


PrecisionBioLogic

Coagulation Factor Inhibitors and the Nijmegen Bethesda Assay



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Coagulation Factor Inhibitors

Bottom Line at the Start (BLATS); The Participant...

- Explains the origin of anti-factor VIII (FVIII inhibitor)
- Detects FVIII inhibitors using factor assays and mixing studies
- Measures FVIII inhibitors using the Bethesda titer, Nijmegen Bethesda assay, chromogenic Bethesda assay, enzyme immunoassay and fluorescence immunoassay
- Describes coagulation factor bypass therapy to resolve bleeding in inhibitor patients
- Describes immune tolerance induction therapy
- Lists new factor concentrates designed to prevent inhibitor formation

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2-yo Hemophilic Boy

Test	Result	RI
HGB	11.8 g/dL	9.6–15.6 g/dL
PT	11.2 s	9.8–12.6 s
PTT	65 s	25–35 s
PLT	310,000/ μ L	150–400,000/ μ L
Fibrinogen	390 mg/dL	220–498 mg/dL

Inflamed, swollen knee and ankle

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Mixing Study: 2-yo Hemophilic Boy

NP: commercial pooled normal plasma from 20 normal donors with ~100 U/dL factor levels

Assay	Result	RI	Comment
Patient PTT	63 s	25–35 s	
Immediate PTT of patient/NP 1:1 mix	34.5 s	NP PTT 30 s	Limit: NP + 10%: Incomplete correction
PTT of Pt/NP 1:1 mix incubated 1 h at 37°C	47.9 s	NP PTT 35 s	Incubate mix and NP: Uncorrected

- R/O lupus anticoagulant (LAC): pediatric, bleeding
- Specific coagulation factor VIII (FVIII) inhibitor; Bethesda titer


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Hemophilia A Symptoms

Spontaneous anatomic (soft-tissue) bleeds




- Bleeding at umbilical stump and circumcision
- Delayed bleeding triggered by injury
 - Joints, large muscles, body cavities, GI, soft tissue, tongue, kidney, testicles, brain, CNS
- Spontaneous bleeds, especially into joints
- Inflammation, hematomas, hemarthroses



	Severe	Moderate	Mild
Prevalence	70%	15%	15%
FVIII U/dL	< 1	1–5	6–30
Bleeding	Spontaneous	Minor trauma	Major trauma

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Hemarthroses


Airway obstruction

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40 YO Hemophilic

- Bleeding into ankle at midnight
 - Attempted DDAVP (Stimate®) inhaler
- Ran out of therapeutic FVIII concentrate
 - In US, Medicare subsidy via ~100 national hemophilia centers
 - Canadian Hemophilia Society Treatment Cntrs
- Night tech and on-call path resident
 - Determine residual patient factor VIII activity
 - Compute FVIII dosage from package insert to prevent potential thrombotic overdose and to avoid waste
 - Order FVIII concentrate from transfusion service
 - Reconstitute with sterile water, administer as IV push
 - Subsequently determine therapeutic factor VIII level



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If Factor Assay not Available

- When timing is critical, assume <1 U/dL FVIII activity or...
- Estimate residual FVIII from PTT:

FVIII	PTT
40 U/dL	35 s
30 U/dL	50 s
20 U/dL	65 s
10 U/dL	90 s
1 U/dL	120 s

*Example only, do not use
Varies by reagent sensitivity*




- Collect baseline specimen
- Freeze, confirm next day shift with FVIII assay
- Maintain patient database



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Plasma-derived FVIII Concentrates



- <25% of FVIII concentrate in industrialized countries
- Theoretical risk of HBV, HCV, HIV transmission 1/60,000
 - Human and animal plasma matrix
 - Purification: immunoaffinity column, solvent-detergent, Pasteurization, viral filtration, combinations
 - Hemofil-M, Monarc-M, Monoclate-P
- Seroconversions per 2003 CDC surveillance: 0

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Recombinant FVIII Concentrates

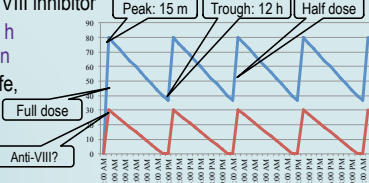
- Serum or albumin in culture medium
 - Helixate, Kogenate, Recombinate
 - Abundant, used for prophylaxis
 - No HBV, HCV, HIV seroconversions
- No protein in culture or preparation
 - No theoretical viral risk: Advate
- B-domain-deleted FVIII concentrate
 - Human albumin in culture: ReFacto
 - No protein: Xyntha
 - FVIII clot assay unreliable

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40 YO Receives Advate

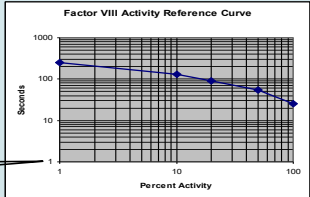
- Peak: collected 15 m after administration
 - If peak reaches expected value, plan for next administration at 12 hours
 - Factor assay result: 30 U/dL
 - Should have reached 80 U/dL, what happened?
 - Suspect anti-FVIII inhibitor
- Trough: collect 12 h after administration
 - Reflects half-life, 50% of peak
 - Continue w/ half doses



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One-stage Factor VIII Assay

- Dilute pt plasma 1:10 in imidazole buffered saline (IBS)
- Add FVIII-depleted reagent plasma 1:1 (FVIIIIDP)
 - Provides all factors except FVIII
 - Typical: 100 uL patient plasma dilution + 100 uL FVIIIIDP
- Add PTT reagent, incubate 3 m
- Add CaCl₂, record interval to clot formation
- Compare result in seconds to calibration curve to derive plasma activity:



1% activity = 1 U/dL

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Factor VIII Assay Plasma Dilutions Parallelism Indicates No Inhibitor

Automated Plasma Dilution	Seconds	Raw Factor VIII Activity	Computed Factor VIII Activity (x dilution)*
1:10 "undiluted"	90 s	20 U/dL	20 U/dL
1:20	105 s	10 U/dL	20 U/dL (parallel)*
1:40	107 s	5.5 U/dL	22 U/dL (parallel)
1:80	110 s	2.6 U/dL	20.8 U/dL (parallel)

* <10% difference from undiluted indicates parallelism, no inhibitor

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FVIII Assay Plasma Dilutions non-Parallelism Indicates Inhibitor

Plasma Dilution	Seconds	Raw Factor VIII Activity	Computed Factor VIII Activity (x dilution)*
1:10 (undiluted)	95 s	10 U/dL	10 U/dL
1:20	99 s	8 U/dL	16 U/dL
1:40	107 s	5 U/dL	20 U/dL
1:80	108 s	4 U/dL	32 U/dL

* >10% difference from undiluted = non-parallel & rising, implies inhibitor

- Inhibitor: IgG alloantibody to FVIII concentrate
 - 30% prevalence, most arise in severe hemophilia
- Reflex to inhibitor assay

Kasper CK. Laboratory diagnosis of factor VIII inhibitors. In Kessler C, Garvey MB, Green D, Kasper C, Lusher J. Acquired Hemophilia 2nd Edition. Excerpta Medica 1995

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Why Measure Inhibitors?

- Confirm refractory response to factor therapy
- Monitor efficacy of prophylactic FVIII or FIX therapy
- Monitor factor bypass preparation efficacy and safety
- Distinguish low response from high response patients
 - Low responders: treat with factor concentrate
 - High response when bleeding: treat with bypass preparations
 - High response when not bleeding: immune tolerance therapy
- Detect factor-induced anamnesis
- Monitor immune tolerance therapy efficacy
- Establish prevalence and population trends
 - Hemophilia severity, correlate to mutation, correlate to therapy

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Limitations of Inhibitor Measurement

- Median 40% of severe hemophilia patients in US hemophilia treatment centers are tested for inhibitors
- Require therapeutic "wash-out" before sampling
- Local laboratory expertise and experience
- Median 32% FP rate, 5% FN rate, interlab CV 50%
- The need for method standardization

- Soucie et al. National surveillance for hemophilia inhibitors in the United States: Summary report of an expert meeting. Am J Hematol 2014; 89:621.
- Favaloro et al. Haemophilia 2014; 20: Suppl 4

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CVs of NASCOLA Inhibitor Measurement

Year	Expected	Average	Min	Max	CV
2010	0	0.1	0	5.0	178
2011	0	0.4	0	2.9	150
2010	0.5-1.0	0.5	0	2.0	83
2011	0.9	1.3	0	3.7	46
2012	0.6	4.0	0	25.5	40
2010	1-1.5	1.0	0	2.0	48
2011	2.0	2.8	0	15.0	47
2012	2.0	3.3	0	15.0	48
2012	1.1	1.3	0	2.7	46
2010	3.5	5.0	0.5	30.0	36
2011	3.9	4.0	0	25.5	40
2012	5.0	7.5	0	30.0	39

53 labs
78 labs

Pruthi et al. Quality of factor VIII inhibitor testing in North American specialized coagulation laboratories. Am J Hematol 2014; 89: E27.

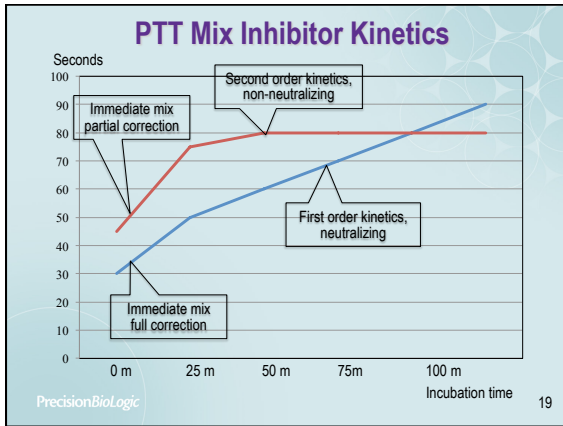
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Variations That Affect Inhibitor Measurement

- Residual patient plasma coagulation factor
- Presence of anticoagulants: dabigatran, heparin
- Presence of other inhibitors: lupus anticoagulant
- Differences in inhibitor epitope specificity
- Elevated coagulation factors shorten PTT results
- Inhibitor kinetics: neutralizing and non-neutralizing

- Soucie et al. National surveillance for hemophilia inhibitors in the United States: Summary report of an expert meeting. Am J Hematol 2014; 89:621.
- Favaloro et al. Haemophilia 2014; 20: Suppl 4

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Inhibitors Effects

- Severe hemophilia A: 30%, moderate, 10%
- Hemophilia B: 1–3%
- Render replacement therapy ineffective
- Most occur in early age factor administration
- Raise rates of hemarthrosis
- More catastrophic bleeds, mortality
- Delay physical maturation
- Raise healthcare costs five-fold

Arruda VR, Samelson-Jones BJ. Gene therapy for immune tolerance induction in hemophilia with inhibitors. *J Thromb Haemost* 2016; 14: 1121–34. Slide added 6-16-16

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Inhibitor Measurement Methods

- Functional, clot-based factor activity inhibition
 - Bethesda titer, 1975
 - Nijmegen Bethesda assay (NBA), 1995
- Functional: chromogenic Bethesda assay (CBA)
- Qualitative immunoassay
 - Solid state enzyme immunoassay (EIA, ELISA)
 - Flow-based fluorescence immunoassay (FLI)
- CDC modification of the NBA, 2012

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Courtesy of Connie Miller, PhD, CDC

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1975 Bethesda Titer

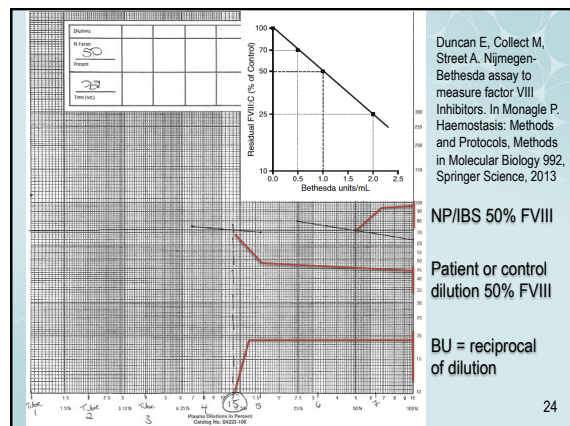
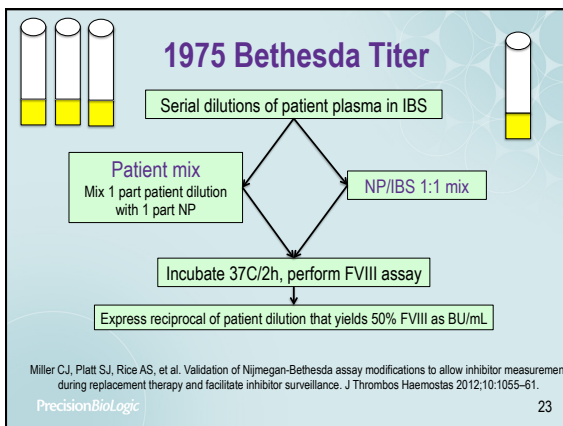
1. Prepare serial twofold patient plasma dilutions in imidazole buffered saline (IBS)
2. Mix patient plasma dilutions 1:1 with commercial NP
3. Prepare 1:1 NP/IBS for normalization
4. Incubate patient dilutions and 1:1 NP/IBS 37°C 2h
5. Add FVIII-depleted plasma to all dilutions after incubation
6. Perform FVIII assay on all dilutions using PTT methodology
7. Report Bethesda units (BU)/mL as reciprocal of dilution that neutralizes 50% FVIII compared to the incubated 1:1 NP/IBS

- NP is the source for FVIII, should be ~100 FVIII U/dL
- Incubated NP/IBS compensates for FV & FVIII deterioration

Kasper CK, Aledort LM, Counts RB, et al. A more uniform measurement of factor VIII inhibitors. *Thromb Diath Haemorrh* 1975;34:869–72.

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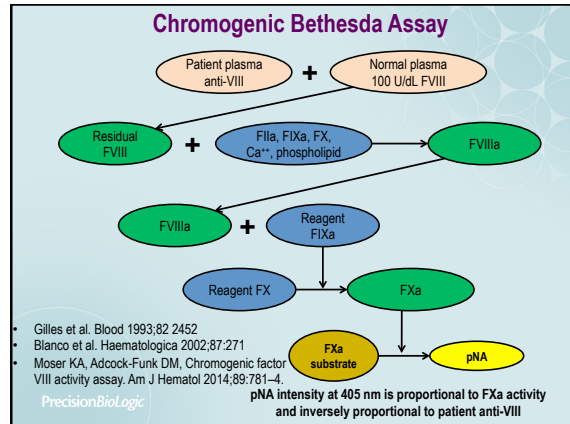
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Chromogenic Bethesda Assay

1. Prepare pt plasma *and control* dilutions as for Bethesda titer
2. Mix pt plasma and control dilutions 1:1 with NP, incubate 2 h.
3. Dilute incubated pt/control plasma/NP 1:31 in IBS.
4. Add reagent: bovine FX, FIXa, thrombin, CaCl₂, & PL.
5. Incubate 90s at 37°C, generates FXa
6. Add FXa chromogenic substrate with thrombin inhibitor and stopping buffer to measure FXa surrogate to FVIII activity
7. Measure FXa: read ΔA/m at 405 nm.
8. 1 chromogenic Bethesda unit (CBU) = level of inhibitor/mL of patient plasma that inactivates 50% of FVIII in 1 mL NP.
9. Limit: ≥0.5 CBU = positive

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Bethesda Titer Vs Chromogenic Bethesda Assay

<p>Bethesda Titer</p> <ul style="list-style-type: none"> • Variable non-specific endpoint: clot detection • Insensitive to inhibitors ≤ 0.5 BU/mL • Interference from lupus anticoagulant • therapeutic A/Cs interfere: heparin and dabigatran 	<p>Chromogenic Bethesda</p> <ul style="list-style-type: none"> • Quantitative endpoint detection system • Sensitive to inhibitors at 0.1 BU/mL • Specific for factor inhibitors • No LAC interference, distinguish LAC from inhibitor
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Miller CH, Rice AS, Boylan B, et al. Comparison of clot-based, chromogenic, and fluorescence assays for measurement of factor VIII inhibitors in the US Hemophilia Inhibitor Research Study. J Thromb Haemost 2013; 11: 1300-9.

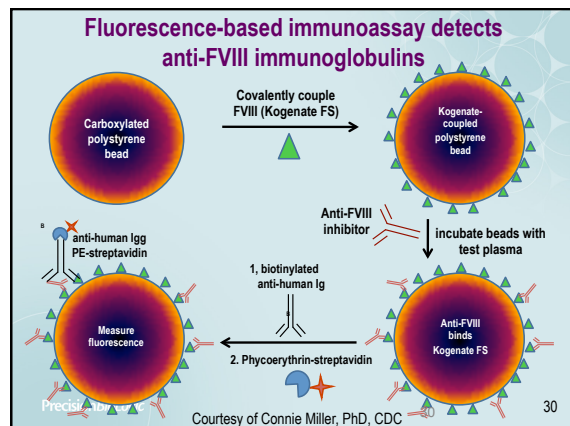
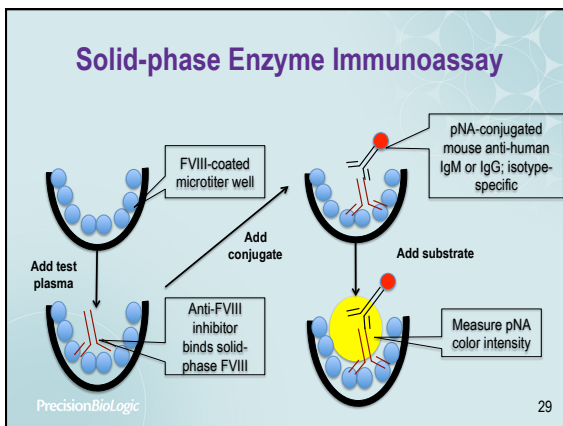
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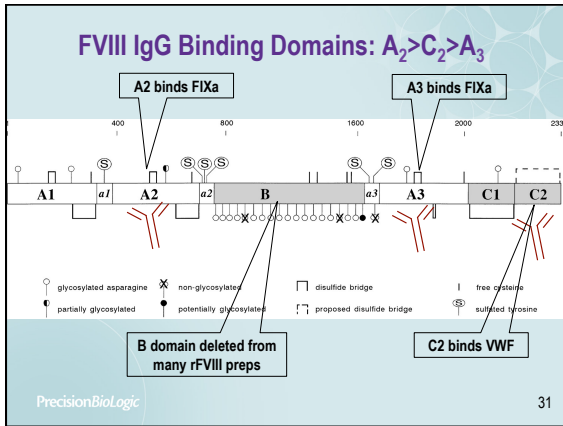
Immunoassay Measurement

- EIA: FVIII antigenic target immobilized in well
- FLI: FVIII target immobilized on fluorescent beads
- More sensitive than functional assays
- Detect neutralizing & non-neutralizing inhibitors
- Detect non factor-inhibiting immunoglobulins
- Non-specific, require functional assay follow-up
- Confirm FVIII reactivity in clot-based assays and distinguish isotypes IgG₁, IgG₂, IgG₄

• Lavigne-Lissalde et al. Thromb Haemost 2008;99: 1090
 • Krudysz-Amblo et al. Blood 2009;113:2587

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Inhibitor Isotype by Fluorescence Immunoassay

- Non-hemophilia subject samples
 - 5% IgG₁ and IgG₂; 2% IgG₃ and IgG₄
- 491 samples from 371 hemophilia A patients
 - 41% IgG₁, 17% IgG₂, 6% IgG₃, 27% IgG₄
 - Many patients with multiple isotypes
- Inhibitor-positive hemophilia A patient isotypes
 - 14% single, 84% multiple, 2% no IgG by FLI
- 7 patients developed NBA-positive inhibitors
 - 5 had prior IgG₁ antibodies, added IgG₄

Boylan B, Rise AS, Dunn AL, et al. Characterization of the anti-factor VIII immunoglobulin profile in patients with hemophilia A by use of a fluorescence-based immunoassay. J Thromb Haemost 2015; 13: 47-53.
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1995 Nijmegen Bethesda Titer

1. Serially dilute patient plasma in FVIII-DP New
2. Mix dilutions 1:1 with IBS-pH 7.4 stabilized NP New
3. Incubate 37°C 2h, perform PTT-based FVIII assay
4. Report Nijmegen Bethesda units (NBU)/mL as reciprocal of dilution that neutralizes 50% FVIII

"Hybrid" assay uses IBS-pH 7.4 NP but substitutes IBS for FVIII-DP to reduce expense

Verbruggen B, Novakova I, Wessels H, et al. The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability. Thromb Haemost 1995;73:247-51.
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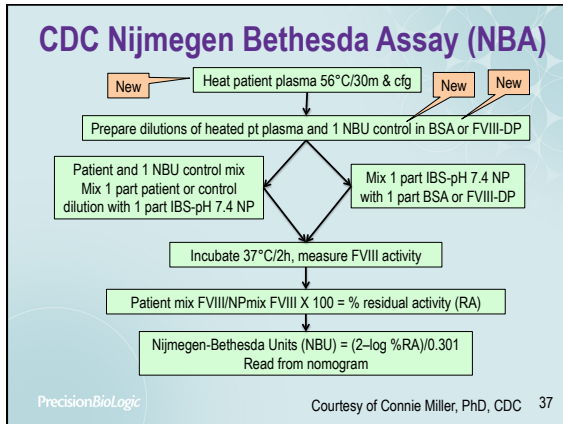
CDC Standard NBA Protocol Updates

- Ship patient specimens on cold packs, not frozen
- Use IBS-pH 7.4 reagent normal plasma (NP) to stabilize FVIII
- Heat specimens 56°C 30' & centrifuge to remove FVIII
 - Residual FVIII from recent prophylaxis or on-demand Rx
 - Non-neutralizing antibody leaves behind residual VIII
 - Heat improves specificity for low-titer inhibitors
 - Factor IX titer, 58°C for 90'?
- Dilute heated pt plasmas and unheated 1 BU positive control in bovine serum albumin (BSA) or FVIII-DP, not IBS
- Confirm all <2 BU/mL samples with alternate assay
 - Miller CH, Adcock DM. The need for standardization of factor inhibitor assays. 2016 THNSA Poster
 - Verbruggen B, Novakova I, van Heerde W. Detecting and quantifying functional inhibitors in haemostasis. In: Kitchen S, Olson JD, Preston FE (eds) Quality in laboratory haemostasis and thrombosis, 2009. Blackwell, Oxford

CDC-modified Nijmegen Bethesda Assay

1. Heat patient plasma 56°C for 30' and centrifuge
2. Serially dilute heated patient plasma in BSA or FVIII-DP
3. Serially dilute unheated commercial 1.0 NBU-positive control in BSA or FVIII-DP
4. Mix dilutions 1:1 with IBS-pH 7.4 NP
5. Incubate 37°C 2h, perform PTT-based FVIII assay
6. Convert residual FVIII activity to NBU/mL using NBA nomogram and multiply the NBU/mL value by the dilution factor

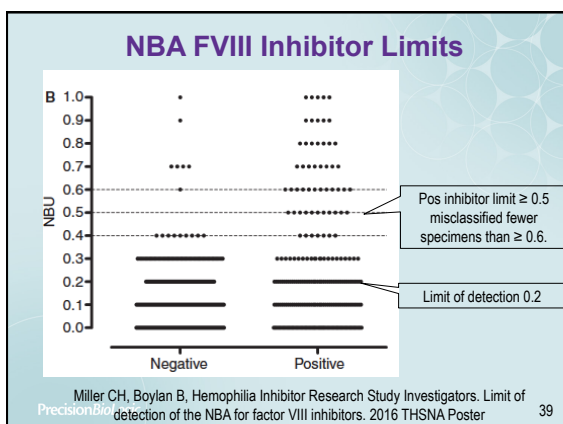
Miller CJ, Platt SJ, Rice AS, et al. Validation of Nijmegen-Bethesda assay modifications to allow inhibitor measurement during replacement therapy and facilitate inhibitor surveillance. J Thrombos Haemostas 2012;10:1055-61.
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The Value of Heating

- 126 (55%) of 228 severe HA samples had measurable FVIII.
- All from patients treated with FVIII within 72 h of specimen collection
- These had residual activity of >100 U/dL and a false inhibitor titer of 0
- Of 159 presumed inhibitor neg samples, 120 had unheated NBU of 0.
- After heating, 45 (37.5%) remained 0
- But 74 (61.7%) rose from 0 to 0.1–0.2 NBU, one rose from 0 to 0.7 NBU
- Of 30 documented inhibitor pos samples with results <0.5 NBU at enrollment, 5 (16.7%) rose to >0.5 NBU after heating.
- FVIII was in samples of patients infused within 24 h of collection.
- in 15 severe patients, all had FVIII before heating and <1 U/dL after.
- In 7 moderate patients, FVIII decreased to <1 U/dL after heating.

Miller CJ, Platt SJ, Rice AS, et al. Validation of Nijmegen-Bethesda assay modifications to allow inhibitor measurement during replacement therapy and facilitate inhibitor surveillance. *J Thrombos Haemostas* 2012;10:1055–61. PrecisionBioLogic 38



Purpose of NBA When Bleeding

- If ≤5 NBU, use high-dose FVIII concentrate
- If >5 NBU, prothrombin complex concentrate (PCC, 1980)
 - BaSO₄ extracted human plasma; II, VII, IX, X: Proplex
 - *Activated* PCC: FEIBA, Autoplex
- FEIBA or Autoplex
 - 50 U/kg/12 h prophylactic
 - 70 U/kg/8 h in hemorrhage
 - Limit 200 U/kg/24 h to avoid DIC
 - No direct monitor: repeat NBA, perform generalized coag evaluation using PTT

Ludlam DA, Morrison AE, Kessler C. Treatment of acquired hemophilia. *Semin Hematol* 1994;31 (Sup 4) 16–19. PrecisionBioLogic 40

FEIBA Alternatives: NovoSeven, Obizur

- NovoSeven (1999): rFVIIa: 90 µg/kg, 6 h FVII half-life
 - Binds cell-bound tissue factor, no DIC risk
 - No direct monitor: repeat NBA, perform generalized coag evaluation using PTT
- Obizur (2014): recombinant porcine sequence FVIII
 - Indication: acquired hemophilia
 - Unlikely to cross-react with anti-FVIII IgGs
 - Initial dose 200 U/kg
 - Titrate dose and frequency based on FVIII recovery levels and clinical response
 - Monitor with chromogenic FVIII

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NBA Purpose When Not Bleeding

- ≤5 NBU/mL in adults or ≤10 in peds, “low responders”
 - Use standard prophylactic FVIII concentrate Rx
- >10 NBU/mL, “high responder”
 - If 5–10 NBU but consecutive Rx generates anamnestic pharmacokinetic response: “high responder”
 - Immune tolerance FVIII therapy for high responders

Rivard GE, Rothschild C, Toll T, Achilles K. Immune tolerance induction in haemophilia A patients with inhibitors by treatment with recombinant factor VIII: a retrospective non-interventional study. *Haemophilia*. 2013;19:449–55. PrecisionBioLogic 42

Immune Tolerance Induction (ITI) Rx

- Success rate 60%. Patient is good candidate when...
 - Historical peak < 200 NBU, < 10 BU at ITI initiation
 - < 2 years from inhibitor identification to ITI initiation
 - Age < 8 years; lower peak titer during ITI
- ITI: use 85–200 NBU FVIII/kg/day
 - Monitor using NBA; 0.6 NBU/mL = “negative”
 - 20% drop at 6 months Rx = satisfactory
 - Use maintenance dose throughout life
 - D/C if no response after 3 periods of 6 m

Arruda VR, Samelson-Jones BJ. Gene therapy for immune tolerance induction in hemophilia with inhibitors. J Thromb Haemost 2016; 14: 1121–34. Slide added 5-15-16

PrecisionBioLogic New Factor Formulations




IDELVION®
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

ELOCTATE™
[Antihemophilic Factor (Recombinant), Fc Fusion Protein]

KOVALTRY
Antihemophilic Factor (Recombinant) with Fc Fusion Protein

Extended Half-life Factor VIII: Eloctate

- Recombinant B-domain deleted Fc fusion factor VIII
- Extended by Fc receptor and IgG recycling pathway
 - 96 HA adult males with >12 annual bleeds, 3–4 doses/week
 - rFVIIIc half-life 19 h vs rFVIII 12h; 1.6–3.6 annual bleeds
- Prophylactic Rx interval up to 5 days versus 3–4 doses/week
- Monitor using clot-based FVIII assay with non-kaolin-based PTT
- Improved monitoring using chromogenic FVIII assay for all B-domain-deleted FVIII preparations



• Shapiro AD, Ragni MV, Kulkarni R, et al. Recombinant factor VIII Fc fusion protein: extended-interval dosing maintains low bleeding rates and correlates with von Willebrand factor levels. J Thromb Haemost. 2014;12:1788–800.
• Mancuso ME, Mannucci PM. Fc-fusion technology and recombinant FVIII and FIX in the management of the hemophilias. Drug Des Devel Ther. 2014 28:365–71.



Additional rFVIII Preparations

Name	MFR		Progress
Bax 111	Baxter	rVWF (not rFVIII)	At FDA
Kovaltry	Bayer	Full-length rFVIII with no human or animal proteins. Reduced inhibitors, normal to slightly extended half-life	Approved
NovoEight	Novo Nordisk		
NuWiq	Octapharma		
Bay 94-9027	Bayer	Pegylated, plasma/albumin free, full-length rFVIII, up to 7.5 d frequency	At FDA
Bax 855	Baxter "Baxalta"	Pegylated plasma/albumin free, full-length rFVIII, 1.5 X Advate half-life	At FDA
rFVIII single-chain	CSL Behring	rFVIII covalently bonds VWF reduces clearance, extends half-life; no inhibitors	Phase II
ACE 910	Chugai & Genentech	Bispecific protein mimics FVIII cofactor, activates IX & X, bypasses inhibitors, SC 1/wk, generates no immune response	FDA breakthrough status

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Extended Half-life Factor IX


- Recombinant Fc fusion factor IX Alprolix, FDA-approved 2014
 - rFIXFc half-life 70–80 h versus 24 h, 7–10 day intervals
 - Monitor using FIX assay with non-kaolin-based PTT
 - Chromogenic FIX valid but not available in the US
- Recombinant albumin fusion FIX Idelvion, FDA 3/4/2016
 - Patients <12 years old: 40–55 U/kg 7 day interval
 - Patients ≥12 years old: 25–40 U/kg 7 day interval
 - For ≥12 YO if controlled, go to 14-d interval at 50–75 U/kg

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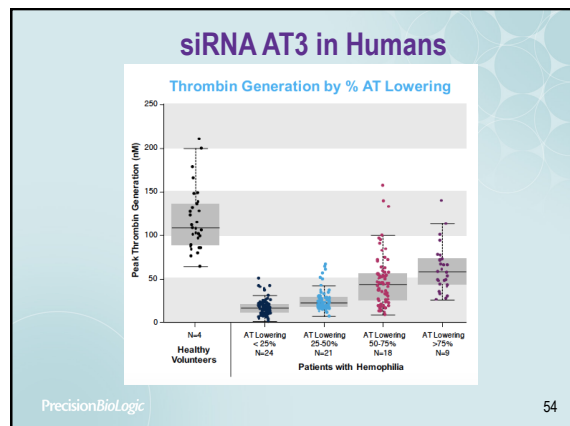
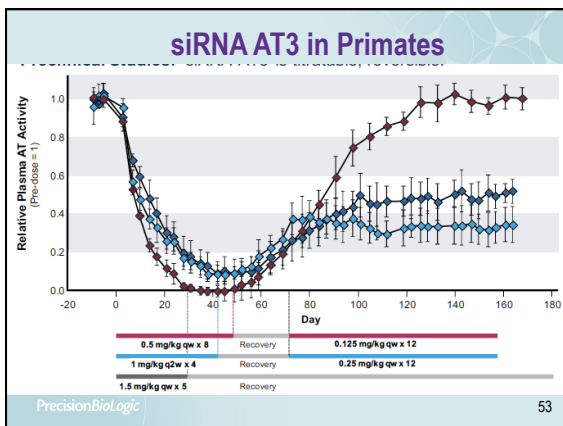
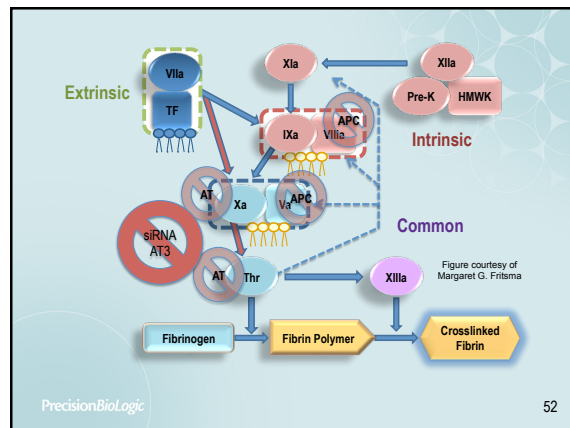
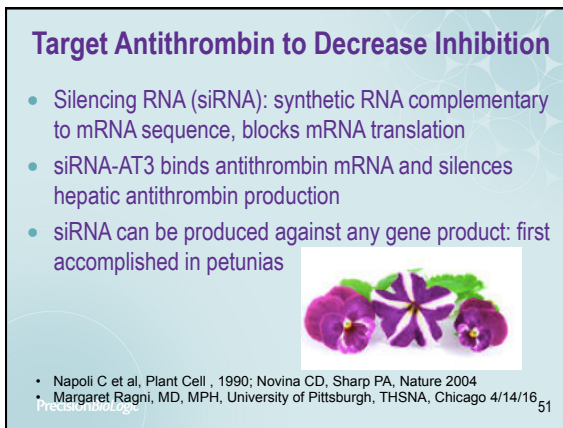
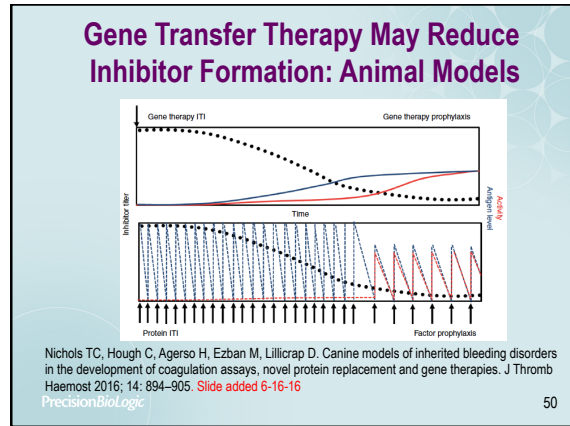
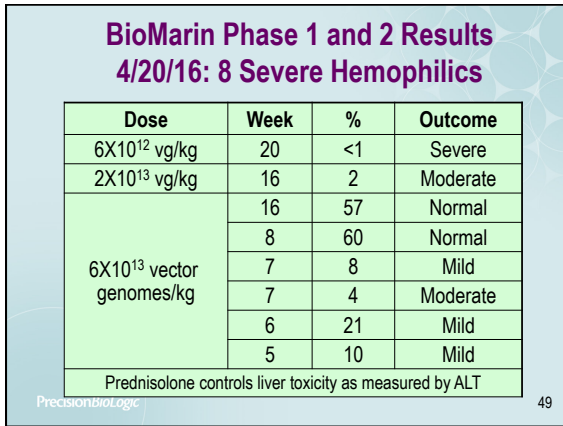
BioMarin BMN270 FVIII Transfer Trial

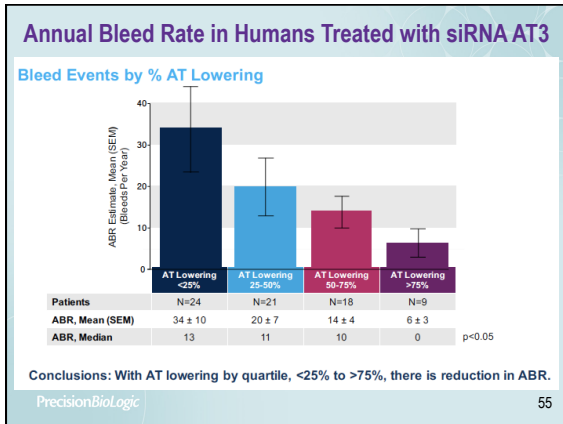
- B-domain-reduced FVIII gene with minimal glycosylation
- Vector optimization: adenovirus-associated vector “8” with adequate capacity for the FVIII gene
 - University College London
 - St. Jude’s Research Hospital
- Phase 1 & 2 trial completed
- Preparing phase III trial



• McIntosh J, Lenting PJ, Rosales C, et al. Therapeutic levels of FVIII following a single peripheral vein administration of rAAV vector encoding a novel human factor VIII variant. Blood. 2013 25:121:3335-44
• Ward NJ, Buckley SM, Waddington SN, et al. Codon optimization of human factor VIII cDNAs leads to high-level expression. Blood 2011;117:798–807.

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siRNA AT3 Phase I Safety

- No discontinuation
- Mild adverse events
 - Transient erythema and pain at injection site, resolved at 24 hours
 - Headache
- Bleeds treated with standard therapy
- No antibody formation
- Normal LFTs, CBC, PLTs, FG, EKG

PrecisionBioLogic Sehgal A et al, Nat Med 2015 56

Coagulation Factor Inhibitors

Bottom Line at the End (BLATE); The Participant...

- Explains the origin of anti-factor VIII (FVIII inhibitor)
- Detects FVIII inhibitors using factor assays and mixing studies
- Measures FVIII inhibitors using the Bethesda titer, Nijmegen Bethesda assay, chromogenic Bethesda assay, enzyme immunoassay and fluorescence immunoassay
- Describes coagulation factor bypass therapy to resolve bleeding in inhibitor patients
- Describes immune tolerance induction therapy
- Lists new factor concentrates designed to prevent inhibitor formation

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Thanks for listening!

QUESTION?

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