confirmatory testing very important
 - Incident inhibitor case surveillance



Why do people get inhibitors?

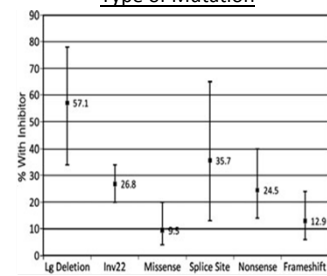
Contributing Factors to the Development of FVIII Inhibitors

- Genetic
 - Related to factor VIII
 - Unrelated to factor VIII
- Environmental
 - Conditions of treatment
 - Therapeutic product




Why do people get inhibitors?

Type of Mutation



Type of Mutation	% With Inhibitor
Lg Deletion	57.1
Inv22	26.8
Missense	9.5
Splice Site	35.7
Nonsense	24.5
Frameshift	12.9

Miller et al Blood 2012




Why do people get inhibitors?

Family Incidence:
Malmö International Brother Study

- 388 hemophilia A
- Overall inhibitor incidence 32%
- Risk if inhibitor in family 48%
- Risk if inhibitor in brother 78%

Astermark J, et al. Haemophilia 2001;7:267-72



Why do people get inhibitors?


Race and Inhibitor Incidence in Severe Hemophilia A

Meta-Analysis on PUP Studies (Scharrer et al. 1999)
Kogenate (Lusher et al 1997)
Recombinate (Gruppo et al. 1998)
U.S. retrospective study (Addiego et al. 1999)

Caucasians	inhibitors: 51/198	25.8%
African origin	inhibitors: 14/27	51.9%

MIBS (Astermark et al. 2001)

Caucasians	inhibitors	27.4%
African origin	inhibitors	55.6%




Why do people get inhibitors?

Non-FVIII Genetics and FVIII products

Polymorphisms in IL10, TNF and CTLA-4 associated with increased rate of inhibitors
Astermark Blood '06, JTH '07


Recent data from several papers suggested that a 2nd generation full length FVIII product has a higher risk for developing inhibitors in PUPs
Gouw et al NEJM '13




Why do people get inhibitors?

Contributing Factors to Development of FVIII Inhibitors:
Conditions of Treatment

- Associated inflammatory reactions
- Continuous infusion¹
- Age at first treatment²
- Episodes of intensive treatment

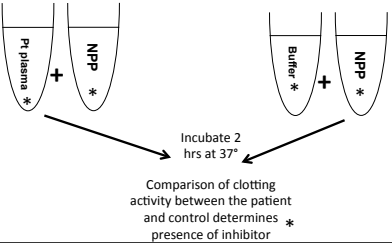


Question & Answer




What testing is being done to determine inhibitor status?

Principles of Inhibitor Assay




Comparison of clotting activity between the patient and control determines presence of inhibitor




What testing is being done to determine inhibitor status?

Differences in Inhibitor Methodology

- Patient plasma
 - Heated vs. not heated
- Control
 - Buffer vs. severe fVIII deficient plasma
- Source of "normal" plasma
 - Normal pooled plasma vs. product specific
- Clotting assay
 - One-stage vs. chromogenic
 - Role of direct antibody detection




Question & Answer



What testing is being done to determine inhibitor status?

CDC Strategies to decrease the number of people affected by an inhibitor


- Surveillance
 - Annual testing for inhibitors at CDC
 - Data collection on new inhibitor cases
- Regular screening to increase the likelihood of early detection when titer is low and more likely to respond to therapy
- Better understanding of risk factors so that treatment can be tailored




What testing is being done to determine inhibitor status?

Why do we care if we miss or over-call the presence of inhibitors?

- Want to know about an inhibitor before patient presents bleeding and not responding to FVIII
- Potential to intervene early if low titer inhibitor is detected
- Product safety
- Population wide trends
- High stress for false-positive
- Cost associated with repeating/confirming test
- Potential exclusion from future clinical trials



Question & Answer



Other Questions

