Congenital Disorders of Coagulation:

Approach to a Comprehensive Bleeding History, von Willebrand Disease and Hemophilia

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Canadian Blood Services

Laboratory Medicine & Pathobiology
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TRANSFUSION MEDICINE 101
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Disclosures

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Mitigating Potential Bias:

- Specific brand names may be used as examples of blood product or drug classes without preference for any manufacturer.

Learning Objectives

- Review the basic principles of hemostasis
- Identify sentinel features of a significant bleeding history
- List appropriate coagulation screening tests for investigation of a suspected bleeding disorder
- Describe the pathophysiology and key treatment principles of the following congenital bleeding disorders:
  - Von Willebrand Disease
  - Hemophilia A and B

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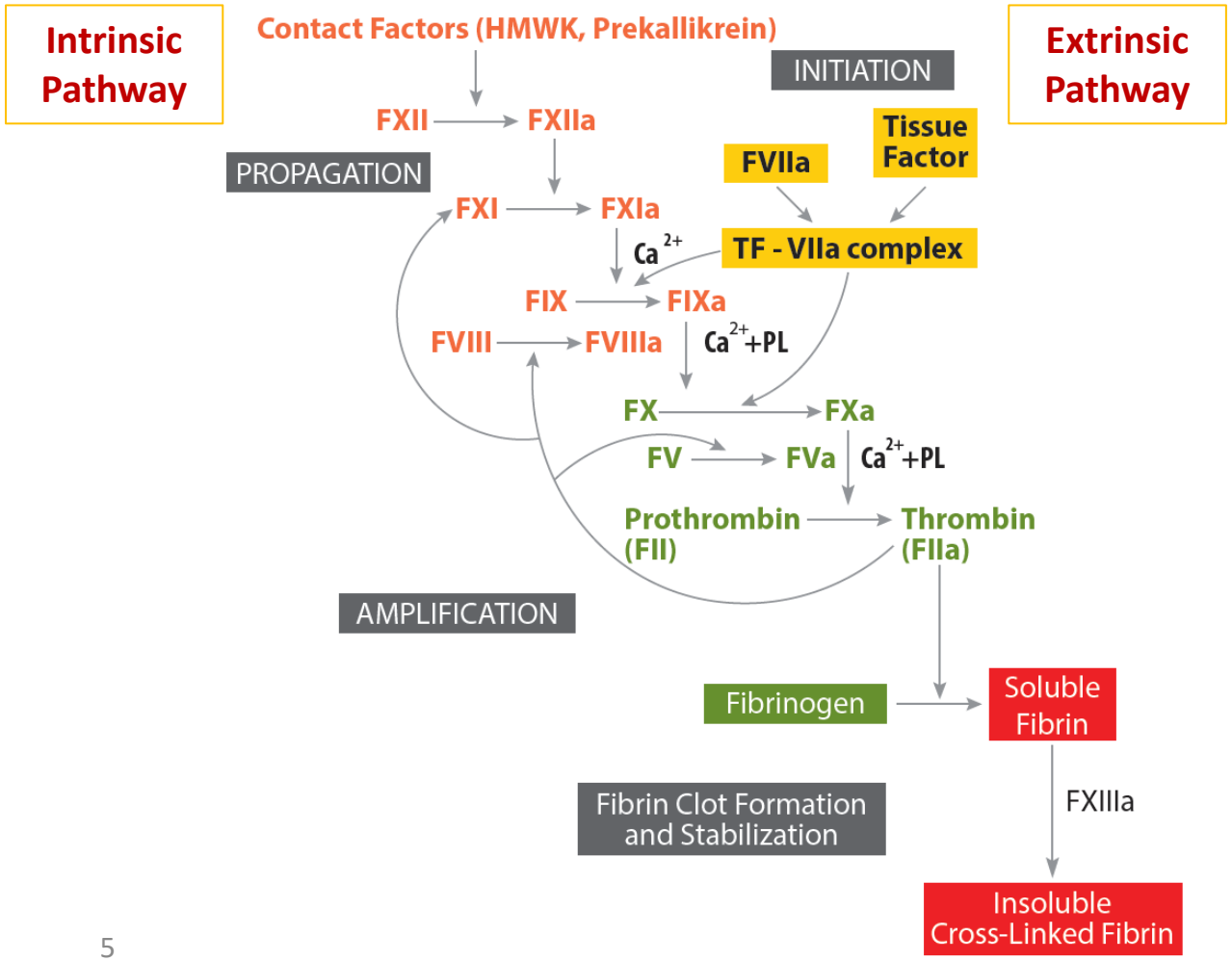
Classic Coagulation Cascade

VIDEO: The Coagulation Cascade Explained



- Hemostasis is complex
- Classically taught linear 'coagulation cascade' is *not* reflective of true physiology – it's more dynamic with simultaneous concurrent processes occurring
  - Significant focus on secondary hemostasis – we cannot ignore primary hemostasis!

Hemostasis Simplified

Primary Hemostasis	Secondary Hemostasis	Clot Stabilization	Fibrinolysis

Trauma to the endothelium = TRIGGER

Platelets 1st on the scene

VWF glues platelets to the endothelium

Coagulation factors assemble to make a clot

Additional factors stabilize clot

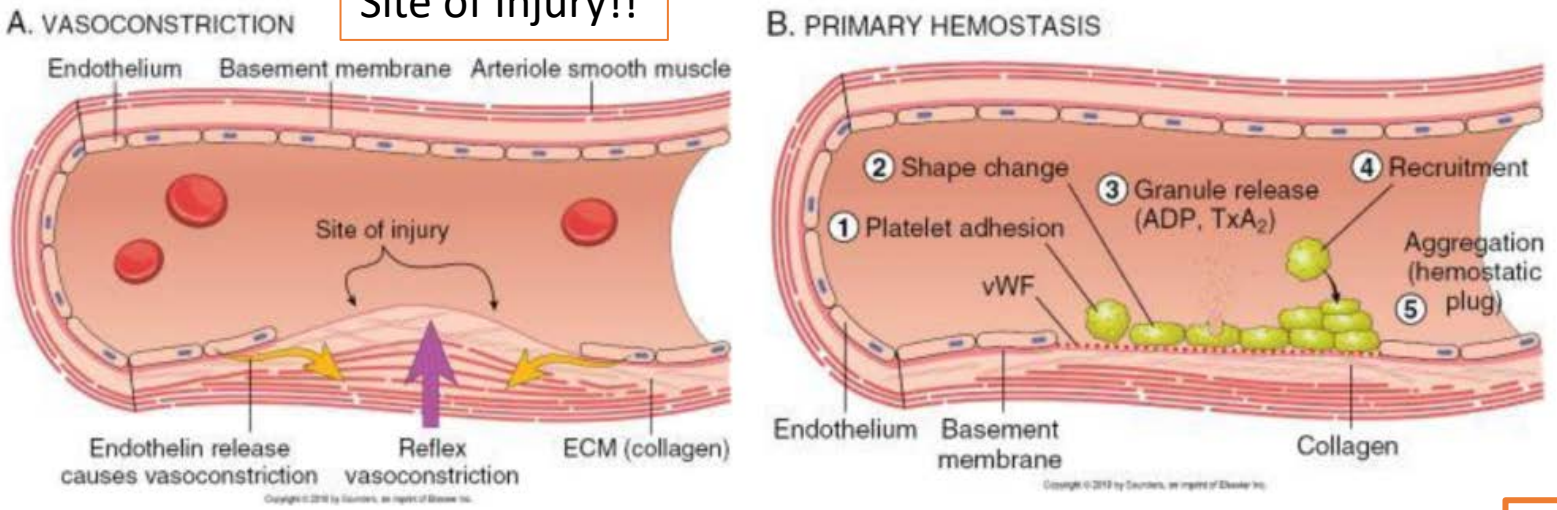
Fibrinolytic system breaks down clot

Slide credit: Dr. M. Sholzberg

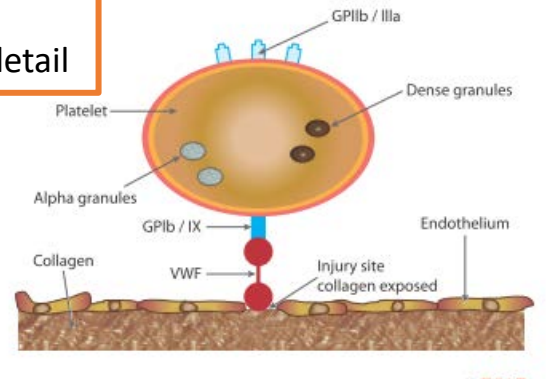
Hemostasis: Primary

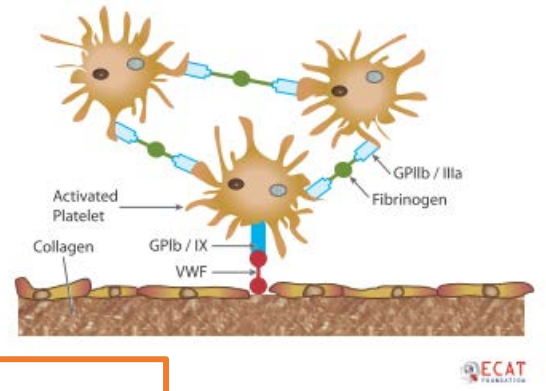
VASOCONSTRICTION AND PLATELET PLUG

Site of Injury!!



Platelet adhesion detail





Platelet aggregation detail

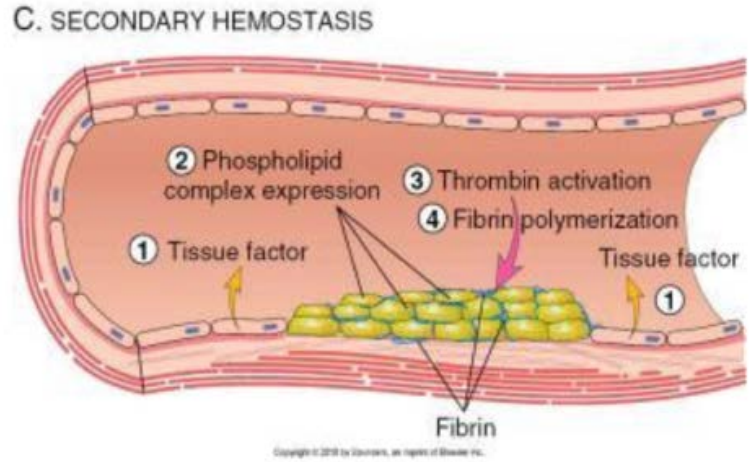
VIDEO: Platelet Activation and Factors for Clot Formation

Robbins Basic Pathology, 10th Ed. Chapter 4, Figure 4.5. 2018.
Bloody Easy Coagulation Simplified 2nd Ed. February 2019
http://transfusionontario.org/en/documents/?cat=bloody_easy

Hemostasis: Secondary

VIDEO: Coagulation Cascade – Physiology of Hemostasis

ACTIVATION OF COAGULATION FACTORS AND THROMBIN GENERATION



Platelets provide the phospholipid (PL) surface for coagulation factor activation

Initiation of coagulation: ("Extrinsic Pathway")
- Tissue factor **(TF)** is released from injured cells
- TF + FVIIa = **TF/FVIIa** complex activates some FIX and X → Xa tp generate some **thrombin (FIIa)**

Amplification phase:
- Thrombin leads to FXI → XIa, FV → FVa, FVIII → FVIIIa and activates more platelets

Propagation phase: ("Intrinsic Pathway")
- TF/FVIIa complex activates FIX → FIXa to make more **FXa**
- Factor Xa + Va + Calcium + PL platelets surface = conversion of prothrombin (FII) → **A LOT of thrombin (FIIa)**

Fibrin clot formation and stabilization:
- Thrombin converts fibrinogen → fibrin monomers
- Thrombin activates **FXIII to cross-link fibrin monomers** to stabilize the clot

Robbins Basic Pathology, 10th Ed. Chapter 4, Figure 4.5. 2018.
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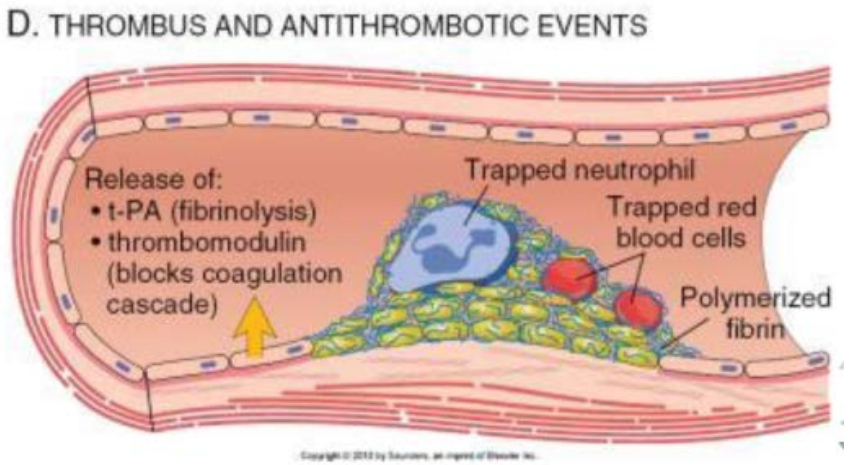
Inhibition of Coagulation

INHIBITION OF THROMBIN GENERATION AND FIBRINOLYSIS



Inhibition of thrombin (IIa) generation

- Thrombin binds to thrombomodulin (on cell membrane) and:
  - becomes inactive in coagulation
  - activates Protein C → Activated Protein C (APC)
- APC combines with Protein S = inhibits FVa and VIIIa
- Antithrombin (endogenous anticoagulant) inhibits thrombin, FXa and other activated factors

Fibrinolysis

- Tissue plasminogen activator (t-PA) converts plasminogen → plasmin, which breaks down cross-linked fibrin to fibrin degradation products (the smallest is the D-dimer)

Robbins Basic Pathology, 10th Ed. Chapter 4, Figure 4.5. 2018.
Bloody Easy Coagulation Simplified 2nd Ed. February 2019
http://transfusionontario.org/en/documents/?cat=bloody_easy

Causes of Bleeding

**Will be discussed today*

Congenital*	Acquired
von Willebrand Disease (vWD)* - Type 1 = quantitative defect - Type 2 = qualitative defect - Type 3 = absence	**Medications** - Antiplatelet agents (COX or P2Y12 inhibitors) - Anticoagulants (heparin, warfarin, DOACs) - Antidepressants (serotonin inhibitors) - Anticonvulsants
Platelet function disorders	Renal disease (uremia affects platelet function)
Factor deficiencies - Factor VIII = Hemophilia A* - Factor IX = Hemophilia B* - Other factor deficiencies	Liver disease - Reduced coagulation factors (except FVIII) - Thrombocytopenia due to decreased TPO
Hypo/dysfibrinogenemia	Immune thrombocytopenia (ITP)
Collagen vascular disorders	Bone marrow disorders (ex. MDS, ET)
	Acquired FVIII or vWF deficiencies

Learning Objectives

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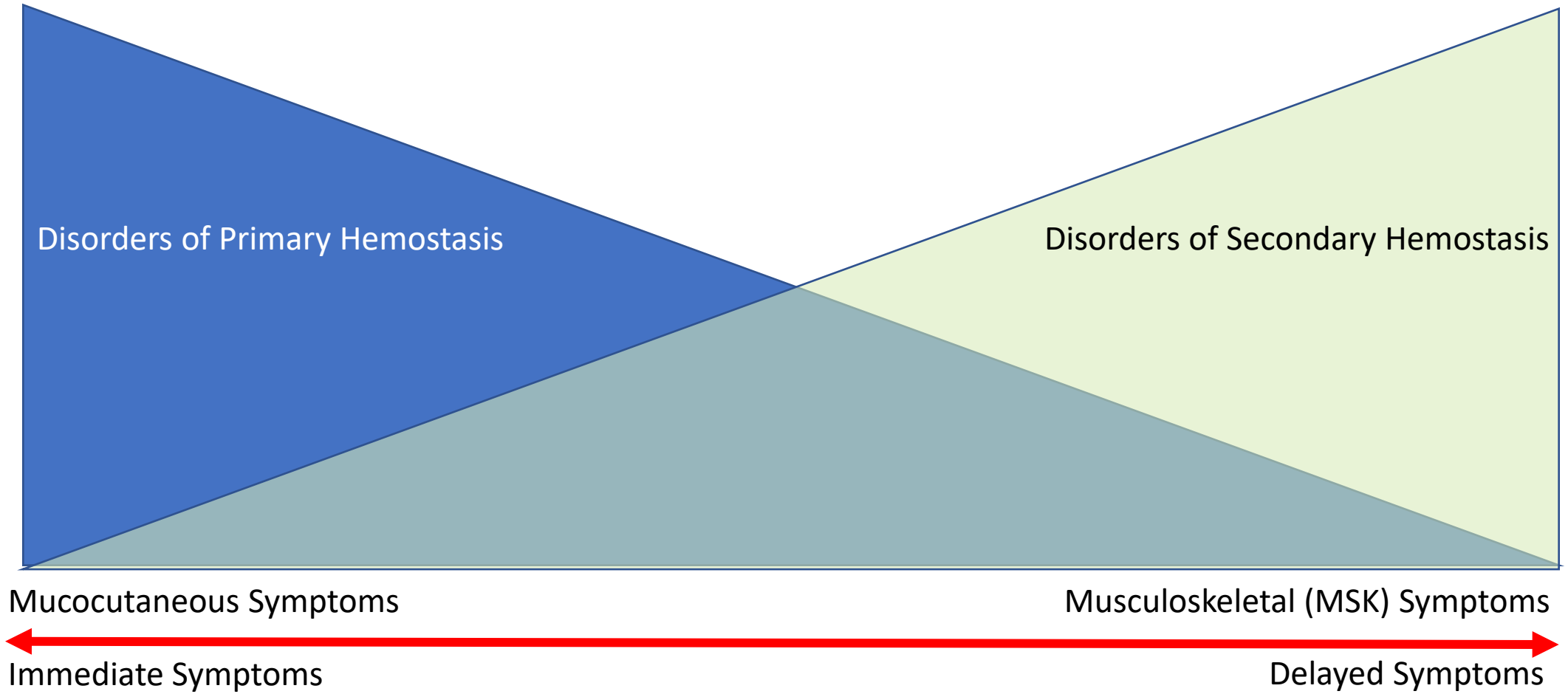
Clinical Case Question 1

- A 16-year-old man presents to the ER for assessment with a swollen, progressively painful right knee following a sports-related injury 3 days ago. Range of motion is limited, and he is now unable to weight-bear. Vital signs are normal. Point-of-care ultrasound suggests presence of blood within the joint (hemarthrosis). He has no known hematologic diagnosis.
- What is the next best step in the care of this gentleman?
    a) Check a CBC, PT/INR and PTT only
    b) Take a more comprehensive history
    c) Request an MRI of the knee to more fully assess the injury
    d) Arrange for outpatient follow-up with Orthopedics
    e) Discharge home with instructions of rest and ice to the knee

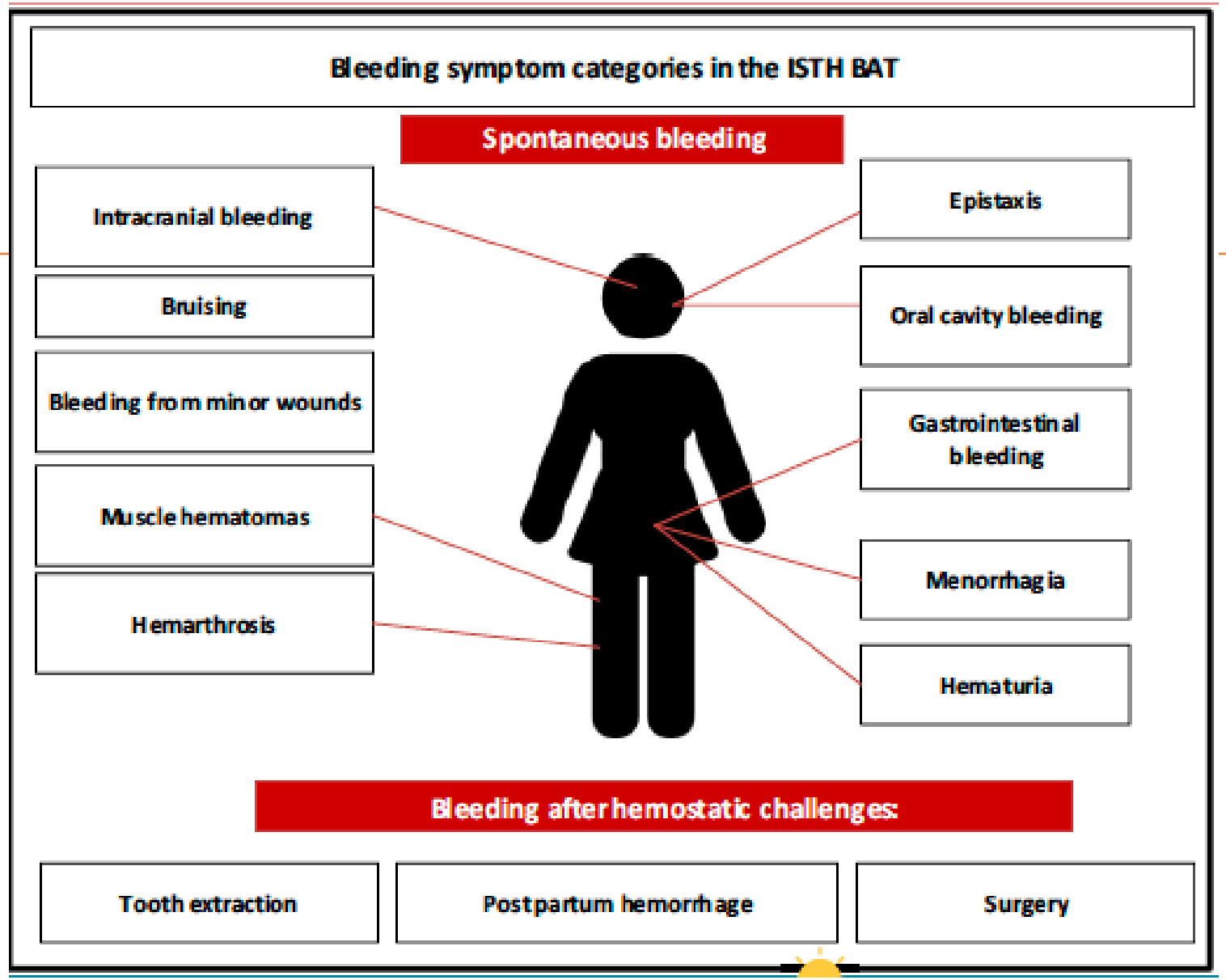
General Bleeding Patterns: History



Slide credit: Dr. K. Brose

Patient History: The Best 'Test' for a Bleeding Disorder

- Standardized Bleeding Assessment Tool (BAT) Questionnaires have been developed for use as a part of assessment for an inherited bleeding disorder (esp. vWD and platelet function defects)
  - Administered by trained Healthcare Professionals; examples:
    - Pediatric Bleeding Questionnaire (PBQ)
    - Vincenza BAT
    - MCMDM-1 VWD Bleeding Questionnaire
    - International Society for Thrombosis and Hemostasis (ISTH)-BAT
  - Patient Administered
    - Self-BAT
- No standardized BAT has been validated for use in the pre-operative setting



Elbaz, C, Sholzberg, M. An illustrated review of bleeding assessment tools and common coagulation tests. *Res Pract Thromb Haemost*. 2020; 4: 761– 773. https://doi.org/10.1002/rth2.12339

Bleeding Assessment Tools (BAT)

A bit about BATs...

The patient history is the most important tool in determining the pre-test probability of a bleeding disorder. Quantitative bleeding assessment tools (BATs) have thus been developed to standardize the bleeding history and guide appropriate testing to investigate bleeding disorders. Bleeding scores are based on symptom frequency and severity (i.e. need for surgical or medical attention).

	Vicenza BAT	Condensed MCMDM-1 VWD	PBQ	ISTH BAT	Self BAT
Sensitivity of a normal score to ***rule out*** the diagnosis of VWD (true positives/all positive tests)	69%	100%	83%	64%	78%
Specificity of an abnormal score to ***rule in*** the diagnosis of VWD (true negatives/all negative tests)	98%	87%	79%	99%	23%

Elbaz, C, Sholzberg, M. An illustrated review of bleeding assessment tools and common coagulation tests. *Res Pract Thromb Haemost*. 2020; 4: 761– 773. https://doi.org/10.1002/rth2.12339

Table 1: Condensed MCMDM-1VWD Bleeding Questionnaire

	-1	0	1	2	3	4
Epistaxis	–	No or trivial (≤ 5 per year)	> 5 per year or more than 10'	Consultation only	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Bruising	–	No or trivial (≤ 1 cm)	> 1 cm and no trauma	Consultation only	–	–
Bleeding from minor wounds	–	No or trivial (≤ 5 per year)	> 5 per year or more than 5'	Consultation only	Surgical hemostasis	Blood transfusion or replacement therapy or desmopressin
Oral cavity	–	No	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Gastrointestinal bleeding	–	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	–
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing or packing	Blood transfusion or replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Menorrhagia	–	No	Consultation only	Antifibrinolytics, oral contraceptive pill use	Dilation & curettage, iron therapy, ablation	Blood transfusion or replacement therapy or desmopressin or hysterectomy
Postpartum hemorrhage	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Consultation only	Dilation & curettage, iron therapy, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin	Hysterectomy
Muscle hematomas	–	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	–	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system bleeding	–	Never	–	–	Subdural, any intervention	Intracerebral, any intervention

The bleeding score is determined by scoring the worst episode for each symptom (each row) and then summing all of the rows together. "Consultation only" refers to a patient consulting a medical professional (doctor, nurse, dentist) because of a symptom but no treatment being given.

Bowman M et al. Generation and Validation of the Condensed MCMDM-1VWD Bleeding Questionnaire. J Thromb Haemost 2008; 6: 2062-6.

For VWD, a bleeding score ≥ 4 has a sensitivity = 100%, specificity = 87%, positive predictive value = 0.20, negative predictive value = 1.00.

More info at www.path.queensu.ca/labs/james/bq.htm

Condensed MCMDM-1 BAT:

- Summative scoring system
- Possible range -3 to +45
- **Abnormal (positive) score ≥ 4**

Prospectively Investigated Bleeders:

- Primary Care Setting n =217
- Bleeding Score ≥ 4
  - Sensitivity = 100%
  - Specificity = 87%
  - PPV = 0.20; NPV 1.0

Overall BAT limitations:

- Administration by trained professional
- Younger patients with fewer bleeding challenges, males (no menses) = false negative score risk
- Not dynamic – static score at diagnosis

Patient Assessment: Practical Approach

- **History – Questions to ask:**
  - *Personal bleeding disorder diagnosis & Hematology involvement
  - Onset of bleeding – after dental extraction or surgery, including acute or delayed onset (within 1 week)
  - Spontaneous or traumatic bleeding that led to MD visit and need for intervention
  - Location and pattern – mucocutaneous; MSK (deep muscle/joint)
  - History of anemia or iron deficiency requiring treatment
  - Previous blood transfusion or coagulation factor therapy
  - Family history

Specific Age Considerations and Bleeding History

Age	Site and Pattern of Bleeding
Neonatal	Heel Poke / umbilical cord bleeding Post-circumcision bleeding CNS bleeds (birth trauma)
Infant	Frenulum bleeding (in mouth from feeding) Tongue / dental as teething Soft tissue / forehead as starting to walk Immunization related hematoma
Children & Adults	Hemarthrosis Muscle or soft tissue bleeds Excess bleeding from loss of primary teeth /tooth eruption Girls/Women: Menarche/heavy menstrual bleeding

Slide credit: Dr. K. Brose

Patient Assessment: Practical Approach

- **Physical Exam – What to look for:**
  - Vital signs → anemia related concerns
  - Skin – colour (pallor, jaundice), size and location of bruising, petechiae, hematomas, telangiectasia
  - Oral mucosa – gingival oozing, petechiae to the mouth
  - Joints – effusion, range of motion, hypermobility

*If there is **any** clinical concern of a bleeding disorder on history or physical exam, delay the case and refer to **Hematology** for a comprehensive assessment!*

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Routine Coagulation Screening Tests

- **PT/INR, aPTT**
- Collection required in a “blue top tube”
- Tubes designed to draw precise volume of blood to achieve 9:1 ratio of blood to *Na Citrate*
- A properly filled tube is *really* important → under or over filled tube = false results!
  - *Na Citrate* chelates calcium, prevents fibrin formation *in vitro*
- Interpretation of *any* test requires clinical correlation

Routine Coagulation Screening Tests: Design and Intent Matters

- Prothrombin Time (PT)/INR
  - Designed to assist with titration of warfarin
  - Standardized reporting (INR) to facilitate cross-lab communication of the degree of warfarin-related anticoagulation for ambulatory patients
- Activated Partial Thromboplastin Time (aPTT)
  - Developed to assist in the diagnosis of hemophilias
  - Designed to be normal with Factor VIII or Factor IX greater than 40-50%

- *Inappropriately* re-purposed to screen for coagulopathies in low-risk patients in the pre-op setting!

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Congenital (Inherited) Bleeding Disorders

Deficient factor (disease)	Incidence of the deficiency*	Heritability	Localization of the abnormal gene (chromosome)	Replacement preparation(s)
von Willebrand Factor (von Willebrand disease)	1:5000	Autosomal, dominant**	12	Plasma-derived concentrates; purified recombinant factor concentrate
Factor VIII (hemophilia A)	1:10,000	X-linked, recessive	X	Plasma-derived concentrates; purified recombinant factor concentrates
Factor IX (hemophilia B)	1:60,000	X-linked, recessive	X	Plasma-derived concentrates; purified recombinant factor concentrates
Factor VII	1:500,000	Autosomal, recessive	13	Plasma-derived concentrates, purified recombinant factor concentrates
Factor XI	1:1,000,000	Autosomal, recessive	4	Fresh frozen plasma+ Plasma-derived concentrate#
Factor XIII	1:1,000,000	Autosomal, recessive	6 (sub. A) 1 (sub. B)	Fresh frozen plasma+ Plasma-derived concentrate# Purified recombinant factor concentrates##
Factor X	1:1,000,000	Autosomal, recessive	13	Plasma-derived prothrombin complex concentrates
Fibrinogen (afibrinogenemia)	1:1,000,000	Autosomal, recessive	4	Plasma-derived concentrates
Factor V (parahemophilia)	1:1,000,000	Autosomal, recessive	1	Fresh frozen plasma+
Factor II	1:2,000,000	Autosomal, recessive	11	Plasma-derived prothrombin complex

Note: Incidence stated reflects any severity of disorder

Haematologica. 2013;98:1495-98

Hemostasis Simplified

Primary Hemostasis	Secondary Hemostasis	Clot Stabilization	Fibrinolysis
Trauma to the endothelium = TRIGGER	Platelets 1st on the scene VWF glues platelets to the endothelium	Coagulation factors assemble to make a clot	Additional factors stabilize clot	Fibrinolytic system breaks down clot

vWD

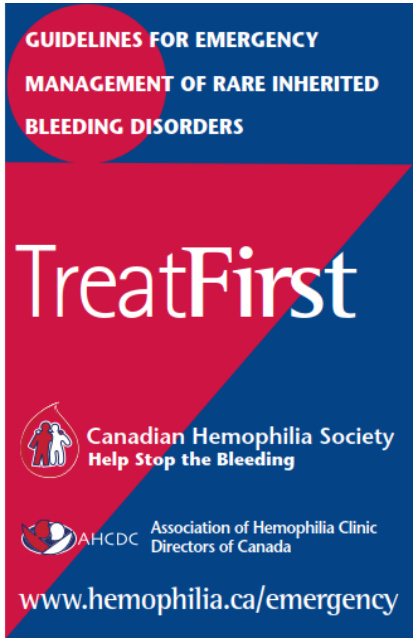
Hemophilia

Slide credit: Dr. M. Sholzberg

Treatment Plans: Patients with Bleeding Disorders

- Patients followed by a comprehensive bleeding disorder care program are counselled to share their diagnosis with healthcare providers and present their Factor First or Treat First Card

Factor Deficiencies



Platelet Function Disorders

MAJOR BLEEDS

- Head (intracranial), ocular and neck (throat)
- Spinal cord
- Intra-abdominal
- Iliopsoas muscle
- Massive vaginal hemorrhage
- Gastrointestinal

MODERATE/MINOR BLEEDS

- Deep lacerations
- Nose (epistaxis)
- Oral (especially tongue)
- Joints (hemarthroses)
- Muscle compartments
- Menorrhagia

TREATMENT FOR MAJOR BLEEDS

Hemophilia A (all severities)
One (1) unit per kilogram of recombinant factor VIII concentrate generally provides a rise of 2% FVIII activity level.
Standard dosing for major bleeding of recombinant FVIII concentrate is 40-60 units/kg.
If known desmopressin responder (see reverse side of card): desmopressin 0.3 mcg/kg SC/IV.

Hemophilia B (all severities)
One (1) unit per kilogram of recombinant factor IX concentrate generally provides a rise of 0.6-1.0% FIX activity level.
Standard dosing for major bleeding of recombinant FIX concentrate is 80-140 unit/kg.
Refer to product monograph for dosing instructions specific to factor replacement product.

It is critical to raise the factor level to 80-100% urgently for all life or limb-threatening bleeds.

Von Willebrand disease
A von Willebrand factor concentrate containing factor VIII such as **Humate-P** 60-80 Ristocetin cofactor units/kg or **Wilate** 40-60 units/kg.
Desmopressin could also be considered for some patients if an adequate response is documented.

TREATMENT FOR MODERATE/ MINOR BLEEDS

Hemophilia A (all severities)
One (1) unit per kilogram of recombinant factor VIII concentrate generally provides a rise of 2% FVIII activity level.
Standard dosing for moderate/minor bleeding of recombinant FVIII concentrate is 20-40 units/kg.
If known desmopressin responder (see reverse side of card): desmopressin 0.3 mcg/kg SC/IV.

Hemophilia B (all severities)
One (1) unit per kilogram of recombinant factor IX concentrate generally provides a rise of 0.6-1.0% FIX activity level.
Standard dosing for moderate/minor bleeding of recombinant FIX concentrate is 40-60 units/kg.
Refer to product monograph for dosing instructions specific to factor replacement product.

Von Willebrand disease
Desmopressin SC/IV. Standard dosing is 0.3 micrograms per kg.
A von Willebrand factor concentrate containing factor VIII such as **Humate-P** 40-60 Ristocetin cofactor units/kg or **Wilate** 20-40 units/kg.
Please note: Desmopressin is NOT a suitable medication for VWD Type 2B or Type 3 patients.

GUIDELINES FOR EMERGENCY MANAGEMENT OF HEMOPHILIA AND VON WILLEBRAND DISEASE

FactorFirst

Canadian Hemophilia Society
Help Stop the Bleeding

AHCDC Association of Hemophilia Clinic Directors of Canada

Dosages are patient specific – these are general guidelines only. Refer to product monograph for dosing instructions. Round doses up to the nearest vial. If the products listed are not available, please call the treatment centre team for advice around suitable alternatives.

www.hemophilia.ca/emergency

Remember ...

FactorFirst

TREATMENT should be given in a timely manner to stop bleeding, improve outcomes and speed up recovery. Contact the care team below for treatment recommendations and support in the management of this patient.

Bleeding disorder treatment centre

Hospital:
Physician(s):
Nurse:
Phone:
After hours contact:
E-mail:

06-2022

PROMPT TRIAGE AND ASSESSMENT

- Determine the location and severity of the bleed.
- Strongly consider factor replacement **PRIOR** to diagnostic procedures or consultation/detailed examination. Early treatment can mitigate further bleeding concerns or complications.
- Recognize that bleeding in the intracranial and intra-abdominal bleeding may be occult and inciting injury may have happened in days prior to presentation.
- With invasive procedures (i.e. arterial punctures, intubation) clotting factors should be normalized with replacement therapy.
- Please note aPTT will likely be shortened if patient is on emicizumab (Hemlibra) and is expected. If coagulation tests are needed, please consult hematology for advice.
- Contact the patient's bleeding disorder treatment centre where a hematologist is always on call. Patients may be very knowledgeable about their bleeding disorder and be able to provide information.
- Communicate ER visit, hospitalization to the patient's bleeding disorder care team.
- Mild disorders can develop serious bleeding in certain circumstances.

Patient information:

Name:
Date of birth:
Diagnosis:
Severity: Level:
Response to desmopressin (DDAVP): ☐ no ☐ yes to ____%
Inhibitors: ☐ no ☐ yes
Patient on emicizumab (Hemlibra): ☐ no ☐ yes
Other medical information:
Date of recommendation: / /
Signature of physician:

Recommended treatment:

Product and dose/kg for life or limb-threatening bleeds:

Product and dose/kg for moderate/minor bleeds:

Major Procedure/Surgery Examples:

- Orthopedic
- Abdominal
- Neurosurgical

Minor Procedure Examples:

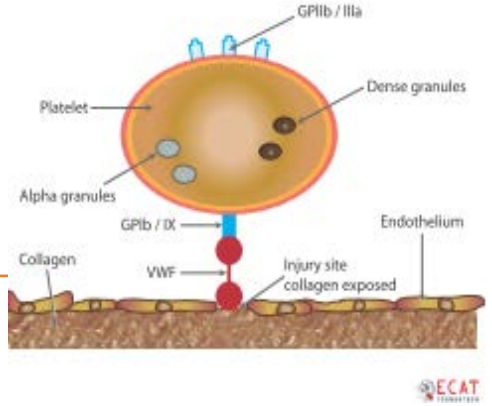
- Dental extractions
- Cutaneous/compressible site excisions

Bleed Treatment of Patients with Bleeding Disorders

- Treat First/Factor First Cards contain:
  - Program contact information
  - Treatment in the event of a bleeding event
- If a Treat First/Factor First Card is presented in an emergency situation and the patient is bleeding:

Give a bleeding treatment dose FIRST and ask more questions later!

Von Willebrand Factor (vWF)



- Characteristics
  - Large multimeric glycoprotein synthesized by megakaryocytes and endothelial cells
  - Cleared by macrophages in the liver and spleen
- Storage
  - Circulating vWF released from Weibel Palade Bodies of endothelial cells
  - vWF stored in platelet alpha granules and released upon platelet activation
- Hemostatic role
  - Primary Hemostasis: Promotes platelet adhesion to exposed endothelium and platelet aggregation
  - Chaperone for factor VIII in the plasma
  - Naturally increases with *stress* = protective!

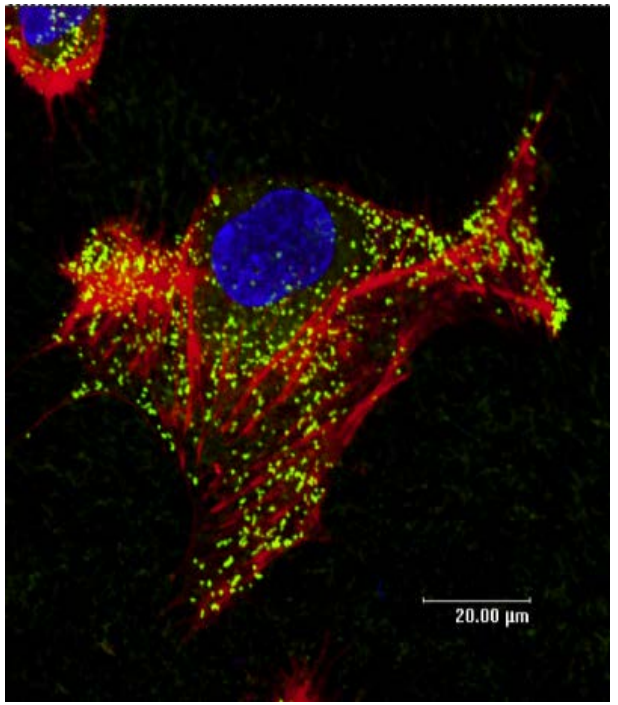
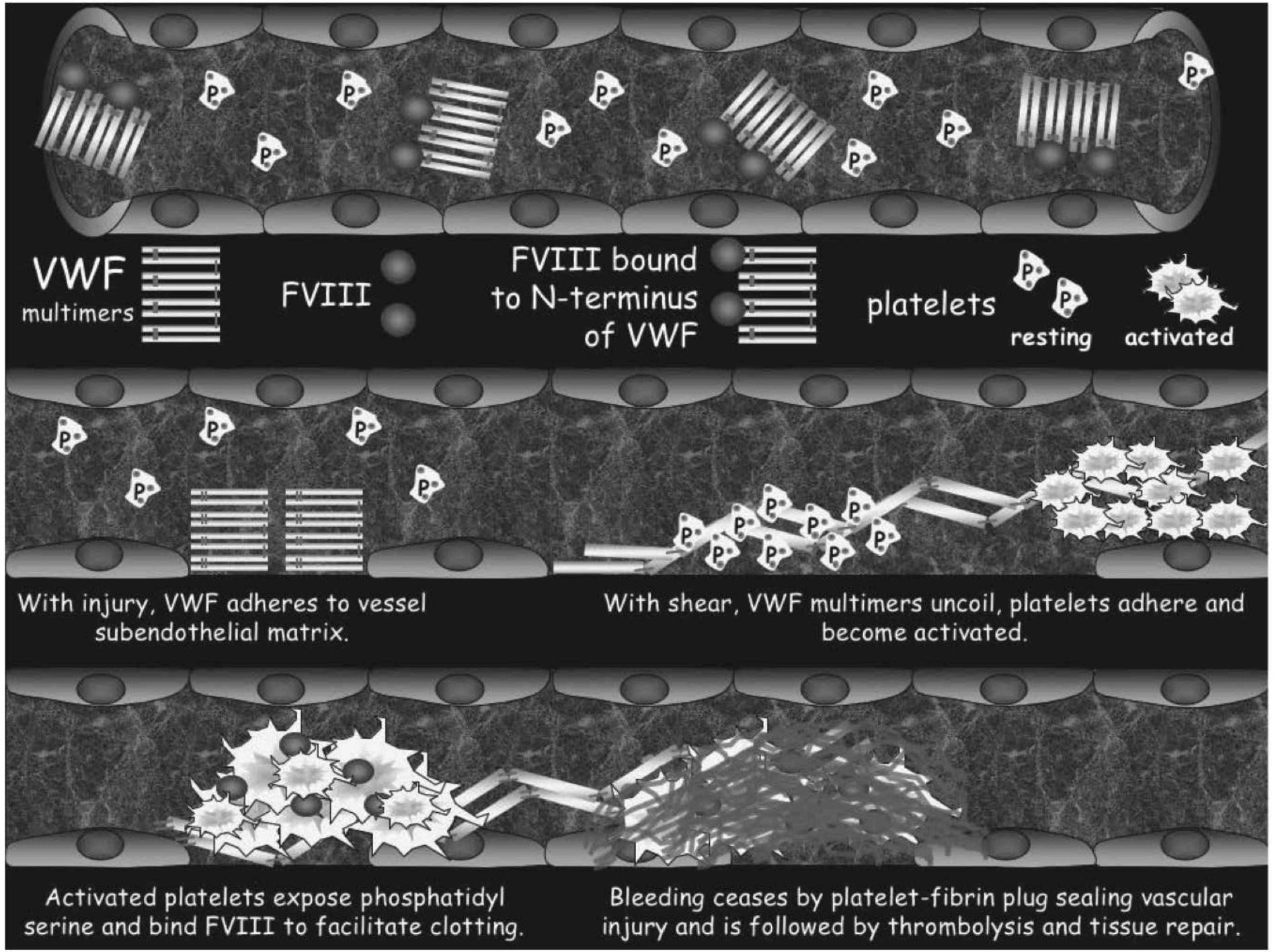


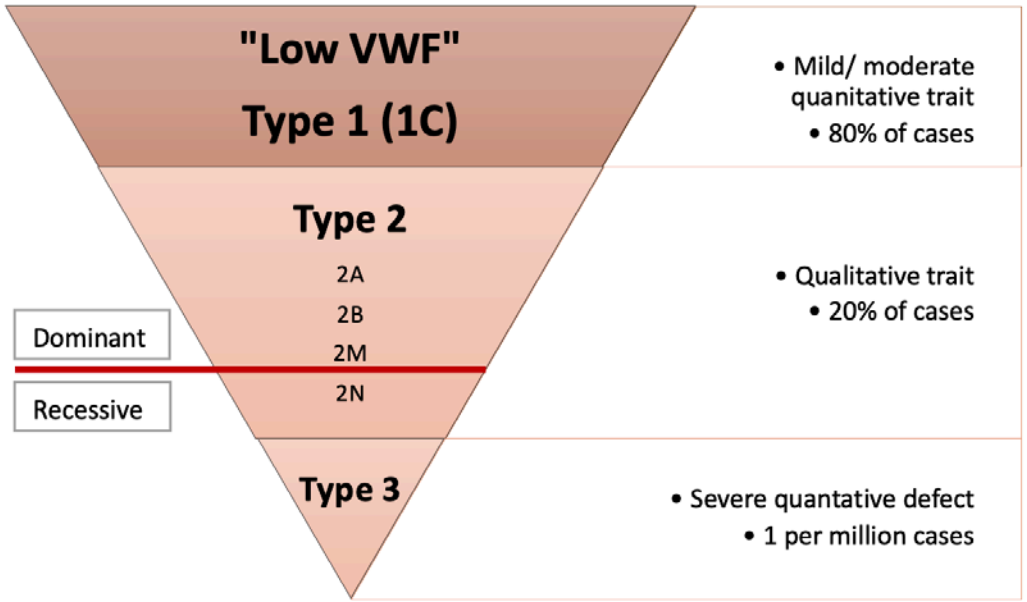
Image courtesy of Dr. Paula James

NHLBI 2007


VWF multimers
FVIII
FVIII bound to N-terminus of VWF
platelets
resting
activated
With injury, VWF adheres to vessel subendothelial matrix.
With shear, VWF multimers uncoil, platelets adhere and become activated.
Activated platelets expose phosphatidyl serine and bind FVIII to facilitate clotting.
Bleeding ceases by platelet-fibrin plug sealing vascular injury and is followed by thrombolysis and tissue repair.

Von Willebrand Disease (vWD)

- Most common inherited bleeding disorder
  - Prevalence up to 1/100; 1/1000 are affected and require attention due to bleeding
- Greatest proportion = Type 1 vWD
- Inheritance
  - Type 1 and 2 → usually autosomal dominant
  - Type 3 autosomal recessive
- Not all patients with a detectable mutation exhibit bleeding symptoms → variable penetrance



Sadler JE, et al. JTH 2006; 4:P2103-2114.

James PD, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of vWD. *Blood Adv* 2021;5:280-300.

vWD Presentation and Assessment

- Classically – **mucocutaneous** bleeding pattern, prolonged post-procedure bleeding due to role in primary hemostasis
  - Bleeding symptoms akin to severe hemophilia may occur in Type 3
- Personal bleeding history (BAT) and family history key to diagnosis
- Screening coagulation tests (PTT and INR) often *normal* → need to interrogate vWF levels
  - PTT may be increased if FVIII level less than 50%, due to insufficient chaperone of deficient or defective vWF
- vWF levels under 30%, or under 50% with a bleeding history = vWD
  - Low vWF Ag (antigen; amount of vWF) = quantitative problem
  - Low vWF Act (activity; function of vWF); if low, qualitative problem

James PD, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of vWD. *Blood Adv* 2021;5:280-300.

vWD Treatment Principles

- **Injury → treat FIRST, investigate later! Check Factor First Card!**
  - Call Hematology and Transfusion Medicine
- Goal is to increase or replace deficient factor to stop bleeding
  - Major bleeding – peak vWF levels to ~140-160%; trough >50%
  - Minor bleeding – peak vWF levels to ~70-80%
- Bleed Therapies – dosing in the Factor First Card
  - DDAVP (Desmopressin) → potentiates endothelial vWF and Factor VIII release and raises circulating levels
    - Effective in most Type 1 and some 2A only; must do a response 'challenge test'
  - VWF:FVIII Concentrate → replaces deficient factor
    - Plasma derived: Humate P, Wilate
  - Adjunct for mucocutaneous bleeding: anti-fibrinolytic agent (tranexamic acid)

Hemophilia (love (-philia) of blood (hemo-))

- Inherited bleeding disorder classically characterized by a low or absent specific coagulation factor level
  - Factor VIII = Hemophilia A (Classic Hemophilia)
  - Factor IX = Hemophilia B (Christmas Disease)
  - Factor XI = Hemophilia C
- Deficient coagulation factors lead to prolonged bleeding following injury or surgery
- Spontaneous MSK bleeding occurs in severe deficiencies

Coagulation Factors VIII & IX

Factor VIII (8)

- Production/Storage
  - Synthesized and released by endothelial cells
  - Stabilized in circulation by vWF
- Hemostatic Role
  - Secondary Hemostais: FVIIIa is a cofactor to FIXa in activation of Factor X

Factor IX (9)

- Production/Storage
  - Synthesized by hepatocytes
- Hemostatic Role
  - Secondary Hemostasis: FIXa interacts with cofactor to VIIIa to activate FX to FXa
  - Inhibited by antithrombin

Hemophilia A & B

Canadian Hemophilia Society:
https://www.hemophilia.ca/hemophilia-a-and-b/

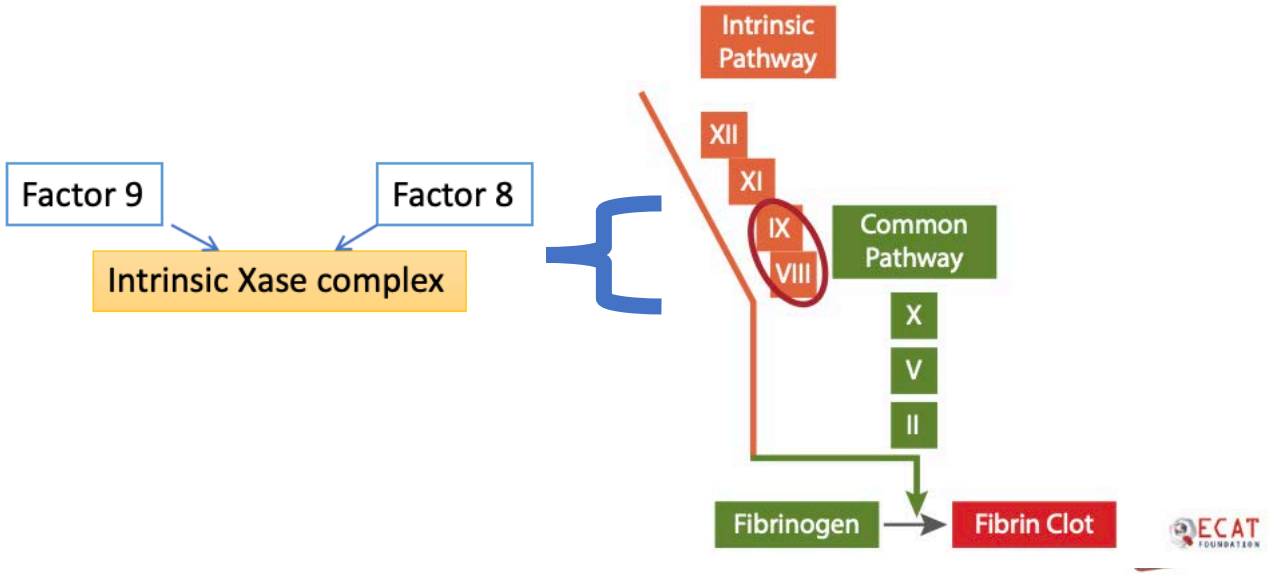
Hemophilia A

- Factor VIII deficiency
- X-linked recessive, *F8* mutation
  - ~1:10,000
    - ~2,500 Canadians

Hemophilia B

- Factor IX deficiency
- X-linked recessive, *F9* mutation
  - ~1:60,000
    - ~600 Canadians

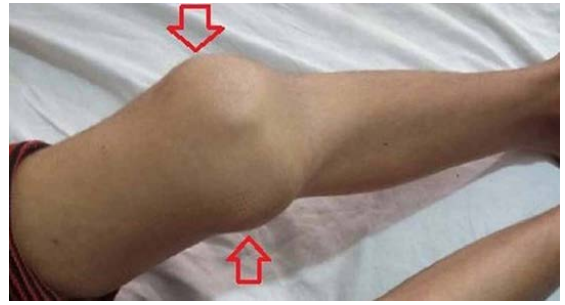
- Possible de-novo mutations with no family history in ~30% cases
- Female carriers of Hemophilia A or B genes ***can*** be symptomatic



Grades of Severity: Hemophilia

Hemophilia Presentation and Assessment

- Classically – **musculoskeletal** bleeding pattern, delayed post-procedure bleeding due to role in secondary hemostasis
    - Hemarthrosis
    - Intramuscular or soft-tissue hematoma
  - Mucocutaneous bleeding may occur
    - Epistaxis, gum oozing; heavy menses in women
  - CNS (intracranial bleeding)
  - Excessive and prolonged bleeding with trauma, procedures/surgery



- Personal bleeding history (BAT) and family history important
- Screening coagulation tests:
  - PTT – prolonged (if Factor VIII or Factor IX less than 40-50%)
  - INR – normal

Image credit:
Majid et. al., 2019. Cureus 11(4): e4524.

Hemophilia Treatment Principles

- **Injury → treat FIRST, investigate later! Check Factor First Card!**
  - Call Hematology and Transfusion Medicine
- Goal is to increase or replace deficient factor to stop bleeding
  - Major bleeding – peak Factor VIII or IX levels to ~80-100%; trough >50%
  - Minor bleeding – peak Factor VIII or IX levels to ~50-70%
- Bleed Therapies – dosing in the Factor First Card
  - DDAVP (Desmopressin) → potentiates endothelial vWF and Factor VIII release and raises circulating levels
    - Effective in mild Hemophilia A only; must do a response 'challenge test'
  - Factor Concentrate → replaces deficient factor *(see next slide)*
  - Adjunct for mucocutaneous bleeding: anti-fibrinolytic agent (tranexamic acid)

Srivastava A. WFH Guidelines for the management of hemophilia. Haemophilia 2020. Table 7-2.

Hemophilia Treatment Principles

- Recombinant (r) factor replacement preferred over plasma derived factor to eliminate risk of transmissible diseases
  - r factors are lab manufactured = not human blood source = blood transfusion consent not required!
- Factor options available, held in Transfusion Medicine:
  - rFVIII Standard half-life ($T_{1/2}$ 8-12h): Xyntha, Kovaltry
  - rFVIII Extended half-life ($T_{1/2}$ 15-20h): Jivi, Eloctate
  - rFIX Standard half-life ($T_{1/2}$ 24h): Benefix
  - rFIX Extended half-life ($T_{1/2}$ 75-110h): Rebinyn, Alprolix

Poon M, et al. Clinical Guide to Transfusion, Chapter 4. 2022.

Emicizumab (Hemlibra): Factor VIII Mimic for Bleed Prophylaxis

- Approved for bleed prophylaxis in patients with severe Hemophilia A with or without inhibitors
- Bispecific antibody given subq and functions *like* Factor VIII without *being* Factor VIII
- Hemophilia A severe patient becomes a mild patient (does not 'cure' Hemophilia A)
- Bleed/perioperative management in patients receiving emicizumab – **call Hematology**:
  - No Factor VIII Inhibitor history: Give top-up rFVIII replacement
  - With a Factor VIII Inhibitor history: Give rFVIIa
    - Do NOT use aPCC (FEIBA)

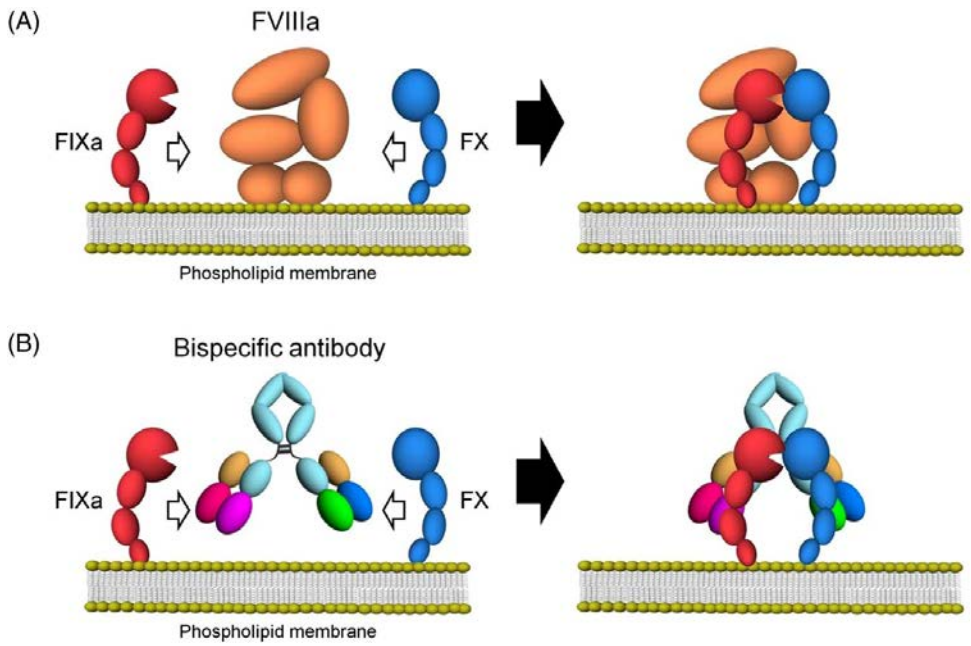


Image credit:
Sampei Z et. al., 2013. PLoS ONE 8(2): e57479.

Perioperative Considerations in Patients with Bleeding Disorders

- Intent of planned factor dosing is to *prevent* bleeding intra- and post-operatively
- Bleeding Disorders Program involvement for assessment and development of a hemostatic plan *before* surgery is essential!!
  - Treatment decisions are made depending on surgical and anesthetic approach
  - Enables communication with lab to ensure factor availability, RN/MD awareness of factor administration timing, availability of staff to test samples
- Factor given 1 hour pre-op to ensure peak factor level (~100%) at incision
  - Peri-delivery – factor level must be at least 50% prior to epidural placement and delivery
- Bloodwork monitoring:
  - Pre-factor, intra-operative 1 hour peak (no need to wait for results before incision)
  - Post-operative monitoring protocol dependent on underlying disorder
- Intra-operative IV tranexamic acid dose as hemostatic adjunct frequently recommended

Clinical Case Question 2

- A 24-year-old woman is referred to you for investigation of heavy menstrual bleeding. There is a history of hysterectomy due to heavy menses in her mother and maternal aunts. Pelvic ultrasound shows no overt uterine abnormalities.
- Recent bloodwork results: hemoglobin 85 g/L (N 123-127 g/L), MCV 75 fL (N 80-100 fL), WBC 6.2 x 10^9/L (N 6.0-10.0 x 10^9/L), platelets 485 x 10^9/L (N 150-400 x 10^9/L); PTT 37 sec (N 28-38 sec), INR 1.0 (N 0.9-1.2).
- Which investigations should you order next?
    a) Factor VII
    b) Factor VIII, Von Willebrand Factor Antigen and Activity
    c) Factors VIII, IX, XI, XII
    d) Factor XIII

Clinical Case Question 3

- A young male with inherited severe hemophilia A (no inhibitor) presents to the emergency room post-motor vehicle accident complaining of a headache and neck pain. The next most appropriate course of action is to:
    a) Administer recombinant factor VIIa and arrange for a CT scan of the head to rule out intracranial bleed
    b) Arrange for a CT scan to rule out intracranial bleed and infuse a major dose of recombinant factor VIII treatment if positive
    c) Infuse a major dose of recombinant factor VIII and arrange for a CT head thereafter to rule out intracranial bleed
    d) Draw blood for factor VIII activity level and treat with factor VIII based on the result when obtained

Key Learnings and Take Aways

- Clinical management of bleeding disorders requires an understanding of disease mechanisms and therapeutic properties.
- The patient history using a validated Bleeding Assessment Tool (BAT) is the ‘best test’ for a bleeding disorder.
- Routine coagulation tests (PT/INR, aPTT) have a poor sensitivity for assessing bleeding risk.
- **Treat First! Investigate Later!** Do not delay treatment in patients with bleeding disorders and ensure Hematology is consulted to manage their care.

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Thank you

Questions?

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Canadian Blood Services

Laboratory Medicine & Pathobiology
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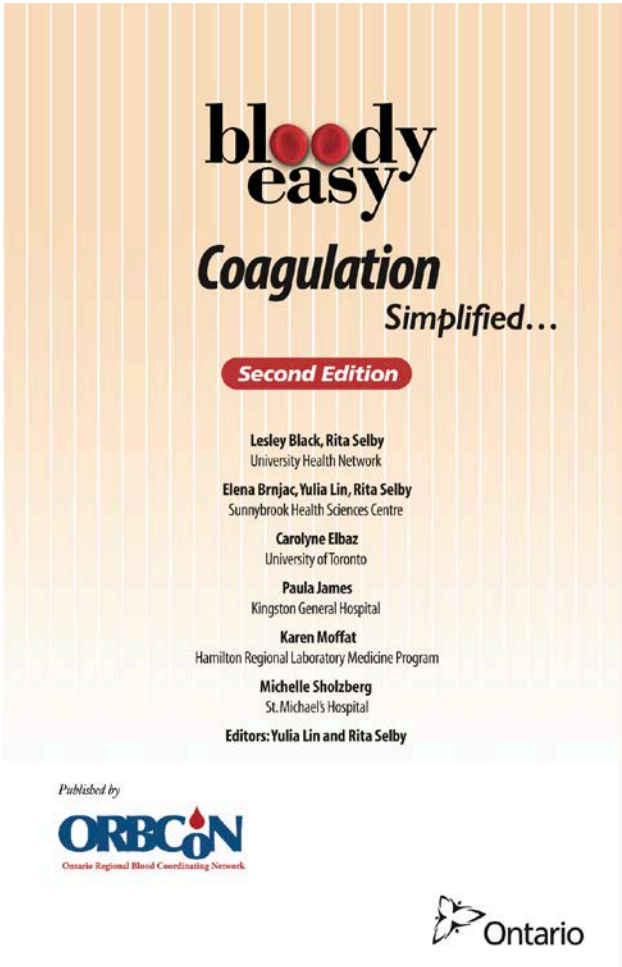
TRANSFUSION MEDICINE 101
CAMP WITH THE BANK

Helpful Resources

- Elbaz C, Sholzberg M. (2020) Illustrated Review of Bleeding Assessment Tools and Coagulation tests
- ASH ISTH NHF WFH Guidelines on vWF (2021):
  - Diagnosis
  - Management
- World Federation of Hemophilia Guidelines 3rd Ed. (2020)
- Canadian Hemophilia Society – Resources
- Bloody Easy Coagulation 2nd Ed. (2019)



vWD Diagnostic Algorithm

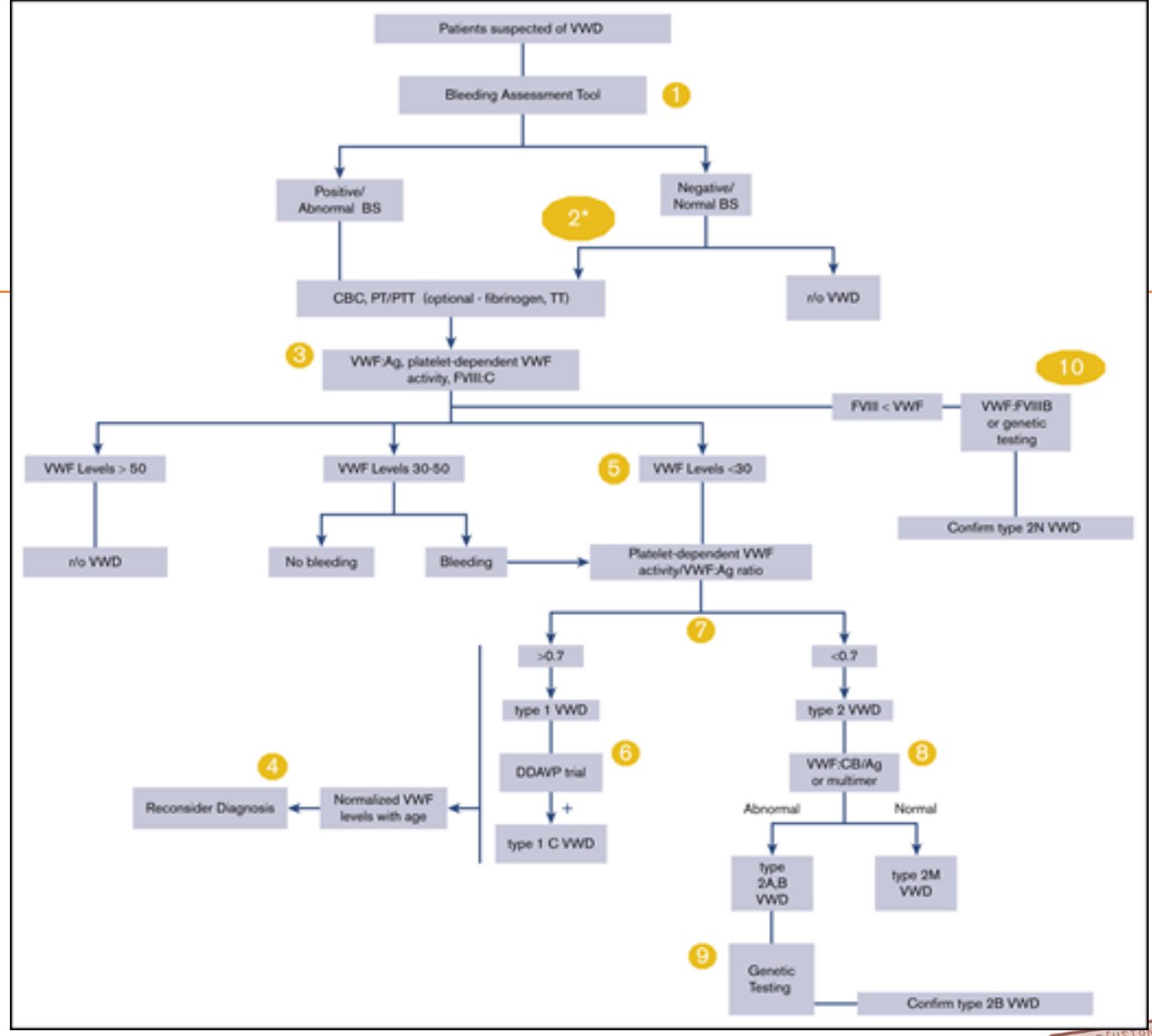
Type 1 = equally low vWF Act and Ag (underproduced); ratio greater than 0.7

- Usually DDAVP responders
- **1C** = rapid clearance of vWF after rise (rise with DDAVP not sustained at 4h)

Type 2 = lower vWF Act than Ag (dysfunctional protein); ratio less than 0.7

- **2A** – impaired vWF-plt adhesion, decreased high MW multimers (HMWM)
- **2B** – excess binding to platelet GP1b; decreased HMWM; thrombocytopenia
- **2M** – impaired vWF-dependent plt adhesion; normal multimers
- **2N** – decreased binding to FVIII, concurrent low FVIII level

Type 3 = absence of vWF



Sadler JE, et al. JTH 2006; 4:P2103-2114.

James PD, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of vWD. *Blood Adv* 2021;5:280-300.

Factor Nomenclature and Reminders!

- Named in the order of discovery, not in the order they appear in the classically presented 'coagulation cascade'
- Factor IV = Calcium!! Easy to replace to enhance coagulation… don't forget to measure it!
- Factor XII is a 'contact factor' and a low factor XII level is *not* associated with bleeding
  - But may significantly prolong an aPTT!
- The PT and aPTT do not consider Factor XIII; must do a level! PT and aPTT will be *normal* in FXIII deficiency

FACTOR	SYNONYM
I	Fibrinogen
II	Prothrombin
III	Tissue factor, thromboplastin
IV	Calcium
V	Proaccelerin, labile factor
VI	—
VII	Proconvertin, stable factor
VIII	Antihemophilic factor
IX	Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor, transglutaminase