Treatment of Bleeding Disorders

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Akron Children's Hospital

Objectives

- Understand basic diagnostics and phenotypes of von Willebrand disease, Hemophilia A and Hemophilia B
- Provide appropriate recommendations for bleed management
- Understand appropriate screening and treatment for iron deficiency and iron deficiency anemia

BLEEDING DISORDER BASICS

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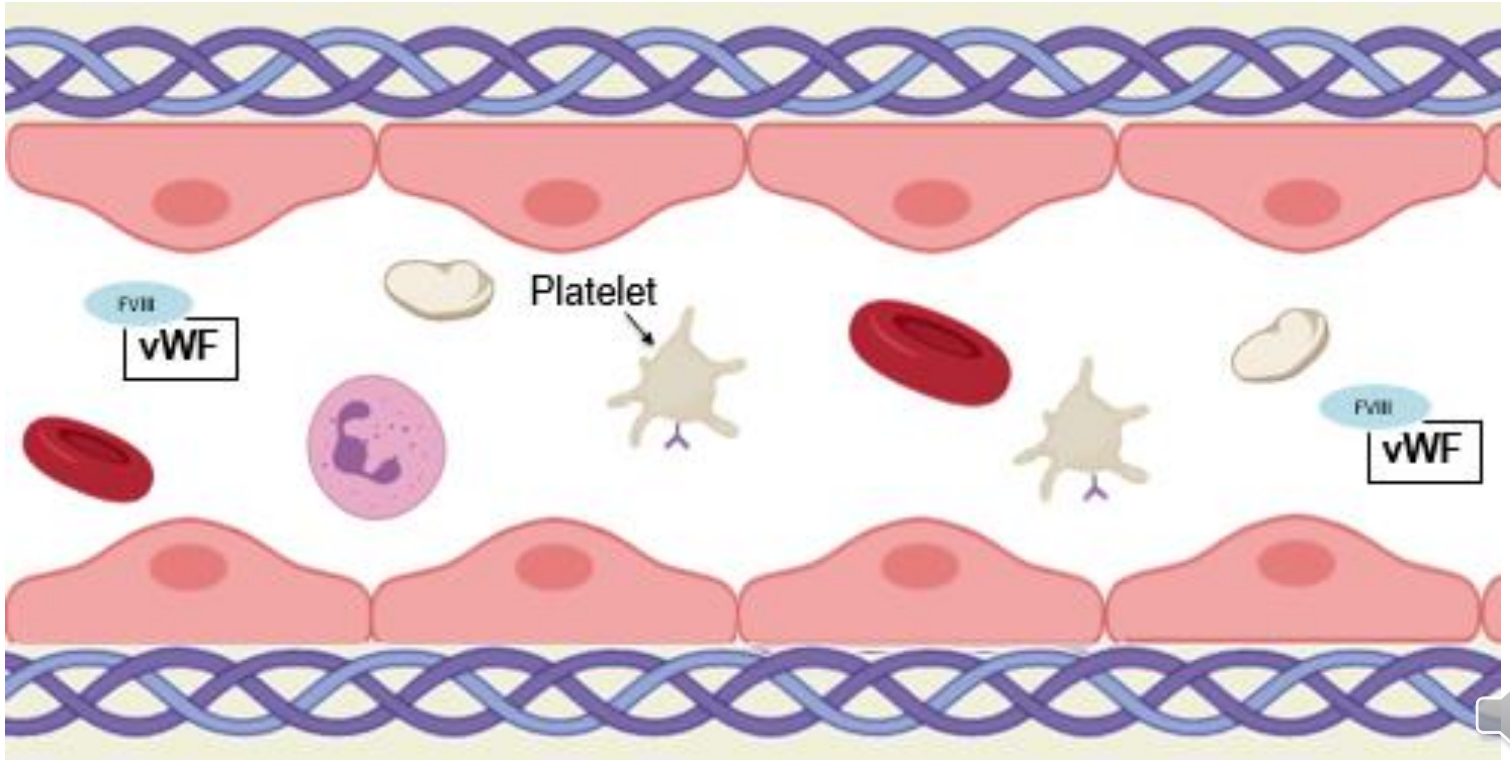
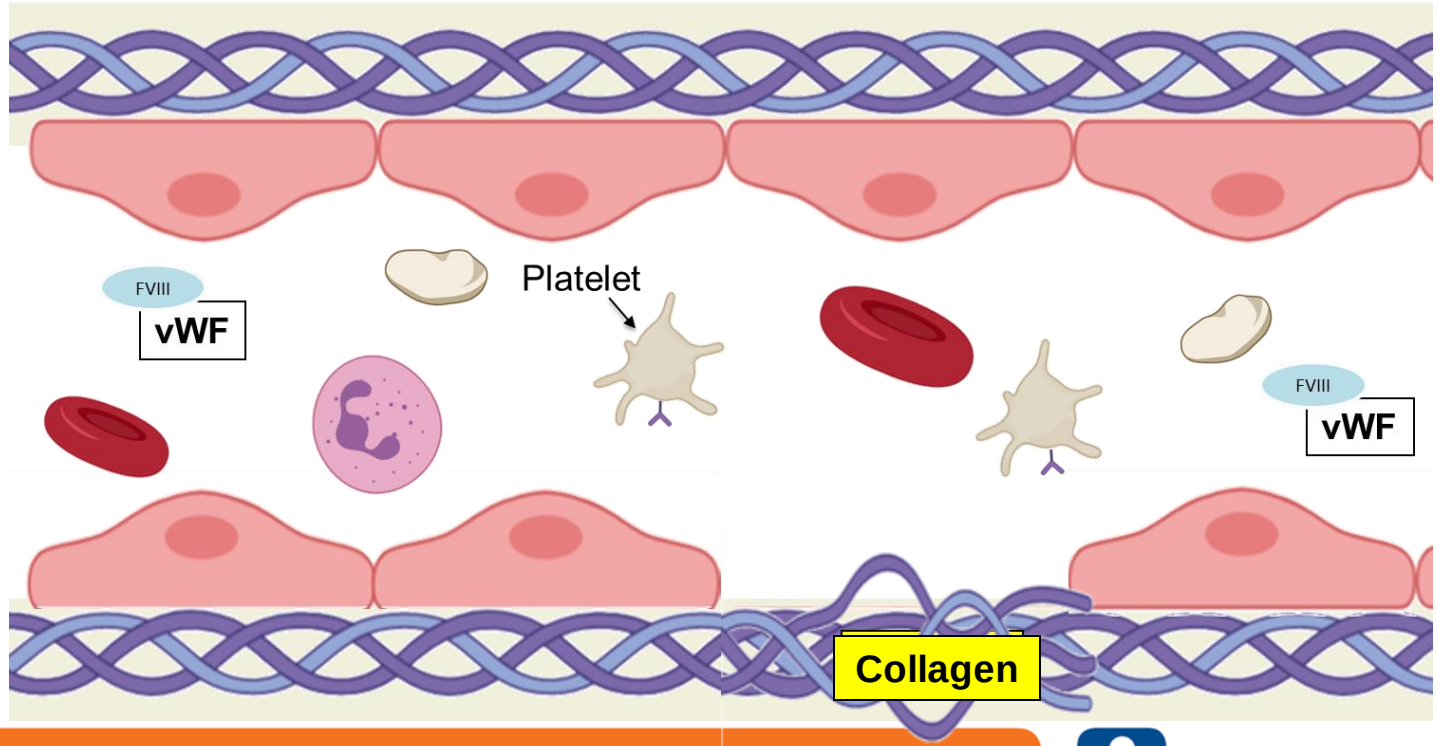
Hemostasis

1. Formation of platelet plug
2. Coagulation (formation of fibrin clot)

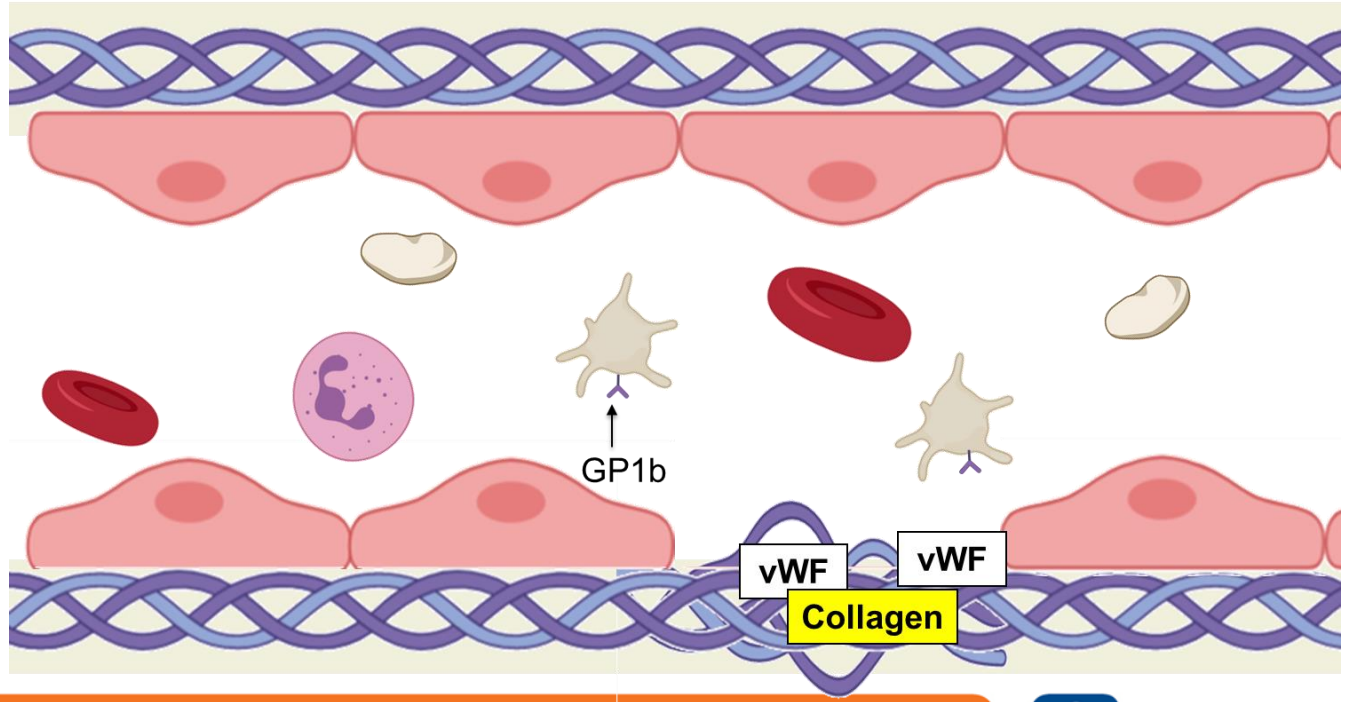
Formation of Platelet Plug



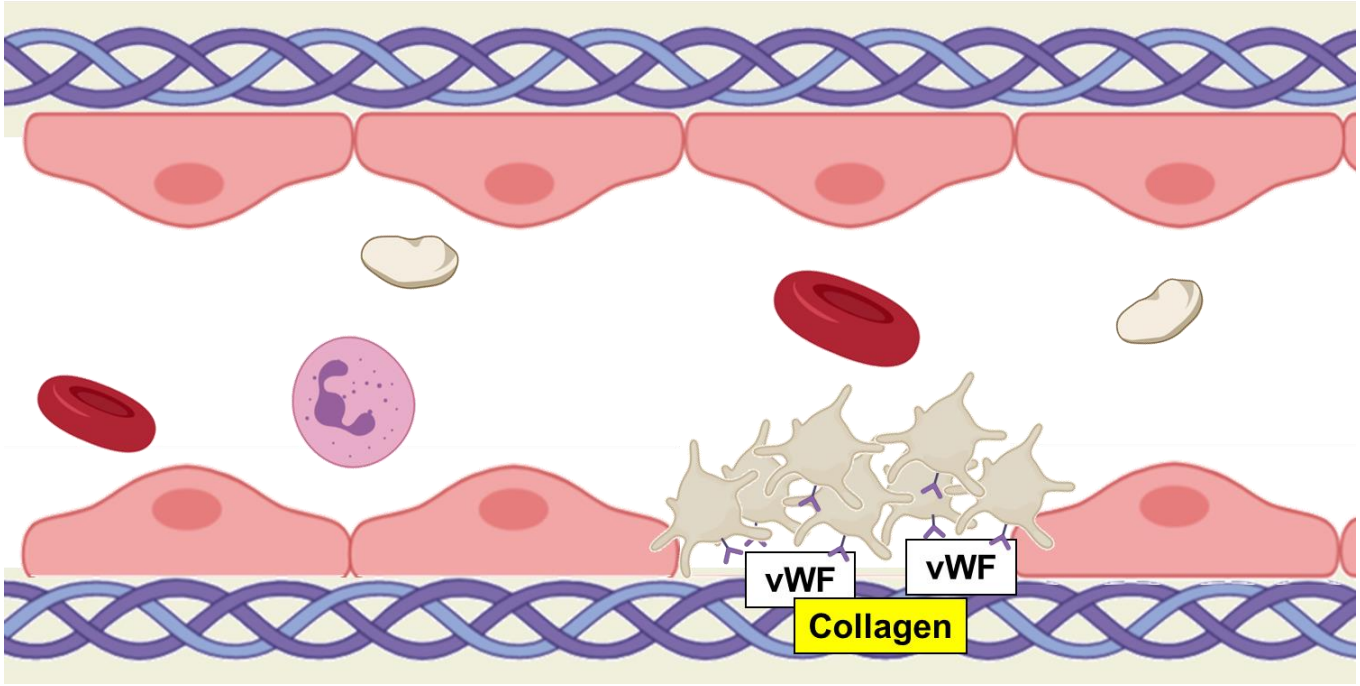
Extracellular matrix (ECM) is exposed…



...VWF binds to the ECM & captures platelets...



… leading to more platelet activation & recruitment and eventual formation of platelet plug



Disruption in Platelet Plug Formation

- Petechiae
- Bruising
- Mucocutaneous Bleeding
  - Nosebleeds
  - Gum bleeding
  - Heavy menstrual bleeding

Von Willebrand Disease

- Von Willebrand Factor:
  - Helps platelets stick
  - Carrier protein for Factor VIII (8)
- Autosomal dominant
- Primary hemostasis = Mucosal Bleeding
  - Oral Bleeding, Epistaxis, GI/GU bleeding
  - Menorrhagia!

Von Willebrand Disease

- Type I: quantitative defect
- Type II: qualitative defect
- Type III: undetectable vWF and low factor 8

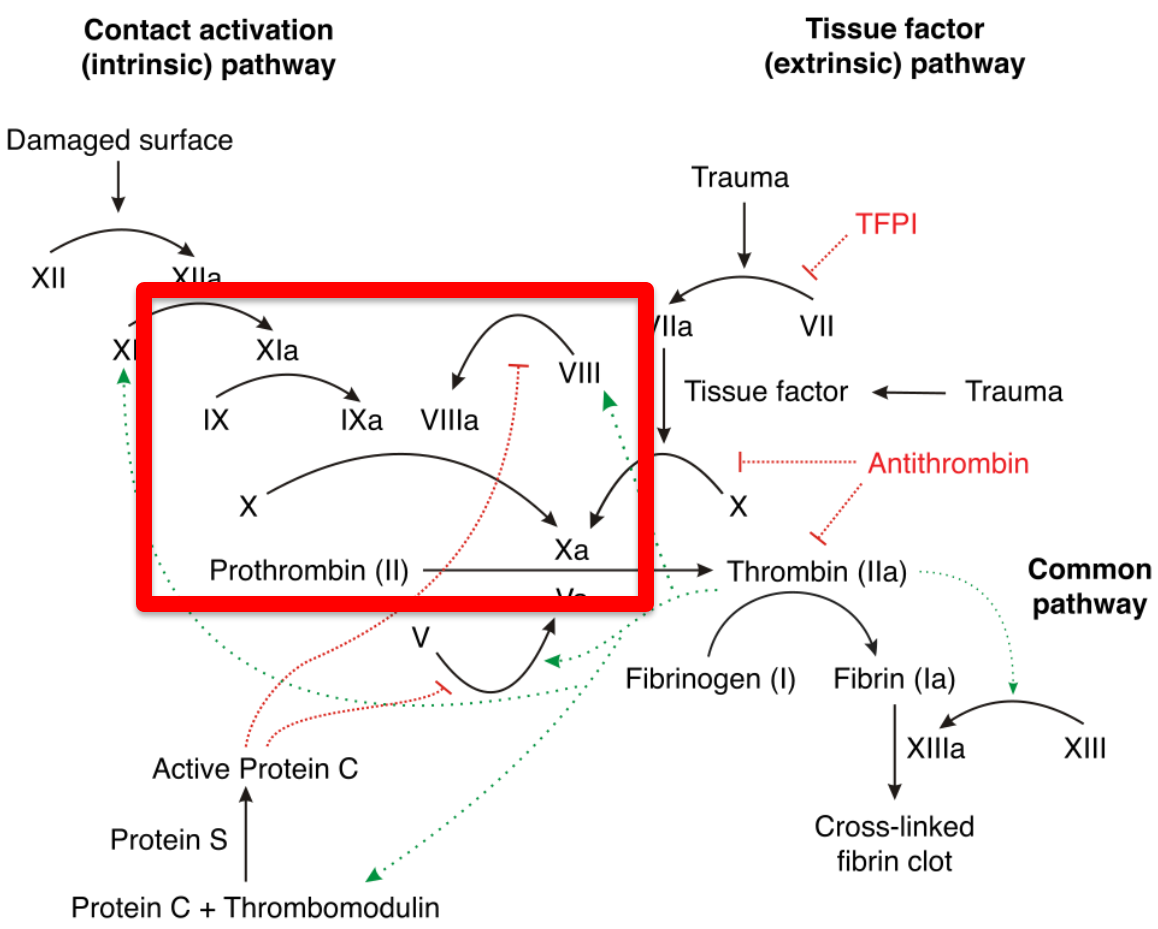
*Also think platelet quantitative and qualitative defects

Diagnostic Considerations

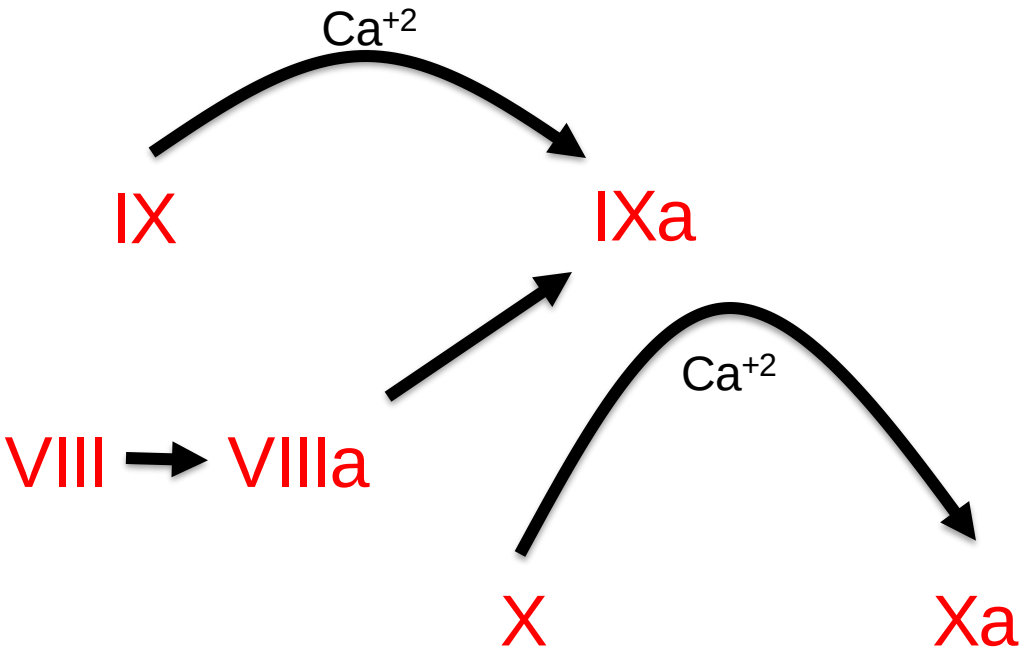
- Diagnostic levels are < 50
- Always obtain a factor VIII level
- Von Willebrand Factor is an acute phase reactant
  - Stress of blood draw may artificially increase value
  - Iron deficiency anemia may artificially increase value
  - Significant bleeding may artificially increase value

Hemostasis

1. Formation of platelet plug
2. Coagulation (formation of fibrin clot)


Contact activation
(intrinsic) pathway
Tissue factor
(extrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIII
VIIIa
X
Xa
Prothrombin (II)
Thrombin (IIa)
V
Active Protein C
Protein S
Protein C + Thrombomodulin
Trauma
TFPI
VII
VIIa
Tissue factor
Trauma
Antithrombin
X
Common
pathway
Fibrinogen (I)
Fibrin (Ia)
XIII
XIIIa
Cross-linked
fibrin clot

Coagulation Cascade



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Disruption in Coagulation

- "Deep Bleeds"
  - Hematomas
  - Hemarthroses
  - CNS bleeds

Hemophilia

- Hemophilia A = Factor VIII (8) Deficiency
- Hemophilia B = Factor IX (9) Deficiency
  - X-linked recessive disorders
    - Male patients
    - History on mom's side of family
- Factor Deficiency = Deep Bleeds

	Severe	Moderate	Mild
Factor Level	<1%	1-5%	5-40%
Age at Presentation*	Birth – 3 years	2-10 years	5- > 21 years
Presentation	• Family history (pre- or post-natal screening) • Neonatal bleeding (circ, heel sticks) • Bruising (< 1 year) • Vaccine-related bleed • Mucosal Bleed • Joint bleed	• Family history (pre- or post-natal screening) • Neonatal bleeding (less likely than severe) • Vaccine-related bleed • Mucosal bleed • Joint bleed	• Post-traumatic bleed • Post-surgical bleed
Risk for Inhibitor Development	~25% in FVIII ~5% in FIX	~1-2%	Very rare
Risk for Hemophilic Arthropathy	Universal without prophylaxis	Very common without prophylaxis	Rare

*Age is highly variable

Diagnostic Considerations in Hemophilia

- PTT may not be prolonged
- Factor VIII and IX levels are available

- Other factor deficiencies do exist: if high suspicion, refer to hematology

TREATMENT OF BLEEDING

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Treatment of Epistaxis

1. Gently blow out mucus/unstable clot through nose
2. Pinch soft part of nose below the bony part with thumb and finger (or nose clip) & hold x 10 minutes
   - Set a timer! Don't check until it is finished
3. Consider Afrin nasal spray BID for 3 days

Prevention of Epistaxis

- Place humidifier in child's bedroom
- Spray nasal saline to each nostril BID
- Place petroleum jelly/saline gel in both nostrils BID
  - At a minimum, do this before bed
  - If using NS spray, place gel after spray
- Avoid nose picking & keep fingernails short

R.I.C.E

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Von Willebrand Disease Management

- Antifibrinolytics
- DDAVP
- VWF Products: Humate-P, Advate, etc.
- Cryoprecipitate as a last resort

Antifibrinolytics = Clot Stabilization

- Aminocaproic acid
  - Available in liquid formulation
  - Dosing: 50mg/kg q6hr
    - Duration dependent on situation
- Tranexamic acid
  - Typically used for HMB (though uses are expanding)
  - Dosing: 1300mg TID for max of 5 days

DDAVP = Increased VWF Release

- IN, IV formulations
  - IN has short shelf-life (~5-6 months)
- Requires fluid restriction due to risk of hyponatremia
  - Younger patients, higher risk of seizures
- Recommend DDAVP challenge before use
- Limited efficacy in type 2 VWD
  - Endogenous VWF is dysfunctional

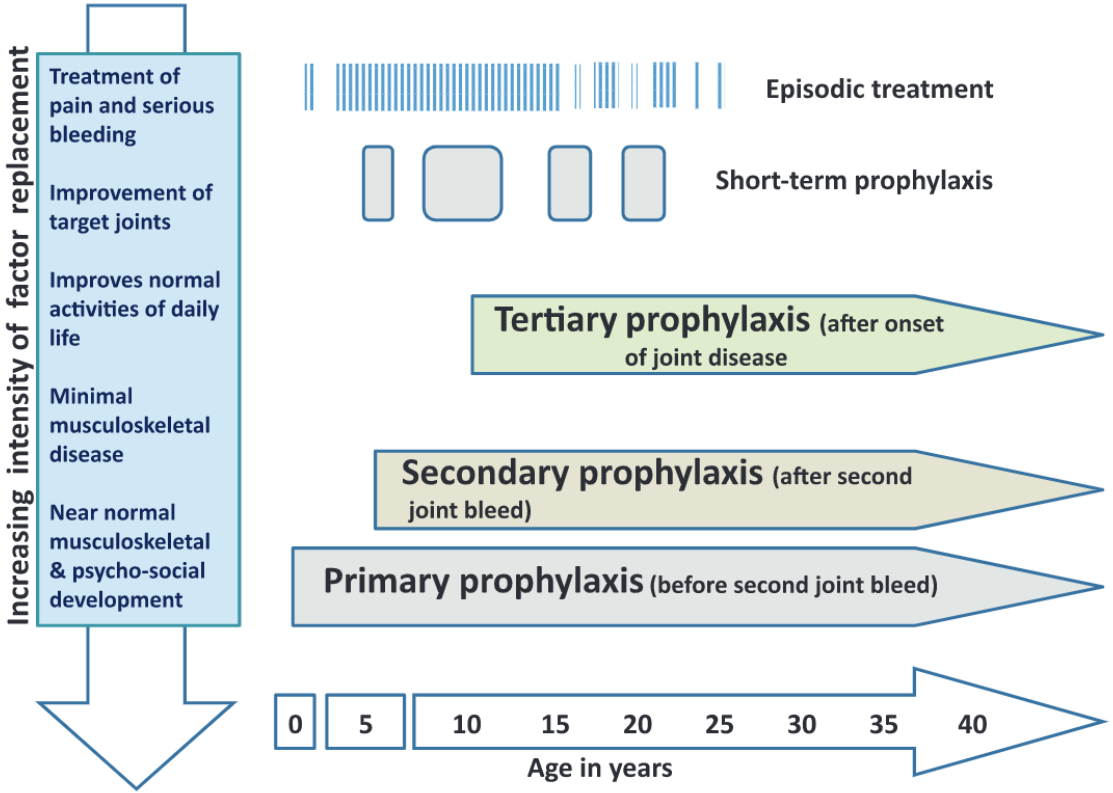
Factor Replacement

- Typically used for major surgeries, when fluid restriction is not possible, when DDAVP challenge has not occurred OR when patient is unresponsive to DDAVP
- Examples: Humate-P, Alphanate, Vonvendi

- Cryoprecipitate as last resort

Hemophilia A/B Management

- Antifibrinolytics
- Factor Replacement
- DDAVP
- Non-Factor Products



Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A; Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. Haemophilia. 2013 Jan;19(1):e1-47. doi: 10.1111/j.1365-2516.2012.02909.x. Epub 2012 Jul 6. PMID: 22776238.

Goal is to Prevent Chronic Arthropathy

- Target Joint: multiple bleeds in same joint
  - 3 bleeds in 6 months
  - 4 bleeds in 1 year

*Arthropathy can develop after only 1 bleed

Hemophilia A/B Management

- Factor replacement
  - Prophylaxis
  - On-Demand
  - Various factors exist
    - Standard and extended half-life
- Give factor ASAP in setting of injury

On-Demand Therapy

- In general: give dose ASAP (prior to imaging)
  - Hemophilia A:
    - Major bleed: 50u/kg FVIII
    - Minor bleed: 25u/kg FVIII
  - Hemophilia B:
    - Major bleed: 120u/kg FIX
    - Minor bleed: 60u/kg FIX

DDAVP in Hemophilia

- DDAVP increases FVIII levels by increasing vWF
  - Not indicated in FIX deficiency
  - Only works with mild hemophilia A patients
  - Typically only used for mucocutaneous bleeding and minor procedures
  - Some mild mutations are non-responsive (require challenge)

Factor Naming Tips

Hemophilia A

- Advate
- Alphanate
- Eloctate
- Recombinate
- Adynovate
- Kogenate

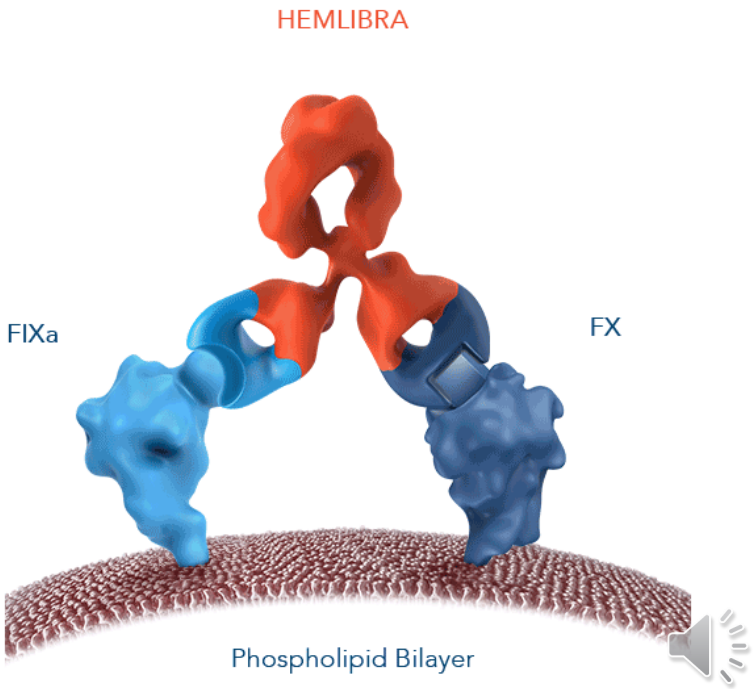
Hemophilia B

- Benefix
- Alprolix
- Rixubis
- Ixinity
- Mononine
- Rebinyn

Emicizumab

- Bispecific monoclonal antibody that bridges factor IXa and X

- **Functions like FVIII!**



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Emicizumab

- Functions like FVIII, but is NOT factor VIII

- Normal FVIII level is inaccurate
  - Requires chromogenic assay
  - Effect on these assays persists for ~6 months following last dose

TREATMENT OF CO-MORBIDITIES

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Iron Deficiency and Anemia Screening

- CBC
  - ↓ hemoglobin
  - ↓ MCV
  - Platelets can be low, normal or high
- Iron Studies
  - ↓ Ferritin:
    - Child: goal ~15
    - Adolescent: goal ~30
    - Acute phase reactant
  - ↑ TIBC
  - Serum iron ≈ glucose

Iron Deficiency & Anemia Treatment

- Improve iron-intake in diet
  - Watch for excessive cow's milk intake
- Control bleeding
  - HMB: OCPs, IUD, antifibrinolytics

Iron Deficiency & Anemia Treatment

- Oral iron supplementation:
  - Children: 3-6mg/kg/day dosed once daily
  - Adolescents: 325mg (65mg elemental iron) daily
  - Ferrous sulfate is best formulation to use
    - Novaferrum tastes slightly better
  - Side effects: abdominal pain, nausea, constipation

Iron Deficiency and Anemia Treatment

- IV iron formulations are available
  - Dosing regimen varies on formulary agents
  - Typically requires multiple infusions
  - Side effects: hyponatremia (with Injectafer), flu-like symptoms, iron tattoo
- Can be given through ACH infusion center

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THANK YOU!

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