Factors for Success:

What Oncology Pharmacists Need to Know

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UVA HEALTH

Disclosures

I have nothing to disclose. I *will* be discussing off-label indications.

Objectives

- Explain the etiology and pathophysiology of hemophilia A and B
- Differentiate current treatment options for the management of hemophilia A and B
- Discuss the pathophysiology of acquired hemophilia A and available treatment options
- Design a treatment regimen for emergent bleeding in patients with hemophilia or acquired hemophilia A

Hemophilia

Hemophilia

- Hemophilia A and B are rare X-linked congenital bleeding disorders:
  - Caused by deficiencies in factor VIII (HA) or factor IX (HB)
  - Typically expressed in males
  - Female carriers may have symptoms
- Approximately 33,000 males in the US
- Affects individuals from all racial and ethnic backgrounds
  - HA occurs in ≈ 1 of every 5000 live male births
  - HA is approximately 4 times as common as HB

HA, hemophilia A; HB, hemophilia B

Srivastava A, et al. *Haemophilia*. 2020;26:1-158; Hemophilia: facts. CDC. Reviewed July 17.2020. Accessed July 29, 2022. www.cdc.gov/ncbddd/hemophilia/facts.html; Data & statistics on hemophilia. Reviewed September 14, 2020. Accessed July 29, 2022. www.cdc.gov/ncbddd/hemophilia/data.html

Classification

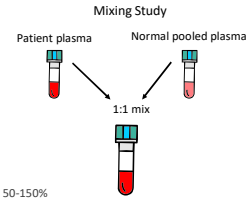
Severe	• Associated with spontaneous bleeding, deep soft tissue and joint bleeding • Factor level <1%
Moderate	• Bleeding following minor trauma or surgery; occasional joint bleeds • Factor level 1%-5%
Mild	• Bleeding with major trauma or surgery; joint bleeds uncommon • Factor level 6%-40%

60% of affected individuals have severe hemophilia

Hemophilia: facts. CDC. Reviewed July 17, 2020. Accessed July 29, 2022. www.cdc.gov/ncbddd/hemophilia/facts.html; Data & statistics on hemophilia. Reviewed September 14, 2020. Accessed July 29, 2022. www.cdc.gov/ncbddd/hemophilia/data.html

Diagnosis

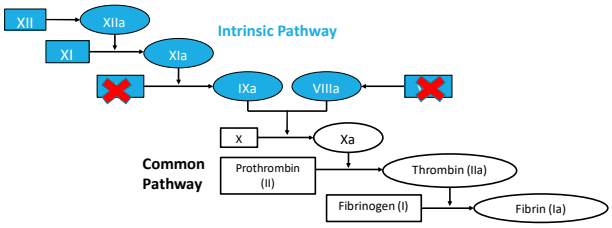
- Family history
  - 1/3 of patients have spontaneous mutations
- Easy bruising
- Abnormal bleeding
- Isolated prolonged aPTT (normal: 25-35 seconds)
- Mixing study
  - aPTT corrects to normal: factor deficiency
  - aPTT does NOT correct: inhibitor present
- Factor activity levels
  - Typically reported as 50-150 IU/dL, 0.5-1.5 IU/mL, or 50-150%



Srivastava A, et al. *Haemophilia.* 2020;26:1-158.

aPTT: activated partial thromboplastin time

Simplified Coagulation Cascade



Hoffman M, et al. *Thromb Haemost.* 2001; 85: 958-65.

Lab Considerations

One-Stage Clotting Assay (OSA)

- Mix serial dilutions of patient plasma with equal volumes of FVIII (or FIX) deficient plasma along with aPTT reagent
- Measure clot formation and aPTT compared to reference plasma
- Lengthening of the aPTT compared to reference plasma correlates to the lower FVIII (or FIX) activity level in patient sample

Chromogenic Substrate Assay (CSA)

- 2 stage assay
- Stage 1: dilutions of patient plasma are incubated with FIXa, factor X, phospholipids and calcium resulting in formation of FXa proportional to the FVIII activity
- Stage 2: the generated amount of FXa concentration is measured by chromogenic substrate which is proportional to the FVIII concentration

Al-Samkari H, et al. *Am J Hematol.* 2018;93:1082-1090; Peyvandi F, et al. *J Thromb Haemost.* 2016;14:248-61.

Lab Considerations

OSA	CSA
• Most widely used assay for clinical monitoring • Higher inter-laboratory variability due to number of available reagents • Sensitive to lupus anticoagulants, heparin, and DOAC drugs • Less sensitive at low FVIII concentrations • Underestimates FVIII activity for BDD rFVIII products	• 2 stage procedure • Lower inter-laboratory variability • Insensitive to lupus anticoagulants • Sensitive to DOAC • Suitable across all FVIII concentrations • More expensive than OSA • Not as widely available as the OSA particularly for diagnosis and monitoring

DOAC: direct oral anticoagulants
BDD: B-domain deleted
rFVIII: recombinant factor VIII

Al-Samkari H, et al. *Am J Hematol*. 2018;93:1082-1090; Peyvandi F, et al. *J Thromb Haemost*. 2016;14:248-61.

Audience Response Question #1

Which of the following is a diagnostic parameter for moderate hemophilia B?

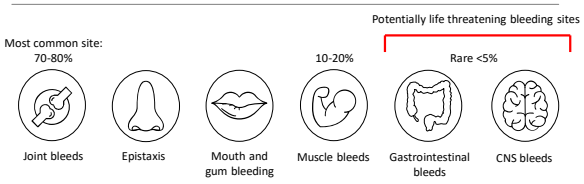
A. Recurrent spontaneous joint bleeding

B. Factor IX < 1%

C. Factor VIII < 1%

D. Factor IX level 1-5%

Symptoms



Srivastava A, et al. *Haemophilia*. 2020;26:1-158.

Slide 10

R11 please define
Reviewer, 9/6/2022

WLP*1 Added DOAC: direct oral anticoagulants
Ward, Leslie P *HS, 9/9/2022

Standard of Care: Prophylaxis

Parameter	FVIII	FIX
Intermediate dose schedule	15-25 units/kg 3 days per week	20-40 units/kg 2 days per week
Half-life	8-12 hours	18-24 hours
Expected change in plasma factor level with each unit infused	+2 IU/dL	+1 IU/dL
Maintain troughs	>1%*	>1%*
Considerations	FVIII circulates bound to von Willebrand factor (VWF) which has t ½ ≈12-15 hours	Allergic reactions may occur with both recombinant and plasma-derived FIX products (≈2%-4%)

*Most clinicians prefer target higher trough >3-5%; should be personalized based on individual's activities, lifestyle, and PK handling of factor

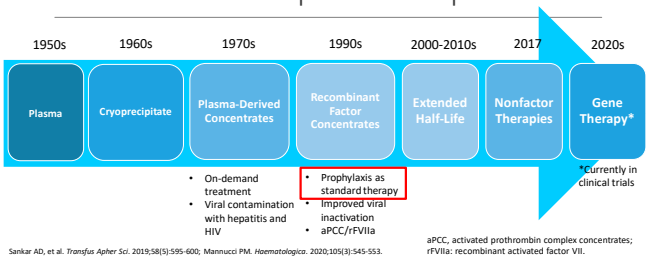
Challenges

- Requires frequent intravenous infusions
- Difficult to maintain adequate trough levels
- Long-term adherence

Srivastava A, et al. *Haemophilia*. 2020;26:1-158; Lambert T, et al. *Ther Adv Hematol*. 2018;9(9):295-308; Pipe S, et al. *Blood*. 2016;128(16):2007-2016.

Treatment Options

Evolution of Hemophilia Therapies



Sankar AD, et al. *Transfus Apher Sci*. 2019;58(5):595-600; Mannucci PM. *Haematologica*. 2020;105(3):545-553.

aPCC, activated prothrombin complex concentrates; rFVIIa: recombinant activated factor VII.

Plasma Derived SHL FVIII Concentrates

Product	Mean half-life (hours)	Technology
Alphanate®	17	Plasma derived containing VWF and FVIII
Humate P®	12	Plasma derived containing VWF and FVIII
Koate-DVI®	16	Plasma derived containing VWF and FVIII
Hemofil M®	15	Plasma derived immunoaffinity purified FVIII

SHL: Standard half life

Lim MY. *Hematology Am Soc Hematol Educ Program*. 2021; 1: 206-214; MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document 263.

Recombinant SHL FVIII Concentrates

Product	Mean half-life (hours)	Technology
Recombinate®	14	First generation: full-length
Kogenate®	14	Second generation: full-length
Advate®	12	Third generation: full-length
Kovaltry®	14	Third generation: full-length
Novoeight®	11	Third generation: B-domain truncated
Xyntha®	11	Third generation: B-domain deleted
Nuwiq®	17	Third generation: B-domain deleted
Afstyla®	14	Third generation: single chain B domain deleted

SHL: Standard half life

Lim MY. *Hematology Am Soc Hematol Educ Program*. 2021; 1: 206-214; MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document 263.

Plasma Derived and Recombinant FIX Concentrates

Product	Classifciation	Source Material	Half life (hrs)
AlphaNine®	High purity, plasma derived	Pooled human plasma with albumin as a stabilizer	21
Mononine®	High purity, plasma derived	Pooled human plasma	25
Benefix®	Recombinant	Chinese Hamster Ovary (CHO)	18
Ixinity®	Recombinant	Chinese Hamster Ovary (CHO)	24
Rixubis®	Recombinant	Chinese Hamster Ovary (CHO)	26

Lim MY. *Hematology Am Soc Hematol Educ Program*. 2021; 1: 206-214; MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document 263.

Extended Half-Life (EHL) Factor Prophylaxis

- Decrease infusion frequency → potential for improved adherence
- Ability for higher trough levels with dosing schedules → better bleed protection
- Consider in patients with:
  - Difficult venous access
  - Poor adherence
  - A need for higher trough levels for activity
  - Bleeding events on appropriate doses of standard half-life (SHL) products
  - Benefit from improved convenience

Modifications to prolong half-life

- Fc fusion and addition of albumin protein: uses neonatal Fc receptor pathway to escape lysosomal degradation
- PEGylation: addition of polyethylene glycol (PEG) molecules to reduce the binding of clearance receptors

Lambert T, et al. *Ther Adv Hematol.* 2018;9:295-308; Peters R, Harris T. *Nat Rev Drug Discov.* 2018;17(7):493-508; Srivastava A, et al. *Haemophilia.* 2020;26:1-158.

FVIII Extended Half-Life Products

	Efmoroctocog alfa	Rurioctocog alfa pegol	Damoctocog alfa pegol	Turoctocog alfa pegol
Brand	Eloctate®	Adynovate®	Jivi®	Esperoct®
Structure	rBDD-FVIII Fc fusion	PEGylated rFVIII (20 kDa)	PEGylated rBDD-FVIII (60 kDa)	GlycoPEGylated rBDT-FVIII (40 kDa)
Half-life	19 hours	14-16 hours	17-21 hours	15-21 hours
FDA-approved indications	On demand Perioperative Prophylaxis			
Pediatric: prophylaxis dosing	Children <6 years: 50 units/kg twice weekly	Children 1 to <12: 55 units/kg twice weekly	Not approved <12 years	Children 1 to <12: 65 units/kg twice weekly
Adult: prophylaxis dosing	50 units/kg every 4 days or 25-65 units/kg every 3-5 days	40-50 units/kg twice weekly	30-40 units/kg twice weekly	50 units/kg every 4 days
FDA approval	2014	2015	2018	2019

rBDD, recombinant B domain deleted; rBDT, recombinant B domain truncated.

Eloctate. Prescribing information. Bioverativ Therapeutics; 2017; Adynovate. Prescribing information. Baxalta; 2018; Jivi. Prescribing information. Bayer; 2018; Esperoct. Prescribing information. Novo Nordisk; 2019; Arruda VR, et al. *Blood.* 2017;130(21):2251-2256; Lambert T, et al. *Ther Adv Hematol.* 2018;9(9):295-308; Srivastava A, et al. *Haemophilia.* 2020;26:1-158.

FIX Extended Half-Life Products

	Eftrenonacog alfa	Albutrepenonacog alfa	Nonacog beta pegol
Brand	Alprolix®	Idelvion®	Rebinyn®
Structure	rFIX-Fc fusion	rFIX-albumin fusion	GlycoPEGylated-rFIX (40kDa)
Half-life	86-97 hours	104-118 hours	103-114 hours
FDA-approved indications	On demand Perioperative Prophylaxis	On demand Perioperative Prophylaxis	On demand Perioperative
Dosing guidelines	• <12 y old PPX: 60 units/kg once weekly • Prophylaxis: 50 units/kg once weekly or 100 units/kg once every 10 days. Adjust dosing interval based on individual response.	• <12 y old PPX: 40-55 units/kg every 7 days • Prophylaxis: 25-40 units/kg every 7 days. If well-controlled, may be switched to a 14-day interval 50-75 units/kg.	• Minor and moderate bleed: 40 units/kg • Major bleed: 80 units/kg
FDA approval	2014	2016	2017

Alprolix. Prescribing information. Bioverativ Therapeutics Inc; 2017; Idelvion. Prescribing information. CSL Behring LLC; 2020; Rebinyn. Prescribing information. Novo Nordisk; 2020; Arruda VR, et al. *Blood.* 2017;130(21):2251-2256; Srivastava A, et al. *Haemophilia.* 2020;26:1-158.

Summary: EHL Factor Products

- FVIII EHL products increase half-life ≈ 1.5-1.7 fold with 30% reduction in number of infusions
- FVIII EHL products able to maintain trough levels: 2-3 IU/dL
- FVIII EHL products half-life extension limited by VWF half-life
- FIX EHL products increase half-life ≈ 4-6 fold with 60% reduction in number of infusions
- FIX EHL products are able to maintain trough levels 5-10 IU/dL

VWF, von Willebrand factor

Peyvandi F, et al. *Lancet*. 2016;388:187-197; Mannucci PM. *Haematologica*. 2020;105(3):545-553.

Emicizumab-kxwh

- Humanized bispecific recombinant monoclonal antibody that binds and bridges FX and FIXa
- Approved for **prophylaxis in hemophilia A** patients with and without inhibitors
- Subcutaneous administration
- Loading dose: 3 mg/kg weekly x 4
- Maintenance regimens:
  - 1.5 mg/kg once weekly
  - 3 mg/kg once every 2 weeks
  - 6 mg/kg once every 4 weeks
- Half-life ≈ 28 days

Not exactly FVIII

- Single site of interaction
- No on/off mechanism
- Low affinity for enzyme and substrate
- Partial cofactor activity
- No distinction (binds FIX, FIXa, FX, FXa)

Lenting PJ, et al. *Blood*. 2017;130(23):2463-2468; Hemlibra. Prescribing information. Genentech, Inc; 2020.

Emicizumab-kxwh: HAVEN 1-4

HAVEN 1 (N=109)
With Inhibitors
Randomized
- Adults and adolescents ≥12 years
- 1.5 mg/kg once weekly maintenance

HAVEN 2 (N=85)
With Inhibitors
Nonrandomized
- Children <12 years
- 1.5 mg/kg once weekly maintenance
- 3 mg/kg once every 2 weeks
- 6 mg/kg once every 4 weeks

HAVEN 3 (N=152)
Without inhibitors
Randomized
- Adults and adolescents ≥12 years
- 1.5 mg/kg once weekly or 3 mg/kg once every 2 weeks maintenance

HAVEN 4 (N=48)
With and Without Inhibitors
Nonrandomized
- Adults and adolescents ≥12 years
- 6 mg/kg once every 4 weeks maintenance

- Demonstrated efficacy in **preventing bleeding** in hemophilia A patients with and without inhibitors by **decreasing the annualized bleed rate (ABR)** and **increasing the % of patients with zero bleeds** at 24 weeks

Oldenburg J, et al. *N Engl J Med*. 2017;377:809-818; Young G, et al. *Blood*. 2019;134(24):2127-2138; Mahlangu J, et al. *N Engl J Med*. 2018;378:811-822; Pipe SW, et al. *Lancet Haematol*. 2019;6:e295-e305.

Emicizumab-kxwh: Safety

Thrombotic Events, n (%)	Total population (N=399)
All Thromboembolic events (TE)	**4 (1)**
• Associated with concomitant aPCC use	2 (0.5)
• Device occlusion of peripheral inserted central catheter	1 (0.3)
• Myocardial infarctions	1 (0.3)
Thrombotic microangiopathy (TMA) events	**3 (0.8)**

- Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of **>100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC)** was administered for 24 hours
- For patients with inhibitors on emicizumab who experience an acute bleed, recombinant factor VIIa (rFVIIa) is recommended over aPCC

Callaghan MU, et al. Blood. 2021;137(6):2231-2242; MASAC Recommendation on the Use and Management of Emicizumab-kxwh for Hemophilia A with and without inhibitors. MASAC Document 268.

Emicizumab-kxwh: Lab Considerations

Coagulation test results affected by emicizumab-kxwh
Activated partial thromboplastin time (aPTT)
One-stage, aPTT-based, single-factor assays (FVIII activity)
Bethesda assays (clot based) for FVIII inhibitor titers
aPTT-based activated protein-C resistance
Activated clotting time (ACT)

These clotting-based tests provide false readings and **should NOT** be used to make clinical treatment decisions. Laboratory interference can be up to **6 months** from the last dose.

Measuring FVIII activity:

✓ Chromogenic FVIII activity tests containing bovine proteins **can be used** to measure endogenous or infused FVIII activity

Measuring FVIII inhibitors:

✓ Bovine chromogenic Bethesda assay **can be used** to measure FVIII inhibitors

Hemlibra. Prescribing information. Genentech, Inc; 2020; Peyvandi F, et al. *J Thromb Haemost*. 2020;18(6):1242-1255.

Acute Bleed Management

Type of Hemorrhage	Hemophilia A Desired factor activity level (%)	Hemophilia B Desired factor activity level (%)	Duration of therapy (days)
CNS/head	Initial → 80-100	Initial → 60-80	1-7
	Maintenance → 50	Maintenance → 30	8-21
Throat/neck and GI	Initial → 80-100	Initial → 60-80	1-7
	Maintenance → 50	Maintenance → 30	8-14
Joint/superficial muscle	40-60	40-60	1-3

Srivastava A, et al. *Haemophilia*. 2020;26:1-158.

Treatment Dosing

General Principles	Factor Recovery	Calculation	Subsequent doses, hrs
Initial dose based on desired factor increase (%):	1 unit/kg of FVIII raises plasma level by 2%	**Hemophilia A:** (Desired factor level – baseline factor level) x Wt (kg) / 2	8-12
	1 unit/kg of FIX raises plasma level by 1%*	**Hemophilia B:** (Desired factor level – baseline factor level) x Wt (kg)	18-24

*Product specific in vivo recovery (IVR) vary, but approximately 1

Clinical pearls:
- If severe hemophilia and bleeding suspected, assume baseline factor activity is 0
- Round to nearest vial (usually calculate lower and upper end of target goal)
- Obtain peak 15-30 minutes after first bolus
- Obtain trough to determine frequency of dosing

Srivastava A, et al. *Haemophilia*. 2020;26:1-158.

Audience Response #2

AP is a 41 year old male with a history of severe hemophilia A presented via EMS for MVC crash with concerns for intracranial hemorrhage. The ER resident calls wanting assistance with dosing his factor VIII prior to CT scans. Pt wt = 89 kg.

A. Recombinant factor VIII (Kogenate®) 9000 units

B. Recombinant factor VIII (Kogenate®) 4500 units

C. Recombinant factor IX (Ixinity®) 9000 units

D. Emicizumab 267 mg subcutaneous

Patient Case: AP

AP is a 41 year old male with a history of severe hemophilia A presented via EMS for MVC crash with concerns for intracranial hemorrhage. The ER resident calls wanting assistance with dosing his factor VIII prior to CT scans. Pt wt = 89 kg.

- Assume baseline factor: 0%
- Goal for intracranial: 80-100%
- **$\frac{(100-0) \times 89}{2}$ = 4450 units**
- **$\frac{(80-0) \times 89}{2}$ = 3560 units**
- **50 units/kg should get to factor level ~100% in severe hemophilia A**

Calculation
Hemophilia A: (Desired factor level – baseline factor level) x Wt (kg) / 2

Continuous Infusion

- Preferred over intermittent bolus for pts requiring prolonged treatment course
- Use products with extended stability information
- Use of smart pump with small volume infusion is necessary
- Avoids peaks and troughs associated with intermittent bolus

Srivastava A, et al. *Haemophilia*. 2020;26:1-158; Holme PA, et al. *Haemophilia*. 2018;24:24-32.

Continuous Infusion Dosing

- Bolus dose followed by continuous infusion
  - Calculate desired factor level (bolus)
  - Initiate continuous infusion

	Initial Continuous Infusion Rate
FVIII	2-4 units/kg/hr
FIX	4-6 units/kg/hr

- Daily Dose (IU) = infusion rate (units/kg/hr) x body weight (kg) X 24 hr
  - Adjust dose based on factor assays (at least daily)
  - Calculate factor clearance at steady state
  - Clearance (mL/kg/hr)= current infusion rate (units/kg/hr) divided by factor level in IU/mL

Srivastava A, et al. *Haemophilia*. 2020;26:1-158; Holme PA, et al. *Haemophilia*. 2018;24:24-32. Morfini M. *Blood Transfus*. 2008; 6(Supple 2):s21-25.

Patient Case: CF

- CF presents to the ED with complaints of bright red blood per rectum. He has a history of severe hemophilia B managed on Alprolix prophylaxis. He ran of factor and his last dose was approximately 12 days ago. He has a h/o GI bleeding in the past with hemorrhoids. His hemoglobin on admission is 3.5g/dL and wt=62 kg.

Initial bolus: (80-0) x 62 = **4960 units**
Initial continuous infusion rate: **6 units/kg/hr**
Daily dose = 6 units/kg/hr x 62 kg x 24 hr = 8928 units

Calculation
Hemophilia B: (Desired factor level – baseline factor level) x Wt (kg)
Initial Continuous Infusion Rate
FIX: 4-6 units/kg/hr

- FIX=68% = 0.68 IU/mL
- Clearance (mL/kg/hr)= current infusion rate (units/kg/hr) divided by factor level in IU/mL
- Patient's calculated clearance (CL) = 6 units/kg/hr ÷ 0.68 IU/mL = **8.82 mL/kg/hr**
- New infusion rate = CL x desired factor level (IU/mL)
- Patient's new infusion rate = 8.82 mL/kg/hr x 0.8 (IU/mL) = **7 units/kg/hr**

Audience Response Question #3

AP is a 41 year old male with a history of severe hemophilia A presents to clinic for routine follow up. He is currently on Advate prophylaxis, but is not very compliant due to having a difficult time getting IV access. He takes his factor approximately once weekly instead of the prescribed every other day regimen.

Which of the following would be MOST appropriate to use for prophylaxis in this patient?

A. Xyntha®
B. Alprolix ®
C. Emicizumab
D. Eloctate ®

Acquired Hemophilia A

Acquired hemophilia A (AHA)

Caused by neutralizing autoantibodies against FVIII

Rare, severe bleeding disorder

1 in a million

Occurs in both men and women

Usually older (>60-70 years)

~ 50% concomitant disorder

Knoebl P, et al. *Blood*. 2021;137:410-419; Tiede A, et al. *Haematologica*. 2020;105:1791-1801.

Clinical Presentation and Diagnosis

Bleeding	Labs
• Acute onset of bleeding • Soft tissue/ muscle bleeding • Hematuria • GI • Intracranial	• Normal platelets • Normal PT/INR • Prolonged aPTT • Abnormal mixing study • Low factor VIII • Elevated FVIII antibody titer (measured as Bethesda units)

Knoebl P, et al. *Blood*. 2021;137:410-419; Tiede A, et al. *Haematologica*. 2020;105:1791-1801; Ma AD, et al. *Hematology*. 2006: 432-437.

Patient Case: NC

NC is a 65 year old female (wt=72.9 kg) transferred from OSH with concern from acquired hemophilia A. Her past medical history is significant for HTN and COPD. She recently diagnosed with PE and started on apixaban approximately 3 weeks ago.

Ten days after starting apixaban she presented to ED for dysphagia in setting of hypopharyngeal hematoma initially thought to be 2/2 to apixaban.

Her aPTT > 200 seconds. She received 2 units of FFP and discontinued apixaban.

One week later she represented for pain, edema, and diffuse ecchymotic lesions on her extremities. Her aPTT elevated (>200 seconds) and significant decrease in hemoglobin.

She had an abnormal mixing study and her FVIII level was <1%. She received 1 unit pRBC, 1 unit FFP, and started on prednisone 40 mg before transfer.

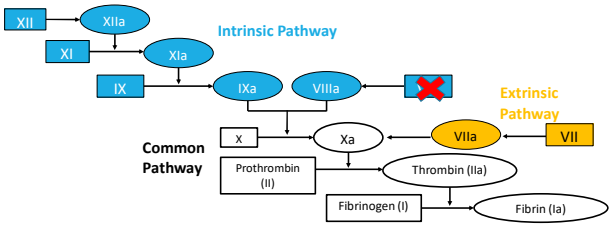
Treatment

Eradicate autoantibodies
- Treatment of underlying condition
- Immunosuppression: corticosteroids, oral cyclophosphamide, rituximab

Hemostatic treatment
- Acute: Bypassing agents
- Acute: Recombinant porcine factor VIII
- Chronic: Emicizumab for prophylaxis

Knoebl P, et al. *Blood*. 2021;137:410-419; Tiede A, et al. *Haematologica*. 2020;105:1791-1801.

Simplified Coagulation Cascade



Hoffman M, et al. *Thromb Haemost*. 2001; 85: 958-65.

Bypassing Agents (BPAs)

Characteristics	aPCC (FEIBA®)	Eptacog alfa (NovoSeven®)	Eptacog beta (Sevenfact®)
Dose	50-100 units/kg every 12 hours max 200 units/day	70-90 mcg/kg every 2-3 hours	225 mcg/kg x 1 then 75 mcg/kg 6 hours later than every 2 hours
Half life	4-7 hours	2.5-3 hours	1.4-1.7 hours
Derivative	Human plasma	Baby hamster kidney cells	Genetically engineered rabbits
Product	FII, FVIIa, FIX, FX	FVIIa	FVIIa
Approved indication	In pts with hemophilia A and B with inhibitors for • Control and prevention of bleeding episodes • Perioperative management • Routine ppx to prevent or reduce the frequency of bleeding episodes	Tx of bleeding episodes and perioperative management in adults with acquired hemophilia	Tx and control of bleeding episodes in adolescents and adults with hemophilia A or B with inhibitors

Ciolek AM, et al. *Ann Pharmcother*. 2022;56:831-838.

aPCC, activated prothrombin complex concentrates

Recombinant Porcine FVIII (rpFVIII): Obizur ®

Approved for treatment of bleed in patients with acquired hemophilia A

- Human FVIII antibodies are less likely to inhibit porcine FVIII
- Risk for developing anti-porcine FVIII antibody during treatment even if not present at baseline

Prospective phase 2/3 multicenter, open label, single cohort study

- 28 patient enrolled, median age 70
- Median anti-hFVIII neutralizing antibody titer 31 Bethesda units (BU)
- Control of primary bleed in 85.7% of patients
- Median 3 doses within the first 24 hours

Dose 200 units/kg every 4-12 hours

- Titrate subsequent doses and frequencies to maintain appropriate FVIII trough levels
- Assess peak FVIII level 30 minutes after dose

Fosbury E, et al. *Ther Adv Hematol*. *2017*; 8: 263-272.

rpFVIII Practical Considerations

- Clinical trials excluded patients with baseline anti-porcine factor VIII inhibitor titer greater than 20 Bethesda units
- UNC published dosing protocol used in case series

Initial dose 100 units/kg → Check peak level → 2nd dose → Target Troughs

- Anti-porcine Bethesda titer does not reliably predict clinical response to rpFVIII

- If > 100% → Draw trough 6-8 hrs & dose 50 units/kg
- If at goal (100%) → Draw trough 4 hrs & dose 50 units/kg
- If <100% → Consider repeat dose 100 units/kg
- If no response (0%) → Consider bypassing agent

30-50%
OR
50-70% for severe life-threatening bleeding

Ellsworth P, et al. *Blood Adv.* 2020; 4: 6240-49.

Audience Response Question #4

NC is diagnosed with acquired hemophilia.

Which of the following is the most appropriate medication for NC's acute bleed?

A. Activated prothrombin protein complex 100 units/kg IV

B. Emicizumab 3 mg/kg subcutaneous

C. Recombinant factor VIII (Kogenate®) 100 units/kg IV

D. Recombinant factor IX (Ixinity®) 100 units/kg IV

Patient Case: NC

Pertinent labs
Hemoglobin: 10.7 g/dL
aPTT 121.6 seconds
Mixing study: aPTT immediate 104.7 seconds aPTT incubated > 200 seconds aPTT mix control 30.3 seconds aPTT mix control incubated: 33 seconds
FVIII <1%
Inhibitor titer: 448 BU

Patient started on aPCC 100 units/kg Q12

Increased prednisone 1 mg/kg

Initiated cyclophosphamide 1 mg/kg/day

Hemoglobin stabilized and held further bypassing agents/dosing

Emicizumab for AHA

Patients remain at risk of bleeding until inhibitors have been eradicated

Immunosuppression significant side effects with a mortality rate up to 16%

Nearly 60% of patient experience recurrent bleeds

BPAs not ideal for ppx due to short half life

Emicizumab is approved for prophylaxis of bleeding in congenital hemophilia

Emicizumab is not affected by FVIII inhibitors

Knoebl P. *Drugs.* 2018; 78:1861-1872; Tiede A, et al. *J Thromb Haemost.* 2021;19:637-644.

Baseline Characteristics

- 12 studies reported on the use of emicizumab in 33 patients with AHA

Characteristic	N=33, (%)
Median age	74 years (range: 21-93)
Male	18 (54.5)
Secondary condition: Autoimmune Malignancy Idiopathic	 3 (9.1) 3 (9.1) 27 (81.8)
FVIII level <1%	20 (60.6)
Received hemostatic therapy prior to initiation of emicizumab • rFVIIa • aPCC • rpFVIII	26 (78.8) 20 7 7

Thomas VM, et al. *Haemophilia.* 2022; 28:4-17.

Dose and Duration

Majority of use in patients with recurrent bleeding

- Avoid combination with aPCC > 100 units/kg/day due to TMA and TE events in congenital hemophilia patients

Majority utilized standard loading dose of 3 mg/kg weekly x 4

- One case series 3 mg/kg for 3-4 doses then maintenance dose at 1.5 mg/kg every 3 weeks

Duration ranged 20 days – 10 months

- Discontinued complete remission with eradication of FVIII inhibitor and normalization of endogenous FVIII
- Discontinued with FVIII > 30%
- Discontinued when FVIII > 10%

Thomas VM, et al. *Haemophilia.* 2022; 28:4-17.

Safety and Efficacy

Safety	Efficacy
• Generally well tolerated • AE data not specifically reported in 10 cases • 2 deaths reported and attributed to other causes (arrhythmia and bowel perforation) • 1 pt suffered stroke with confounding issues	• Maintained hemostasis • Bleeding symptoms controlled after the first dose • Bleeding occurred during surgical procedures or trauma induced injuries

Clinical trials:
- NCT04188639 – phase II in Germany – active, not recruiting
- NCT05345197 – phase II not yet recruiting (6 mg/kg on day 1 and 3 mg/kg on day 2 followed by 1.5 mg/kg weekly)

Thomas VM, et al. *Haemophilia*. 2022; 28:4-17; Emicizumab in Acquired Hemophilia A. NCT04188639. Updated June 29, 2022. Accessed August 21, 2022. clinicaltrials.gov/ct2/show/NCT04188639; Emicizumab in patients with Acquired Hemophilia A (AHAEmi). NCT05345197. Updated April 25,2022. Accessed August 21,2022. clinicaltrials.gov/ct2/show/NCT05345197.

Patient Case: NC

Readmitted with AKI and new thigh hematoma

Pertinent labs
Hemoglobin: 7.2 g/dL
Scr 2.9
aPTT 91.5 seconds
FVIII <1%
Inhibitor titer: 461 BU

Patient started on aPCC 100 units/kg Q12

Held cyclophosphamide

Initiated rituximab 375 mg/m^2 weekly x 4

Initiated prior auth/assistance for emicizumab

Patient Case: NC

```
Emicizumab FVIII Inhib Panel
Factor VIII Activity                221   High        %
      The factor VIII activity result, obtained using our standard
      one-stage clot aPTT-based reagent, shows marked elevation,
      while the chromogenic (bovine-based reagent) factor VIII
      activity is low, and this pattern is consistent with
      emicizumab therapy. The heat-inactivated, chromogenic
      Nijmegen Bethesda assay results in a titer of 10.7 BU/mL.
      Reference Range:
      57 - 163
FVIII Chromogenic                   <4  Alert       %
      ~~ALERT VALUES - Please notify physician! This result has been~~
      electronically transmitted and client receipt will be
      confirmed. SLJ 22aug2020 0610 MT.
      Reference Range:
      18 - 60y: 50 - 170
FVIII Chrom Nijmegen Bethesda
                                    10.7   High        CBU/mL
      This test was developed and its performance characteristics
      determined by LabCorp. It has not been cleared or approved
      by the Food and Drug Administration.
      Reference Range:
      <0.6
```

Hemostatic Treatments: Acute and Chronic

BPAs	rpFVIII	Emicizumab
• Used to treat acute bleed • Different agents are considered equally effective • Unable to monitor • Guided by clinical response • Risk of thrombosis especially in elderly and comorbid pts • Short dosing intervals	• Used to treat acute bleed • Able to monitor FVIII • Possible cross reactivity • Risk of induction of anti-porcine antibodies • High treatment costs	• Reduced risk of recurrent bleed • Unknown efficacy during surgery and interventions • Chromogenic assay with bovine FVIII needed for monitoring • Caution with aPCC for breakthrough bleed management

Knoebl P, et al. *Blood*. 2021;137:410-419; Tiede A, et al. *Haematologica*. 2020;105:1791-1801; Ellsworth P, et al. *Blood Advances*. 2020;4:6240-6249; Tiede A, et al. *J Thromb Haemost*. 2021; 19:637-644.

Summary

- EHL factor products decrease infusion burden and increase trough concentration compared to SHL products for prophylaxis
- Emicizumab offers a subcutaneous prophylactic option for hemophilia A patients with or without inhibitors
- Consider continuous infusions for severe bleed management or prolong treatment course to minimize peak/trough associated with intermittent bolus dosing
- Acute bleeds in acquired hemophilia should be managed with either bypassing agents or rpFVIII