Connecting The Dots: Managing Hemophilia Inhibitors

Lisa B.Pullens B.S.N, R.N., C.P.H.N.

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OBJECTIVES

- 1. Define Hemophilia Inhibitors
- 2. Discuss the impact of inhibitors on the clinical care of a hemophilia patient.

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DISCLOSURE STATEMENT

I HAVE NO FINANCIAL DISCLOSURE!

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Understanding Basic Hemophilia

- Definition: "Hemophilia is a hereditary disorder. One of the proteins causing blood to clot is missing or decreased".[1]
- This leads to a delay or disruption in blood clotting and can result in prolonged, spontaneous, trauma/injury related bleeding, or bleeding after surgery.

1. Butler, Crudder, Riske, Toal, Basic Concepts of Hemophilia 2007, 1-2

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2 Most Common Types of Hemophilia

- Hemophilia A(Classic Hemophilia)-missing or decrease of factor VIII(8) clotting protein.
- Hemophilia B(Christmas Disease-named after pt. Stephen Christmas in1952):disorder first recognized as a different kind of hemophilia(molecule size larger). Missing or decrease of factor IX(9) clotting protein.

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Genetic Inherited Disorder

Hemophilia is genetic/inherited/recessive

- Mother's are carrier's with 1 affected X and one unaffected X gene (each son of a carrier mother has a 50/50 chance of being affected). Daughter's of a female carrier can also be a carrier(possibly with a low FVIII level below 50%=mild hemophilia) if they inherit her affected X.

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Genetic Disorders Cont.

- Boys receive one of the X genes from the mother and a Y gene from the father(even if the father has hemophilia he can't pass this gene to his son only his daughters).Girl's of the affected father are "obligatory carriers" since they inherited his affected X.

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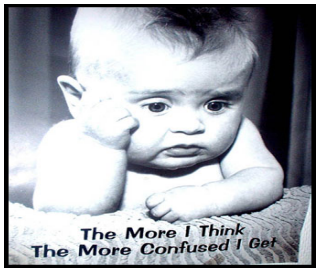
Confused Now?



Statistics

Currently 20,000 males in the U.S. are living with Hemophilia. Care and cost of treatment is estimated at $3.5 billion annually.[2] Data is aggregated and published collectively by 135 HTC's(Hemophilia Treatment Center's) via the ATHN(American Thrombosis Hemostasis Network) annually. Above values obtained from the 2016 calendar year collected data.

2. www.cdc.gov, accessed March 2017

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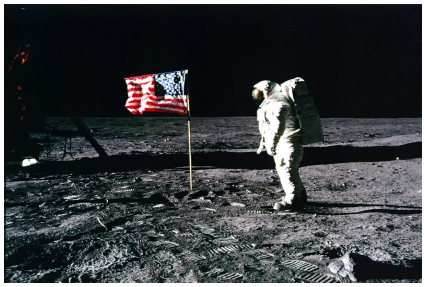
Exploring Clotting



3 Steps Of Normal Clotting

1. Blood vessel narrows/tightens/vaso-constricts.
2. Platelet plug forms.
3. Fibrin clot forms to seal platelet plug.

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Clotting continued

Fibrin clots are formed when plasma proteins(clotting factors) are "active", then "interact" with each other. These factors have been identified by Roman numerals I-XIII(1-13) of a "clotting cascade".[3]

3. Peter Jones. Living with Haemophilia. Fourth Edition, New York, N.Y.: Oxford University Press, 1995

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What Happens In Hemophilia?

Steps 1 and 2 of the clotting process occur but if one of the clotting factors(8=VIII, or 9=IX) is missing or in decreased amounts the process of making a "stable clot" does not work.

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Normal Factor Levels

Normal levels of factor 8(VIII) and 9(IX) range from 50%-150%(some references say 150-200%).

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Levels Of Severity(Factor Levels in %)

- Mild=5%-49%: prolonged bleeding typically with trauma or surgery.
- Moderate=1%-4-5%:potential bleeding with minor surgery. Can have evidence of joint bleeding.
- Severe=< 1%:bleeds with minor injury, "spontaneous bleeding occurs without known trauma", bleeds with trauma.[4]

4. National Hemophilia Foundation. What You Should Know About Hemophilia. New York, New York: National Hemophilia Foundation, 1991.

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Spotlight On Inhibitors

What Is An Inhibitor?

An inhibitor is an antibody that binds to active factor sites and destroys/neutralizes factor 8(VIII) or 9(IX). The persons immune system will identify clotting factor as foreign and "attack" circulating clotting factor . Since a person with hemophilia has had minimal exposure to "normal" clotting once a child is exposed to factor product on a regular basis the potential of inhibitor formation increases(in relation to other factors).[5]

5. DiMichele DM. Inhibitors in Hemophilia: A Primer. Montreal, Canada :World Federation of Hemophilia 2008.

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Factors Associated With Inhibitors

1. Patients with "severe" A or B disease.
2. Typically appears by age 2(first 9-50 factor treatments)[1] but can occur later in life("acquired").
3. Family history of inhibitors-genetic mutations(current ongoing studies related to DNA mutations and inhibitor development).
4. Increased exposure to clotting factor.
5. Infections or inflammatory events such as surgeries or vaccines(stimulation of the immune system).
6. Race and ethnicity(increased in Hispanic, Native American, African Americans). [6]

1. Butler, Crudder, Riske, Toal. Basic Concepts of Hemophilia 2007, 4-11
6. Carol Kasper, Inhibitors in Hemophilia A and B, An Introductory Discussion 2016.

In the Western States Region IX(includes California, Hawaii, Nevada, Guam) collected data counted 289 patients with inhibitors.[7]

Approximately 1 in 5 people with hemophilia A,[8], and about 3 in 100 people with Hemophilia B,[9], will develop an inhibitor to the product(medicine/factor) used to treat or prevent their bleeding episodes.

7. www.cdc.gov 2016, 8. Wight J. Paisely S.. The epidemiology of Inhibitors In Hemophilia A:A systematic review. Hemophilia.2003. 9(4):418-435., 9. Puetz J, Soucie JM, Kempton CL, Monahan PE, and Hemophilia Treatment Center Network Investigators. Prevalent Inhibitors in Hemophilia B subjects enrolled in the Universal Data Collection database. Haemophilia. 2015:20(1)25-31.

Indications Of An Inhibitor

1. Factor VIII(8) or Factor IX(9) given to a patient with respective factor deficiency the clotting activity does not occur.
2. Patient on prophylaxis experiences "breakthrough bleeding".

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Method Of Measuring Inhibitors

1. Initial screening test aPTT prolonged.
2. Bethesda Assay or BU-method takes about 2-3 hours(Introduced in 1975). In some situations results can be inconclusive.
3. Nijmegen Assay method(more sensitive for detection)-now being used more widespread(introduced in 1995) specifically in clinical trials which can detect "low titer inhbitors".[10,6]

10. Aledort, Louis, Management of Inhibitors in Patients With Hemophilia A,2008 pg 8
6. Kasper, Carol K. Inhibitors In Hemophilia A and B, An Introductory Discussion. 2016.

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Classification Of Inhibitors

- Low Titer Inhibitors=5.0 BU or less.
- High Titer Inhibitors=greater than 5.0 BU(can be as high as 1000 BU or more).
- Low Responding Inhibitor=if factor is given and inhibitor does not rise over 5 BU(often these inhibitors can be transient-come and go over time). For emergencies this person could potentially be treated with the factor they are deficient in/missing if the titer is low enough(0.6 BU but less than 5.0 BU).
- High Responding Inhibitor=within 4-6 days of factor exposure titers will rise > 10 BU. This stimulation is also referred to as "anamnesis"(increase in inhibitor antibodies, in some cases value can rise into the thousands!).[10,11]

10. Aledort, Louis. Management Of Inhibitors In Patients With Hemophilia A, 2008 pg8-9
11. Lusher, J.M. Factor VIII Inhibitors. Etiology, characterization, natural history, and management. Ann NY Acad. Sci. 1987. 509:89-102.

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Classifications continued

- Low Titer/ Low Responding Inhibitors= Patients with Hemophilia A for emergent treatment(i.e. surgeries, major life/limb threatening trauma) person can receive FVIII or high doses of FVIII can be used to "eradicate" inhibitor(Immune Tolerance).
- High Titer/High Responding Inhibitors= use of an alternative treatment called "by passing agents" are given to generate steps for clot formation.

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What about patients with Hemophilia B inhibitors ?

- Hemophilia B inhibitors are more complex.
- The factor IX gene is a larger molecule.
- Large gene deletions cause an increase risk of anaphylaxis if a higher dose of FIX is used, thus treatment is slightly different for FIX inhibitors.

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Treatment Options

- Low Titer/Low Responding Inhibitor Treatment(</= 5.0 BU): some treat with higher dose of factor(dose may vary from Hemophilia A or B pt. 50U/kg-100U/kg of their factor product. Examples=50U/kg – 80U/kg for Hemophilia A, 80U-100U/kg for Hemophilia B.

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Product Choice

Type of product used should be joint a decision with physician, parent and or patient.

There are still ongoing studies weighing pros/ cons for use of "plasma derived products"=factor made from human plasma vs "recombinant factor"= no human plasma involved in production of product.

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Product Choice continued

Prophylaxis with a "bypassing agent"(factor action works by "going around" the production path blocked by the missing factor/inhibitor=antibody or destruction activity).[12]

12. MASAC Recommendation #167 Regarding the use of bypassing agents in patients with Hemophilia A or B inhibitors. National Hemophilia Foundation Website.http:// www.hemophilia.org/NHF Web/MainPgs Accessed August 31 2009.

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Product Choice continued

2 products currently being used

- Activated prothrombin complex concentrate=aPCC otherwise recognized in use by the name FEIBA®.[13]
- Recombinant activated factor VII=rFVIIa otherwise recognized in use by the name Novoseven®[14]

13. FEIBA NF (package insert)Westlake Village, C.A.: Baxter Healthcare Corporation May 2009.
14. Novoseven Coagulation Factor VIIa R. (package insert). Princeton, NJ Novo Nordisk Inc. Oct. 2006.

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Product Choice continued

How do these products work????

Product Choice continued

- aPCC uses Factor II and X to change prothrombin to thrombin to make a clot(key biochemical step for clot structure and clot function).
- rFVIIa activates Factor X restoring platelet surface thrombin.

10. Wong, Wing Yen, Aledort, Louis, Management Of Inhibitors In Patients With Hemophilia A, 2008

Due to concerns of nephrotic syndrome and allergic reactions Factor IX(9) inhibitor patients (lower incidence of occurrence compared to Hemophilia A patients) have less treatment data available. Safety and efficacy of by passing agent outcome predictors of inhibitor eradication are not well defined(lack of documented data).

15. DiMichele D. Inhibitor development in Hemophilia B: an orphan disease in need of attention Br. J Haematology 2007:138:305-315.

Immune Tolerance Induction Therapy

Goal: Eradicate inhibitor to restore factor replacement. Various protocols of high dose, intermediate dose, or low dose with variances in time frames for periods up to 2 or more years(average being about 33 months) are used worldwide at HTC's.

Some examples:

- High doses of factor VIII daily(plasma derived or recombinant) generally requiring a central line especially in the young infant, small child. There are variances in doses from the original "Bonn"treatment=high doses of factor VIII daily with or without aPCC(depends if child is at high risk for bleeds). Dose regimens of FVIII=100-150 as high as 200U/kg IV Q 12hrs. If aPCC added 50-100 U/kg IV Q 12 hrs with a min. of 30 min. between infusion of factor VIII and aPCC to lessen risk of thromboembolisms. 16

16. Brackmann HH, Oldenburg J., Schwaab R. Immune Tolerance for the treatment of factor VIII inhibitors-twenty years "Bonn protocol. Vox Sang. 1996:70 Suppl 1:30-35.

Immune Tolerance Induction Therapy continued

- Dose de-escalations/Low dose(Dutch): FVIII about 25U/kg every other day. Dose is decreased each time factor VIII recovery(timed factor level draws after dose is given) exceeds 30%. This dose decrease continues until a prophylactic dose of 10-15 U/kg every other day is reached. Method is less demanding and more economical for insurance carriers.17

17. Mauser-Bunschoten EP, Nieuwenhuis HK, Roosendaal G, van den Berg HM. Low-dose immune tolerance induction in hemophilia A patients with inhibitors.Blood.1995;86(3): 983-988.

Immune Tolerance Induction Therapy continued

- Combination of intense high dose factor VIII and immune suppression including corticosteroids, cyclosphosphamide & IVIG.(Malmo) 18,19,20
- The intensity necessitates patient be hospitalized. This particular regimen no longer widely routinely followed due to decrease in success rates and lack of sustained responses.

18. Freiburghaus C,Berntorp E, Ekman M, Gunnarsson M, Kjellberg B, Nilsson IM. Tolerance induction using the Malmo treatment model 1982-1995. Haemophilia. 1999;5(1):32-39.
19. Nilsson IM, Berntorp E, Zettervall O. Induction of immune tolerance in patients with hemophilia and antibodies to factor VIII by combined treatment with IVIG, cyclophosphamide, and factor VIII. N. England J Med 1988; 318(15):947-950.
20. Berntorp E. Nilsson IM. Immune tolerance and the immune modulation protocol. Vox Sang 1996;70 Suppl 1:36-41.

Factors For Success of ITI Treatment

- Age of < 5 y.o. at time of inhibitor detection.
- Low historical peak titer(< 100 BU).
- Peak titer during ITI(<500 BU).
- "Compliance"=uninterrupted treatment.
- No line infections(immune system triggers)during treatment.

Factors Predicating Non-Response(Failure)

- Age > 10 y.o. at time of inhibitor detection.
- Long standing inhibitor.
- High titer at start of ITI(> 10 BU).
- Peak titer during ITI > 500 BU.
- "Non-compliance"=interrupted treatment.
- Infections central line or systemic during treatment.

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ITI Product Choice

What FVIII product for ITI should be used?

- Most children are tolerized with the product they were receiving when they developed their inhibitor. [21]

21. DiMichele D, Rivard G, Hay C. Antunes S. Inhibitors in haemophilia: clinical aspects. Haemophilia. 2004; 10 Suppl 4:140-145.

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ITI Product Choices continued

Plasma derived vs. recombinant?

Varies in many parts of the world due to preferences and safety concerns of disease transmission. Safety of products has drastically improved over the past 20 yrs. Viral inactivation of plasma products and now various alternate methods of production to decrease incidence of inhibitor formation and viral transmission are ongoing with product manufacturers.

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When should ITI treatment start?

- Ideally when inhibitor titer is < 10 BU. This will increase the chances of successful tolerization. [22]

22. DiMichele DM, Kroner BL. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. Thromb Haemost. 2002; 87(1):52-57.

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What do you do until the inhibitor titer is < 10 BU?

- Prophylaxis with an aPCC product(commonly used FEIBA® or a rFVII product(commonly used Novoseven®) avoiding exposure to factor VIII & IX products. [23]

23. N. Ewing, C. Escuriola-Ettingshausen, W.Kreuz. Prophylaxis with FEIBA in paediatric patients with haemophilia A and inhibitors. Haemophilia (2015), 21, 358-364

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Considerations

- Special challenges-staggering cost of products regardless of protocol used. Example ITI for the average 5 y.o. easily exceeds $1million/year. [24]
- Central lines and infection risks! YIKES!
- Other risks of treatment such as "too much clotting" or "clots in the wrong places"(pulmonary embolisms!).

24. Colowick AB, Bohn RL, Avorn J, Ewenstein BM. Immune tolerance induction in hemophilia patients with inhibitors: costly can be cheaper. Blood 2000; 96(5): 1698-1702.

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Treatment Success

- Current studies related to DNA mutation of inhibitors may aid in knowledge of how successful treatment will be.[6]

6. Kasper, Carol K, Inhibitor in Hemophilia A and B An Introductory Discussion 2016

How Can I Help My Patient?

- Encourage activity-sedentary lifestyles contribute to weak muscles and joint increasing bleeds and bleed related arthropathy.
- Discuss options, working with treatment schedules and activities. Don't let them live in "Bubble Wrap"!
- Teach "Early and Consistent treatment"!
- Reinforce calling the HTC, having open dialogue between patient and HTC staff for good comprehensive care and better outcomes!

Thank You!

Questions?

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1. Butler, Cruder, Riske, Toal. Basic Concepts of Hemophilia, 2007.
2. www.cdc.gov accessed March 2017
3. Jones, Peter. Living With Hemophilia, Fourth Edition. New York, N.Y. : Oxford University Press, 1995.
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11. Lusher J. Factor VIII Inhibitors: Etiology, characterization, natural history and management, Annals of the New York Academy of Science. 509:89-102, 1987.
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13. FEIBA NF(Package insert). Westlake Village, C.A.: Baxter Healthcare Corporation. May 2009.
14. Novoseven Coagulation Factor VIIa R.(Package insert) Princeton, N.J.:NovoNordisk Inc. October 2006.
15. DiMichele D. Inhibitor development in haemophilia B: an orphan disease in need of attention. Br. J Haematology 2007; 138:305-315.
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17. Mauser-Bunschoten EP, Nieuwenhuis HK, Roosendaal G. van Den Berg HM. Low-dose immune tolerance induction in hmeoophilia A patients with inhibitors. Blood. 1995;86 (3):983-988.
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24. Colowick AB, Bohn RL, Avorn J, Ewenstein BM. Immune tolerance induction in hemophilia patients with inhibitors: costly can be cheaper. Blood. 2000;96(5):1698-1702.