Introduction to Congenital Bleeding Disorders

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Transfusion Medicine Boot Camp Day #3
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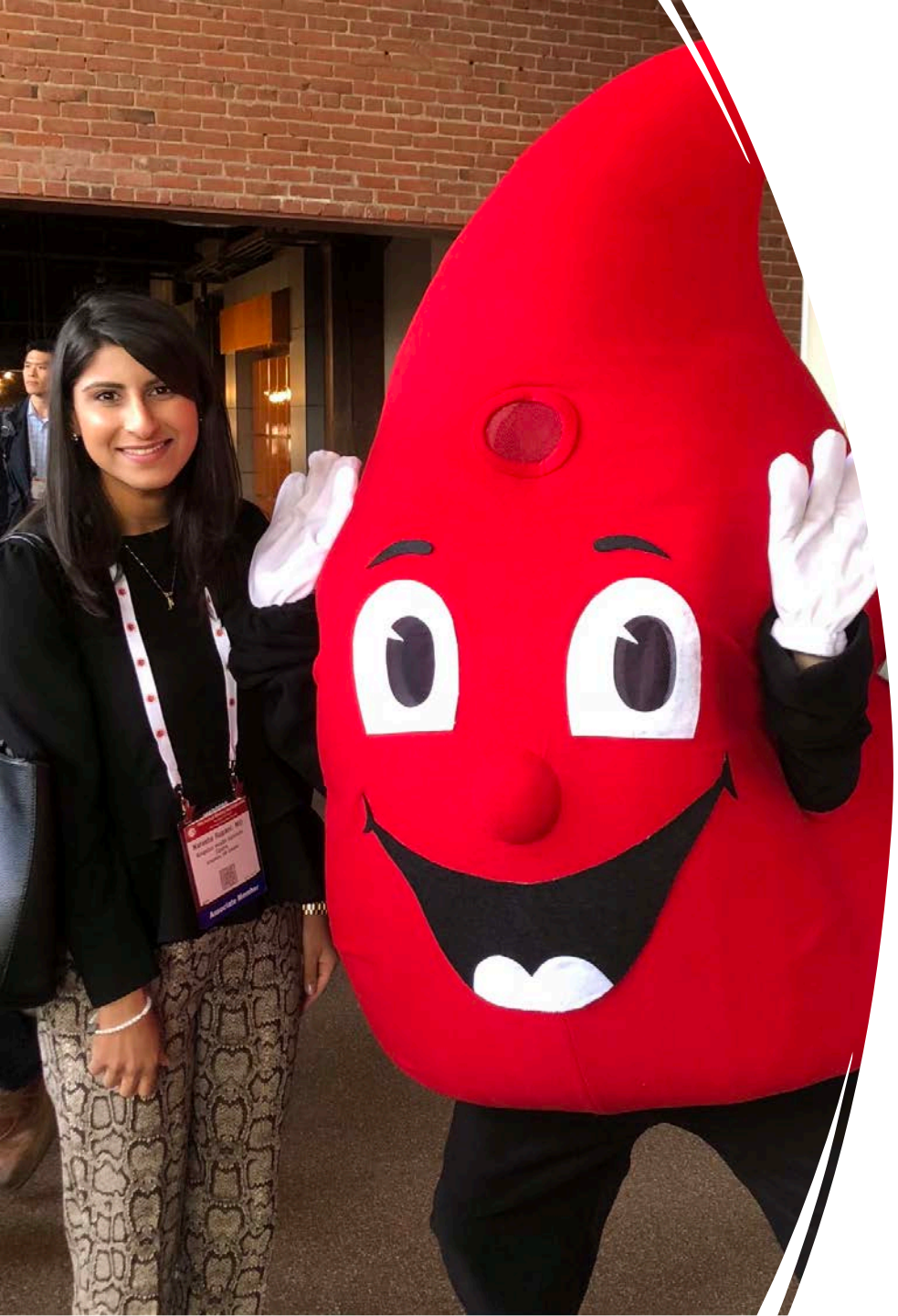
Medicine
UNIVERSITY OF TORONTO

St. Michael's
Inspired Care. Inspiring Science.



Acknowledgement & Disclosures

- Dr. Michelle Sholzberg – adaptation of her slides.

- No relevant conflicts of interest.

Objectives

1

Review the basics of hemostasis

2

Review the basics of routine coagulation testing

PT/INR, PTT

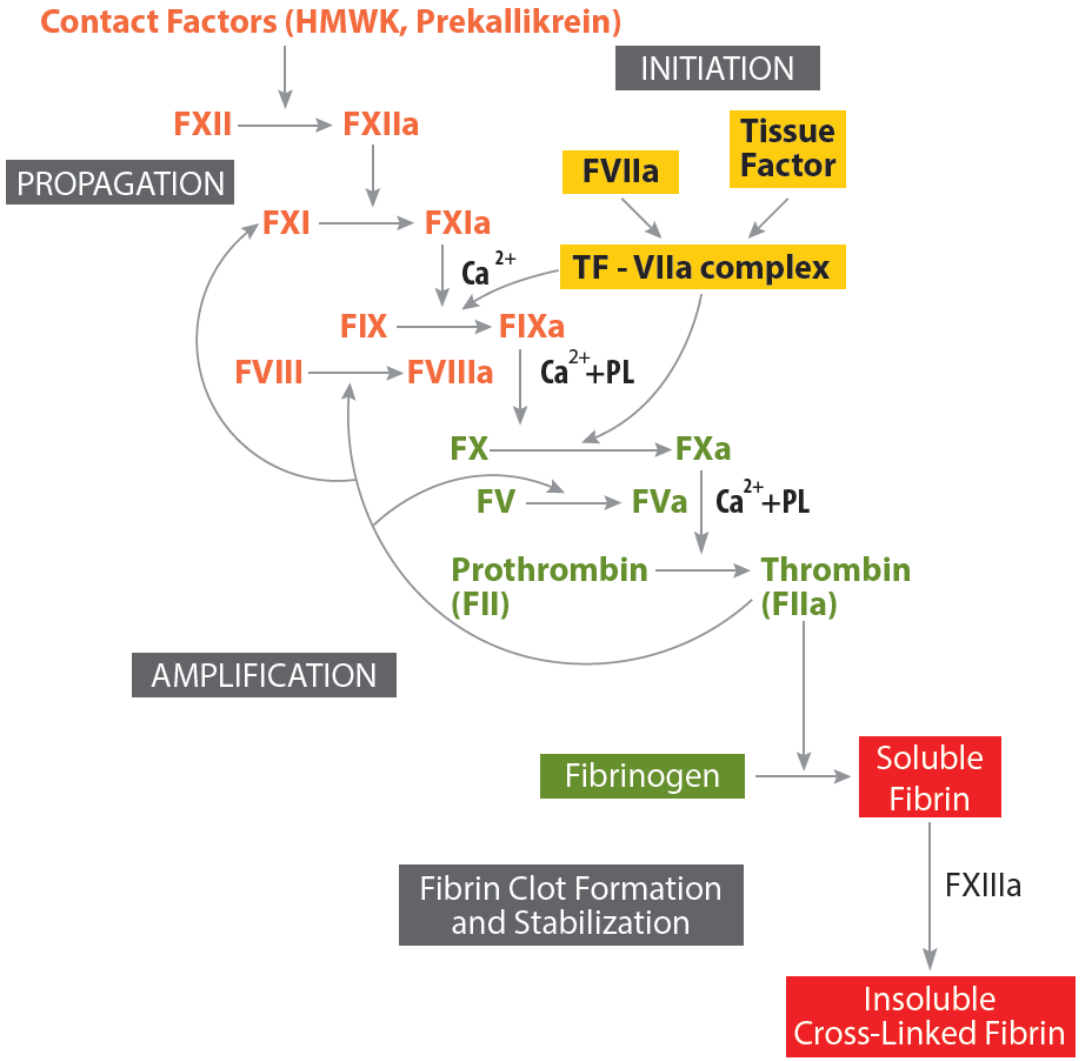
3

Review selected disorders of hemostasis and the ***key*** treatment principles

- Von Willebrand Disease
- Hemophilia A and B

Basics of Hemostasis

Coagulation Cascade



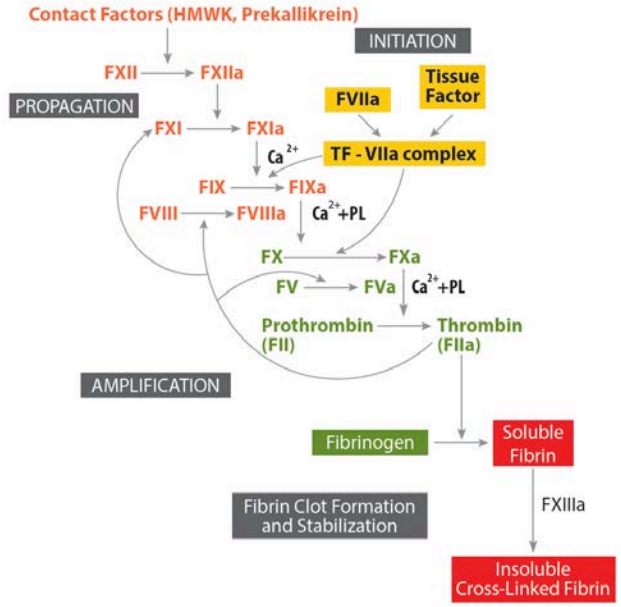
It is not the be it and end all…

1. **Hemostasis is complex**
   - Reflects in vitro rather than in vivo using routine coag assays (PT/INR/PTT)

2. **“Cascade” is a misnomer**

3. **Roman numerals not in order but in order of discovery**
   - F1 = fibrinogen
   - F2 = prothrombin
   - F3 = TF
   - F4 = calcium
   - No factor VI!
   - HMWK, PK, FXII not clinically relevant for bleeding

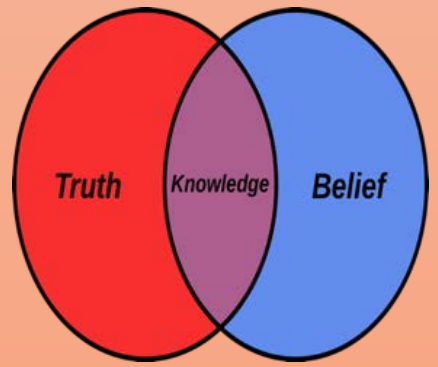
4. **Overemphasizes secondary hemostasis**
   - What about primary hemostasis, fibrinolytic pathway?



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

Coagulation Cascade

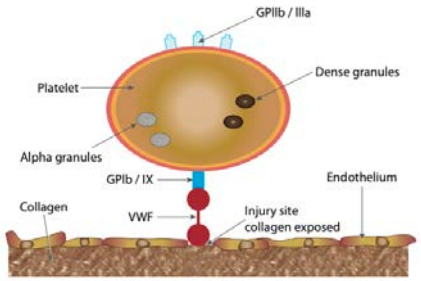
BIG PROBLEM!



Hemostasis simplified … let’s build a house

Hemostasis Simplified

Primary Hemostasis



Secondary Hemostasis

Clot Stabilization

Fibrinolysis

A short video

Basics of Routine Coagulation Tests

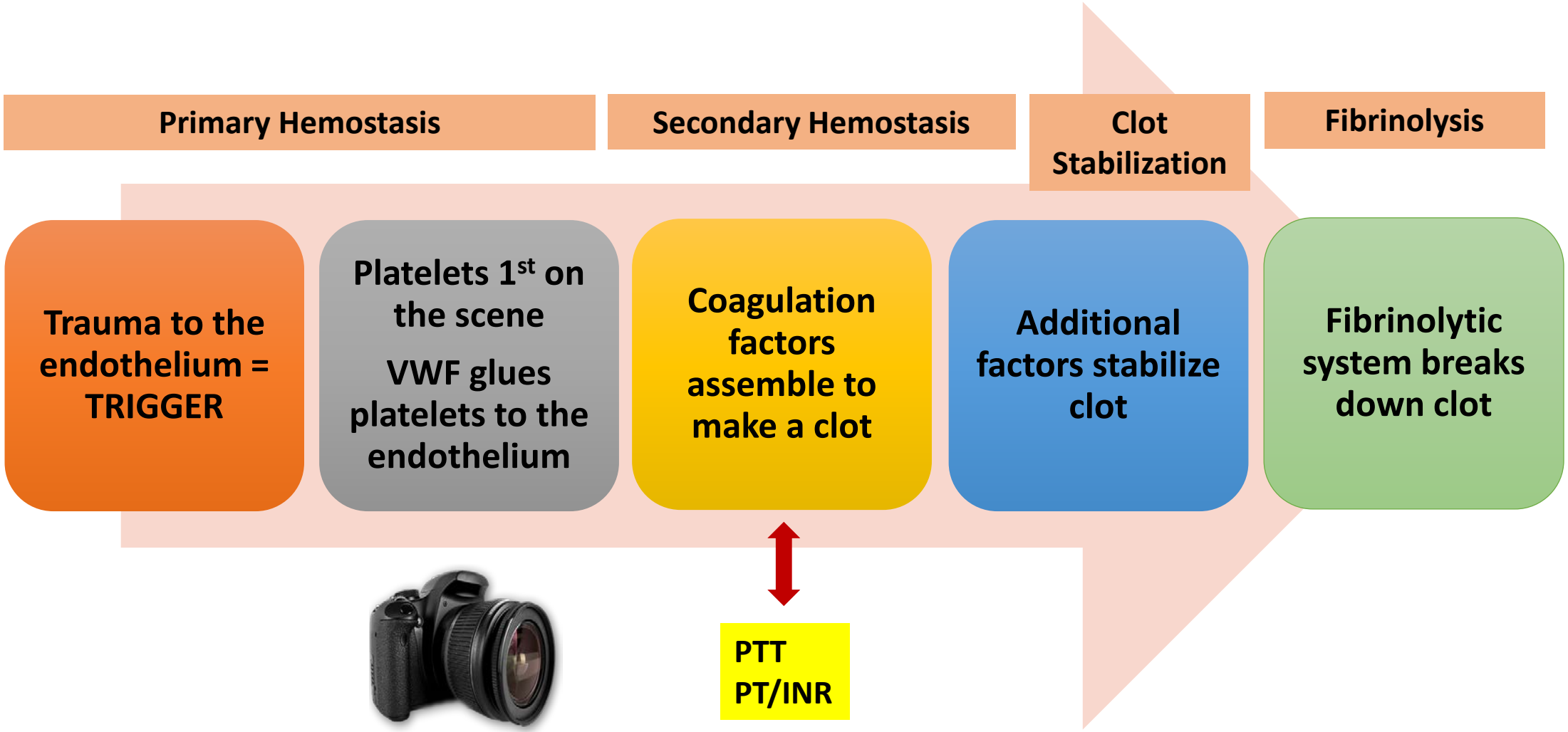
Basic Clot-Based Tests

- Prothrombin Time (PT)
  - International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (aPTT)

END RESULT – CLOT FORMATION

Sensitivity of 1-2% → normal PT/aPTT does not rule out a bleeding disorder

Hemostasis Simplified: *STATIC* Assays



Importance of the Bleeding History

Utility of Bleeding Assessment Tools (BATs)

How important is the bleeding history?

THE BLEEDING HISTORY IS THE MOST IMPORTANT…

TEST OF HEMOSTASIS

Hemostasis Simplified: *BAT*

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
BAT	BAT	BAT	BAT	BAT

Bleeding Assessment Tools

- Standardized and validated clinical bleeding assessment tools
  - ISTH-BAT
  - Vincenza questionnaire
  - **Condensed MCMDM-1 (James et. al)**
  - Self-BAT
    - Menstrual specific
    - Pediatric specific
  - Dynamic BAT (in development)

- Key inquiry
  - ✓Personal and FamHx of bleeding d/o
  - ✓Spontaneous bleeding?
  - ✓Bleeding in response to hemostatic challenges

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

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- Summative scoring system
- Possible range -3 to +45
- Normal range determined on 100 controls
- **Abnormal (positive) BS ≥ 4**

Prospectively Investigated Bleeders:

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

Limitations of BATs

- Many require administration by a health care professional
- Lack of bleeding challenges in younger patients
- Males without prior hemostatic challenge (no menses)
- Easily saturable
- False negative score with prior prophylactic treatment
- Not dynamic – static score at diagnosis

Selected Disorders of Hemostasis

Von Willebrand Disease

Hemophilia A and B

Von Willebrand Factor

- Large multimeric glycoprotein
- Synthesized by megakaryocytes and endothelial cells
- Cleared by macrophages in the liver and spleen

Storage:

1. Circulating VWF released from Weibel Palade Bodies in endothelial cells
2. VWF stored in platelet alpha granules and released on platelet activation

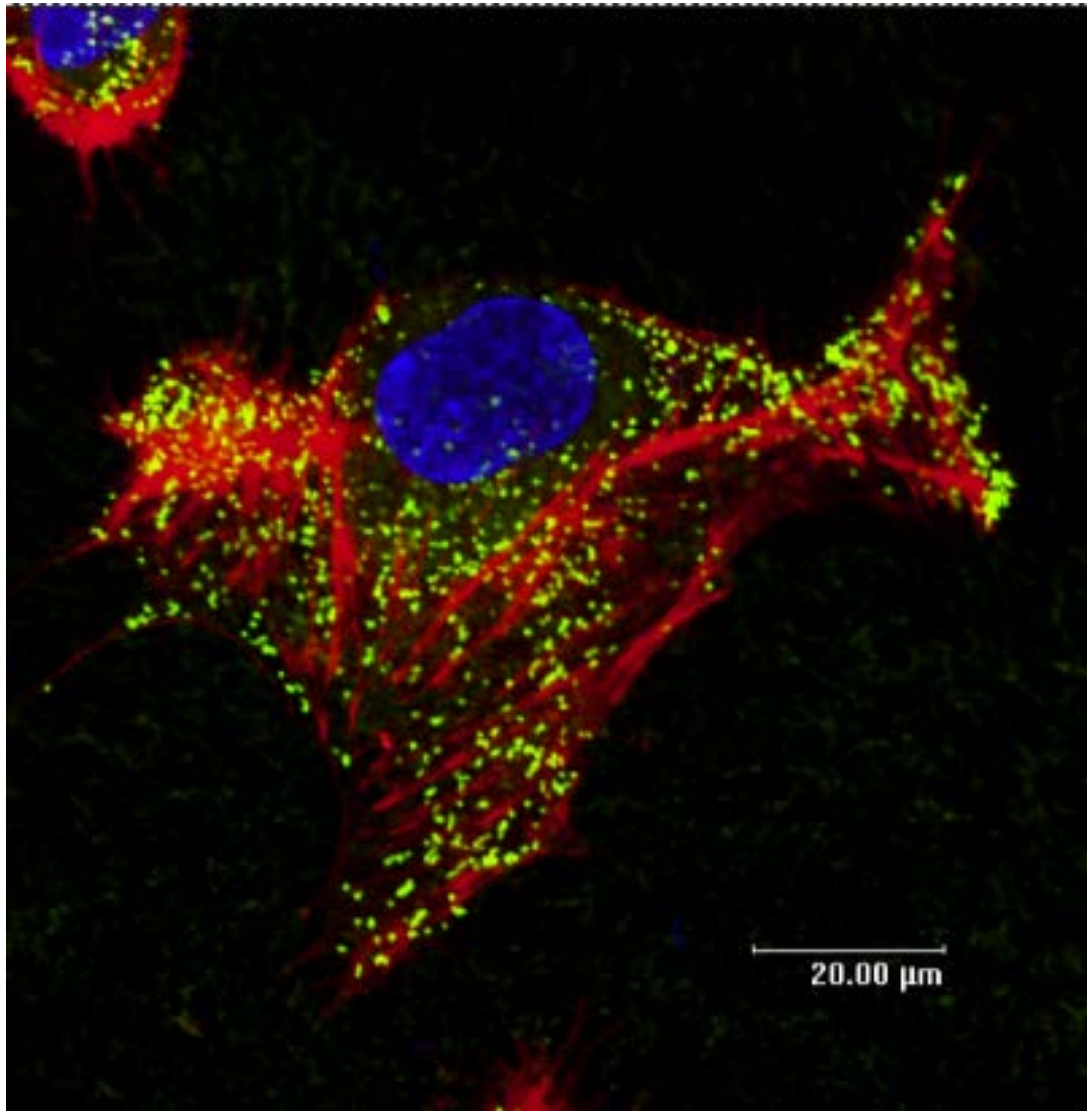
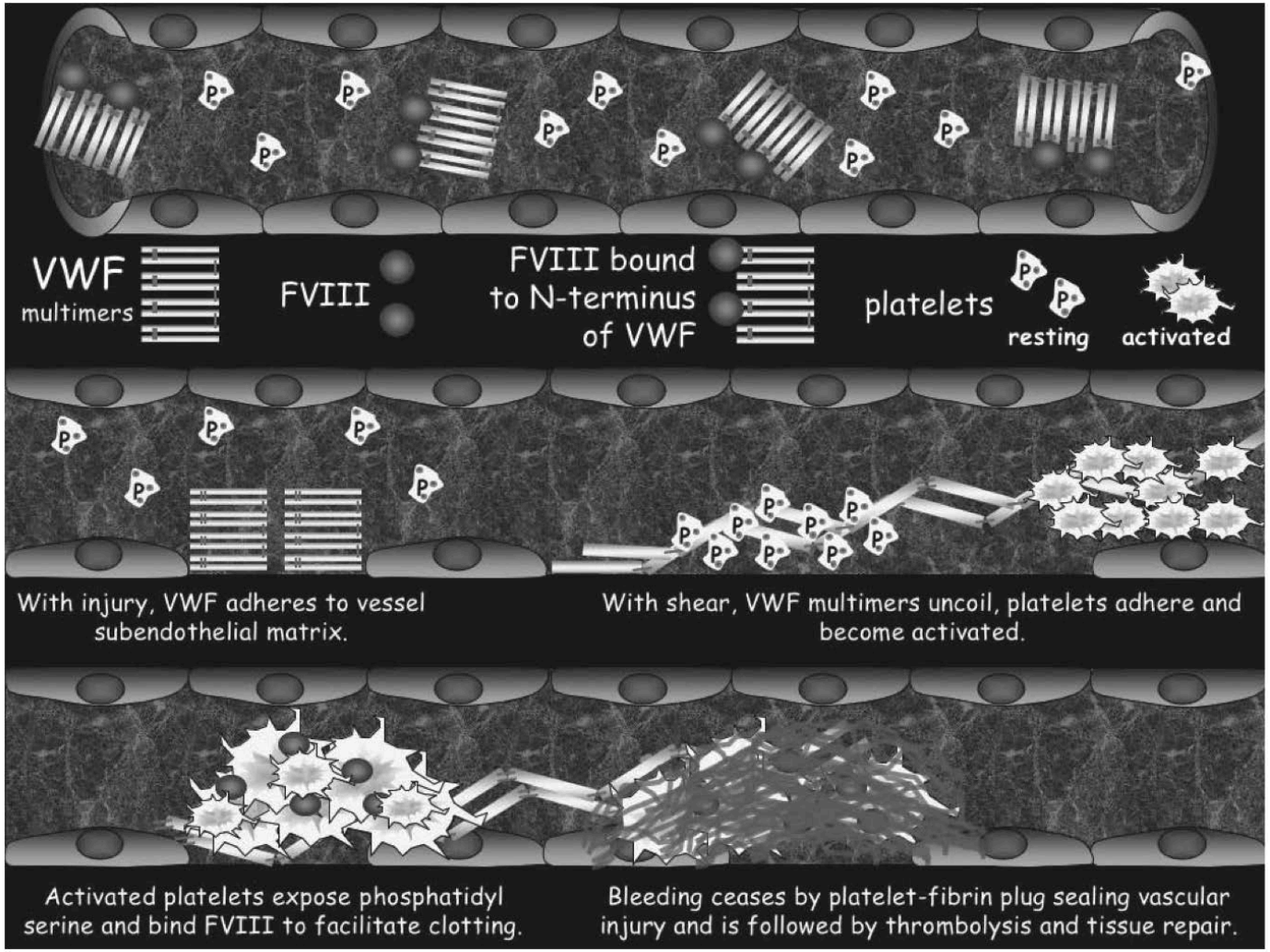
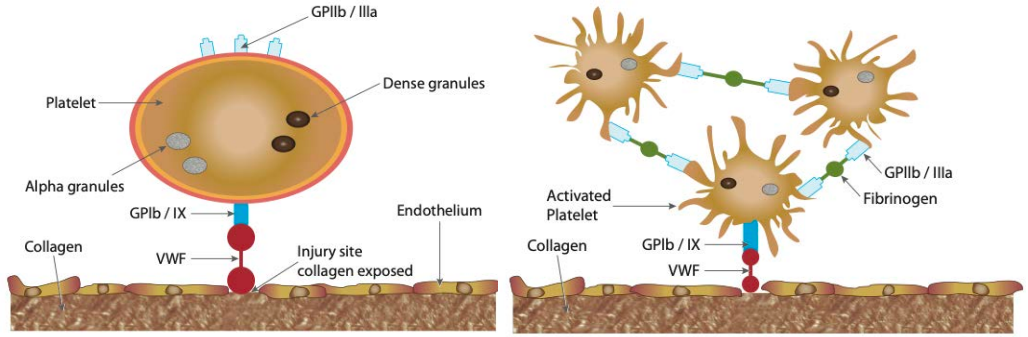


Image courtesy of Dr. Paula James

Role in Hemostasis



NHLBI 2007

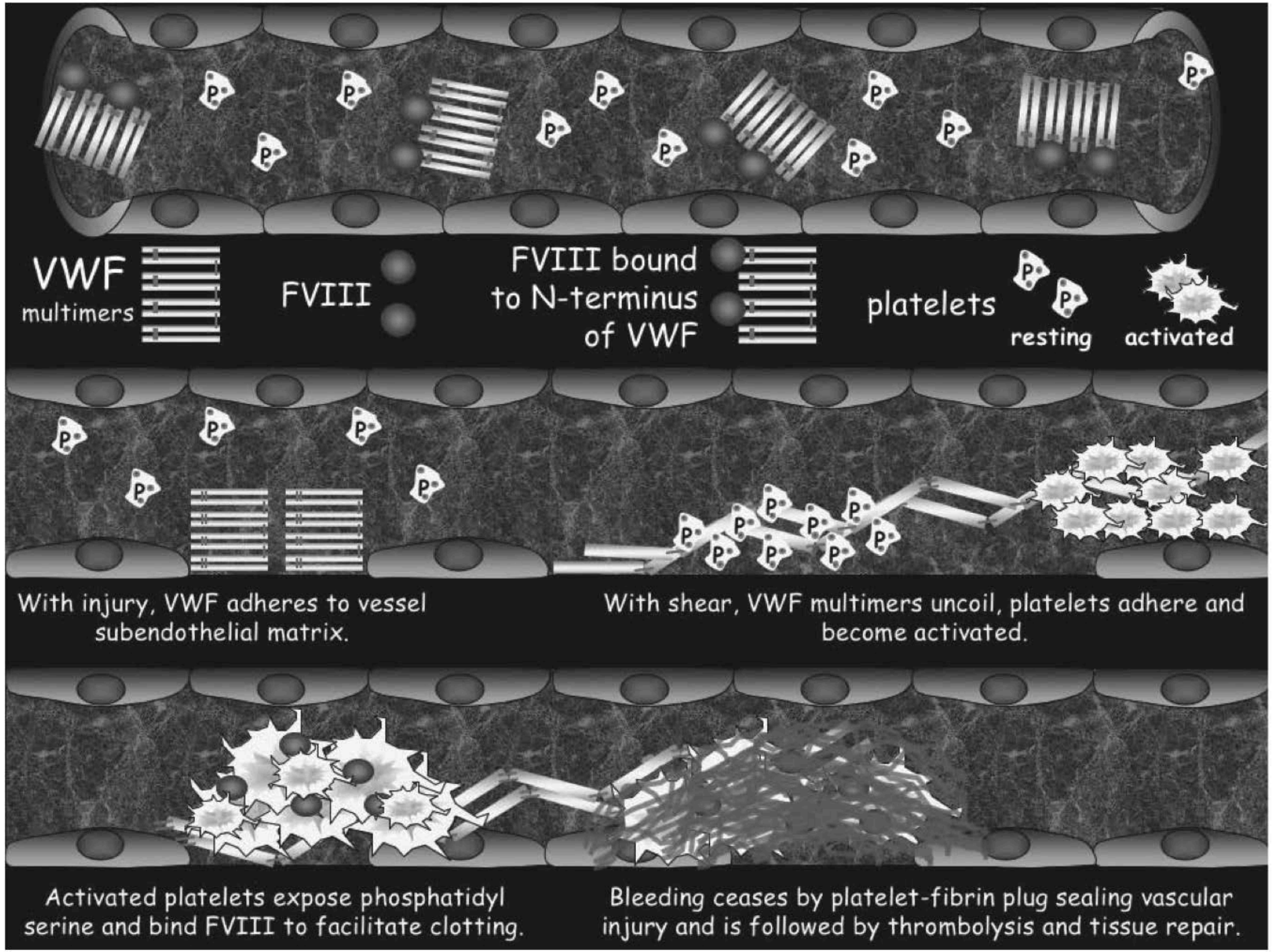


Primary Hemostasis

- Promote platelet adhesion to exposed endothelium
- Promote platelet aggregation

Secondary Hemostasis

- Act as a chaperone for factor VIII in plasma


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.

Hemostasis Simplified: VWD

VWD

Trauma to the endothelium = TRIGGER

Platelets 1st on the scene

VWF glues platelets to the endothelium

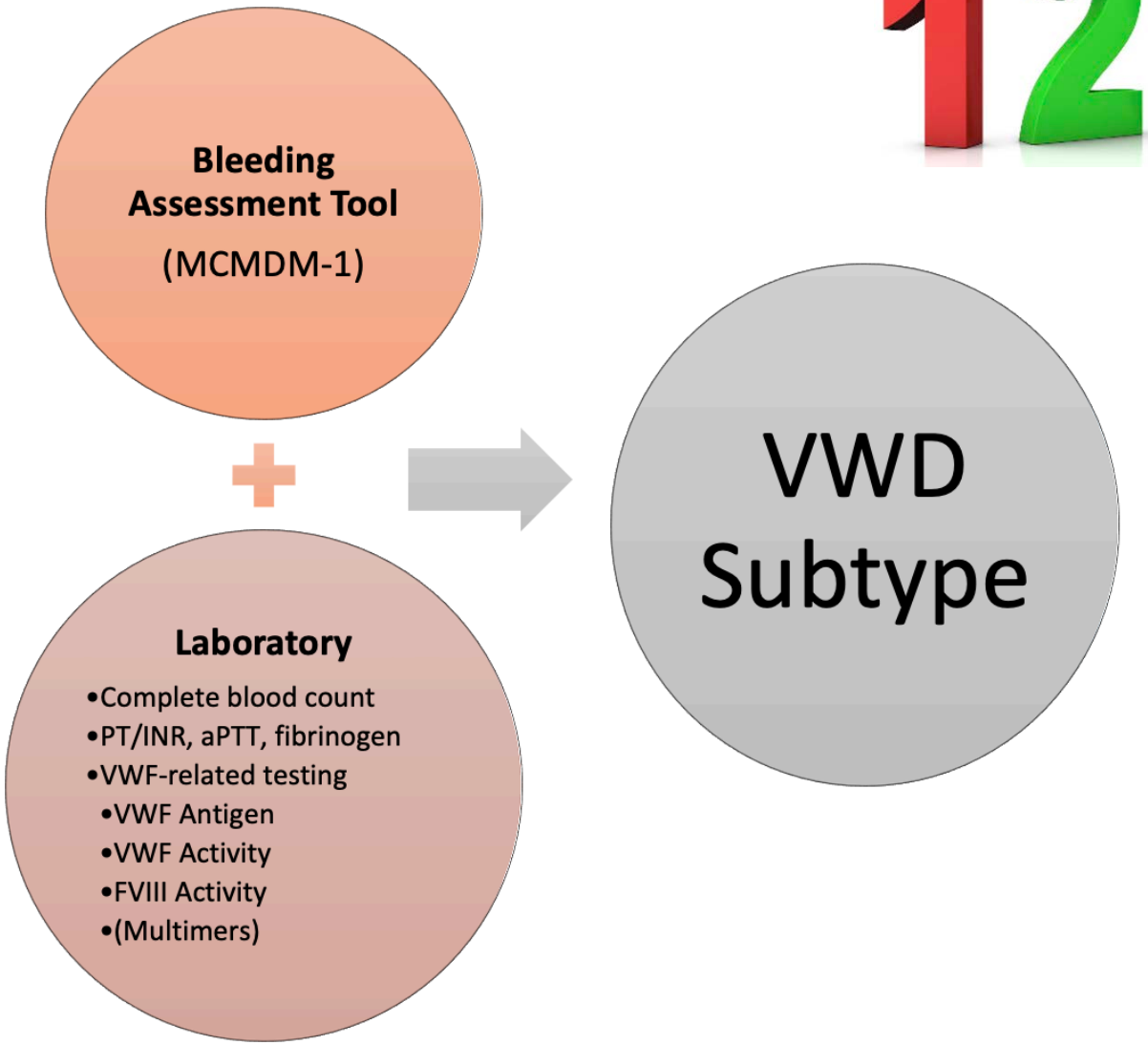
Coagulation factors assemble to make a clot

Additional factors stabilize clot

Fibrinolytic system breaks down clot

Diagnoses

- Bleeding symptoms
- Family History
- Laboratory results



Bleeding Symptoms

Type 3, 2N

- Bleeding from minor wounds
- Bruising
- Heavy menstrual bleeding
- Muscle hematoma (rare)

- Epistaxis
- Oral cavity bleeding
- Gastrointestinal Bleeding
- Hemarthrosis (rare)

Type 3, 2N

Bleeding post hemostatic challenges

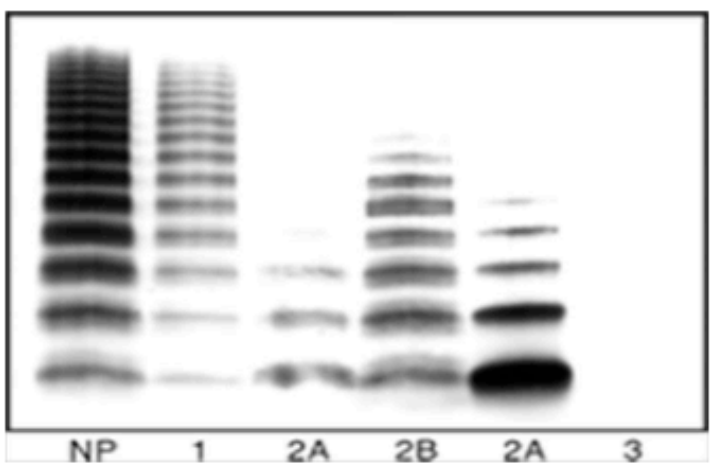
- SURGERY
- POST PARTUM HEMORRHAGE
- DENTAL EXTRACTION

Laboratory Tests

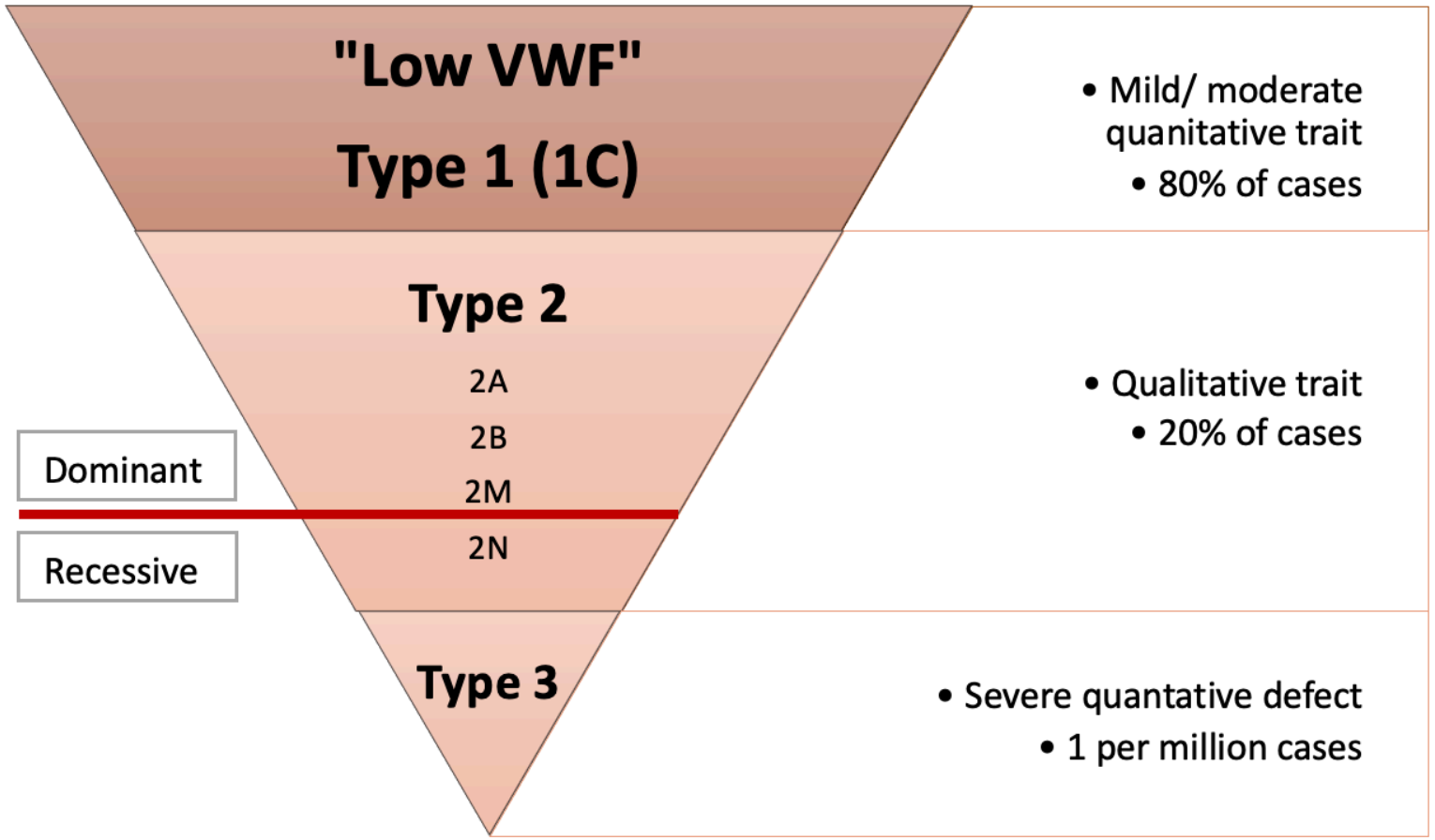
- CBC, INR normal, PTT often normal

1. VWF Antigen (*how much VWF?*) → **decreased**
2. VWF Ristocetin Cofactor Activity *(does do its job in primary hemostasis?)* → **decreased**
3. Factor VIII activity *(does VWF do its job in secondary hemostasis?)* → **decreased**

- Multimers
- Ristocetin Induced Platelet Agglutination (2B)
- VWF:FVIII binding activity
- VWF:Collagen binding activity
- VWF propeptide antigen
- Genetic testing – Types 2 and 3



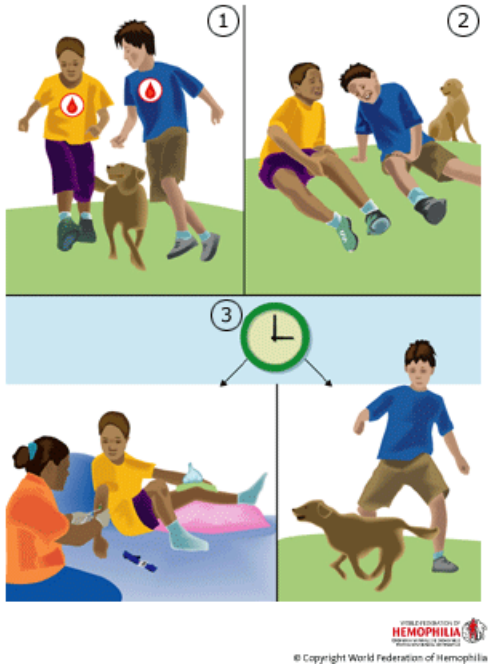
ISTH VWD Classification



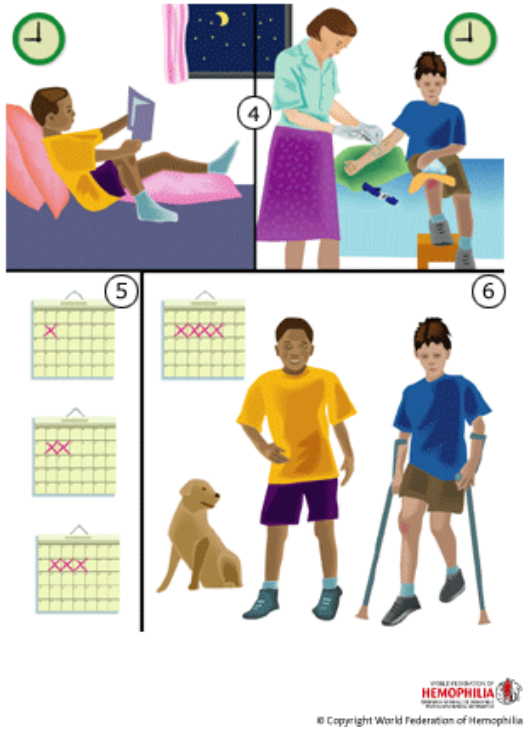
Sadler et al JTH 2006

Principles of Bleed Management

1. TREAT FIRST!



2. INVESTIGATE LATER!



Remember…
FactorFirst

PROMPT INFUSION will halt bleeding, minimize long-term complications and can save life. If bleeding persists, follow the guidelines for life or limb-threatening bleeds and call the:

Hemophilia Treatment Centre

Physician: _____

Nurse: _____

Day Phone: _____

Night Phone: _____

Delay in the restoration of hemostasis to the patient with hemophilia or von Willebrand disease may be life or limb-threatening.

- **PROMPT TRIAGE AND ASSESSMENT.**
- Determine the severity of the bleed.
- Recognize that bleeding in the head, spine, abdomen or pelvis may initially be occult and potentially life-threatening.
- **TREAT FIRST AND INVESTIGATE LATER – "FACTOR FIRST".**
- Avoid invasive procedures such as arterial punctures unless the patient has factor replacement.
- **NO** IM injections and **NO** ASA.
- The patient or guardian may be your most important resource, so do ask about specific treatment protocols.
- Contact the patient's Hemophilia Treatment Centre where a hematologist is always on call.
- Provide clear discharge instructions and arrange a follow-up plan or admit to hospital if necessary.

Use Universal Precautions

Patient Information:

Name: _____

Date of Birth: _____

Diagnosis: _____

Severity: _____ Level: _____

Response to desmopressin (DDAVP): ❑ no ❑ yes to _____ %

Inhibitors: ❑ 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:

LIFE OR LIMB-THREATENING BLEEDS

- Head (intracranial) and neck
- Chest, abdomen, pelvis, spine
- Iliopsoas muscle and hip
- Massive vaginal hemorrhage
- Extremity muscle compartments
- Fractures or dislocations
- Any deep laceration
- Any uncontrolled bleeding

MODERATE/MINOR BLEEDS

- Nose (epistaxis)
- Mouth (including gums)
- Joints (hemarthroses)
- Menorrhagia
- Abrasions and superficial lacerations

TREATMENT FOR LIFE OR LIMB-THREATENING BLEEDS

PATIENT MUST RECEIVE PRODUCT URGENTLY

Hemophilia A: (all severities)
Recombinant factor VIII concentrate 40-50 units/kg

Hemophilia B: (all severities)
Recombinant factor IX concentrate 100-120 units/kg >15 yrs
Recombinant factor IX concentrate 135-160 units/kg <15 yrs
The dosage for recombinant factor IX is substantially higher because of its lower recovery, particularly in children.

Von Willebrand Disease:
A VW factor concentrate containing factor VIII such as Humate-P 60-80 Ristocetin cofactor units/kg

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

TREATMENT FOR MODERATE/MINOR BLEEDS

PATIENT MUST RECEIVE PRODUCT WITHIN 30 MINUTES WHENEVER POSSIBLE

Hemophilia A: (severe/moderate)
Recombinant factor VIII concentrate 20-30 units/kg

Hemophilia A: (mild)
Desmopressin (Octostim/DDAVP) 0.3 mcg/kg (max. 20 mcg) -SC/IV

Hemophilia B: (severe/moderate/mild)
Recombinant factor IX concentrate 35-50 units/kg >15 yrs
Recombinant factor IX concentrate 50-70 units/kg <15 yrs
The dosage for recombinant factor IX is substantially higher because of its lower recovery, particularly in children.

Von Willebrand Disease:
Type 1 and Type 2A or 2B known to have used desmopressin safely and effectively – (Octostim/DDAVP) 0.3 mcg/kg (max. 20 mcg) -SC/IV
For patients not responding to desmopressin (such as Type 3 or Type 2B) use a VW factor concentrate containing factor VIII such as Humate-P 60-80 Ristocetin cofactor units/kg

For mucosal bleeds in all above add:
Tranexamic Acid (Cyklokapron) 25 mg/kg po tid 1-7 days (contraindicated if hematuria)

Dosages are patient specific – these are general guidelines only. Round doses up to the nearest vial. If the products listed are not available, please call the nearest Canadian Blood Services or Héma-Québec Centre.

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

www.hemophilia.ca/emergency

Phone Numbers:

Nurse Coordinator: Phone: 416.864.5129
Fax: 416.864.5310
Pager: 416.685.9404 (enter return number on touch tone phone)

Medical Directors: 416.864.5128

Off-Hours Emergencies: 416.864.5431

Toronto and Central Ontario Comprehensive Hemophilia Program

St. Michael's Hospital
30 Bond Street
4th Floor, Cardinal Carter Wing
Toronto, ON M5B 1W8 Canada
stmichaelshospital.com

St. Michael's
Inspired Care.
Inspiring Science.

Fully affiliated with the University of Toronto.

Name: _____

Diagnosis: _____

Notes: _____

Give replacement therapy **immediately** for obvious or suspected bleeding or major trauma. Treat first, and then investigate.

Recommended Treatment:

Severe Bleed/Major Trauma

Mild/Moderate Bleed

Please contact the clinic for further information

Physician's Name _____

Physician's Signature _____

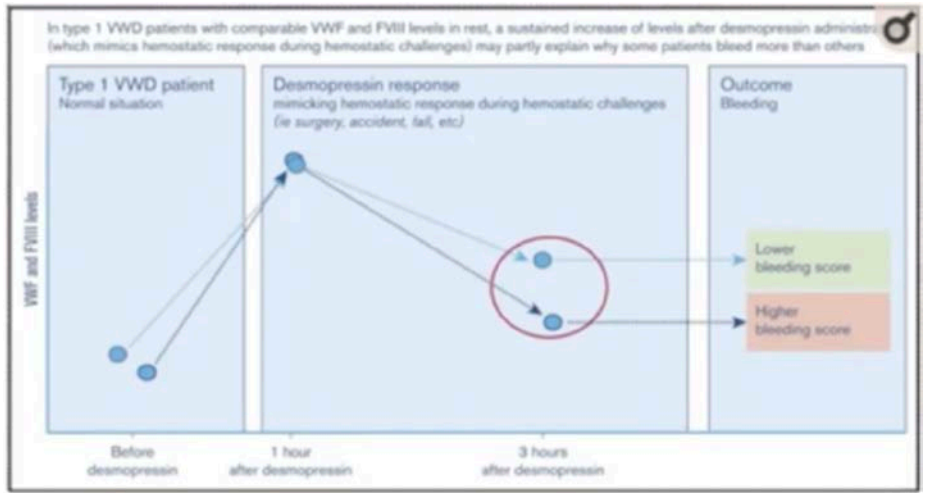
Treatment Basics – Acute Bleed

- ***Call Hematology / Transfusion Medicine***

- 1) Increase or 2) Replace VWF

- Medications
  - DDAVP (Desmopressin)
  - VWF:FVIII Concentrate (Humate P, Wilate)
  - Adjunctive anti-fibrinolytic agent (TXA)

- Consider prophylaxis
  - Severe recurrent bleeding
  - Hemarthrosis
  - Angiodysplasia with recurrent GIB
  - Heavy menstrual bleeding



VWD Therapies

Therapies that can be used to treat VWD and AVWS

Medication	Dose	Comments
DDAVP	▪ **Intravenous:** 0.3 mcg/kg (maximum dose, 20 to 30 mcg) in 50 mL saline over 20 minutes -or- ▪ **Nasal spray:** Weight >50 kg: 300 mcg (1 spray in each nostril); weight <50 kg: 150 mcg (1 spray in 1 nostril)	▪ Adequate response to a test dose is ideally established before use, but a patient with AVWS and acute bleeding may receive the first dose as a therapeutic trial. ▪ Use caution when an antifibrinolytic agent is given concurrently due to risk of thrombosis. ▪ Dose may be repeated after 12 hours and 24 hours. ▪ Tachyphylaxis and hyponatremia may occur; monitor hemostasis and serum sodium.
VWF concentrates (these contain all VWF multimers)	▪ **Major bleeding or surgery:** Initial dose 40 to 60 ristocetin cofactor units/kg followed by 20 to 40 ristocetin cofactor units/kg every 12 to 24 hours to keep VWF level 50 to 100 international units/dL for 7 to 14 days, or as indicated clinically ▪ **Minor bleeding or surgery:** Initial dose 30 to 60 ristocetin cofactor units/kg followed by 20 to 40 ristocetin cofactor units/kg every 12 to 48 hours to keep VWF level >30 international units/dL for 3 to 5 days, or less as indicated clinically	▪ Dose and duration based on clinical experience. ▪ Case reports have described the use of continuous infusion (2 to 15 international units/kg per hour) in cases of serious bleeding that does not respond to intermittent dosing. ▪ Increased doses or more frequent administration may be necessary in AVWS.
Recombinant VWF	▪ **Major bleeding or surgery:** Initial dose 50 to 80 international units/kg, followed by 40 to 60 international units/kg every 8 to 24 hours to keep the VWF level 50 to 100 international units/kg for 2 to 3 days or longer, as needed clinically ▪ **Minor bleeding or surgery:** Initial dose 40 to 50 international units/kg, followed by 40 to 50 international units/kg every 8 to 24 hours as needed clinically	▪ In patients with less than 40% factor VIII activity, 1 dose of recombinant factor VIII is given (dose ratio of 1 to 1.3 for rFVIII to rVWF) within 10 minutes of the first dose of rVWF. ▪ Published studies using rVWF are limited, and more data are needed to assess responses in patients of differing ages and severities of VWD and in specific clinical settings.
Antifibrinolytic agents	▪ Aminocaproic acid, 25 to 50 mg/kg per dose orally (maximum 5 g dose) 4 times per day -or- ▪ Tranexamic acid, 25 mg/kg per dose orally every 6 to 8 hours or 10 mg/kg intravenously 3 times per day	▪ Can be used alone or in conjunction with other therapies; use caution when combined with DDAVP. ▪ Especially useful for mucosal bleeding (often used for dental procedures). ▪ Dose reduction may be required in patients with impaired kidney function.
IVIG (only applies to AVWS)	▪ 1 g/kg intravenously once daily for 2 days¶	▪ May be particularly helpful in monoclonal gammopathies. ▪ May be used in conjunction with VWF concentrates and/or DDAVP, particularly when treating AVWS associated with autoimmune disease.

Refer to UpToDate topics on the management of VWD and AVWS for additional information.

VWD: von Willebrand disease; AVWS: acquired von Willebrand syndrome; DDAVP: desmopressin; VWF: von Willebrand factor; rFVIII: recombinant factor VIII; rVWF: recombinant VWF; IVIG: intravenous immune globulin.

* Thrombocytopenia may worsen in some type 2B patients.

¶ Divided doses may be required; refer to UpToDate topics on IVIG for details.

Adapted from: Rick ME. Diagnosis and management of von Willebrand's syndrome. Med Clin North Am 1994; 78:609. Copyright 1994 WB Saunders.

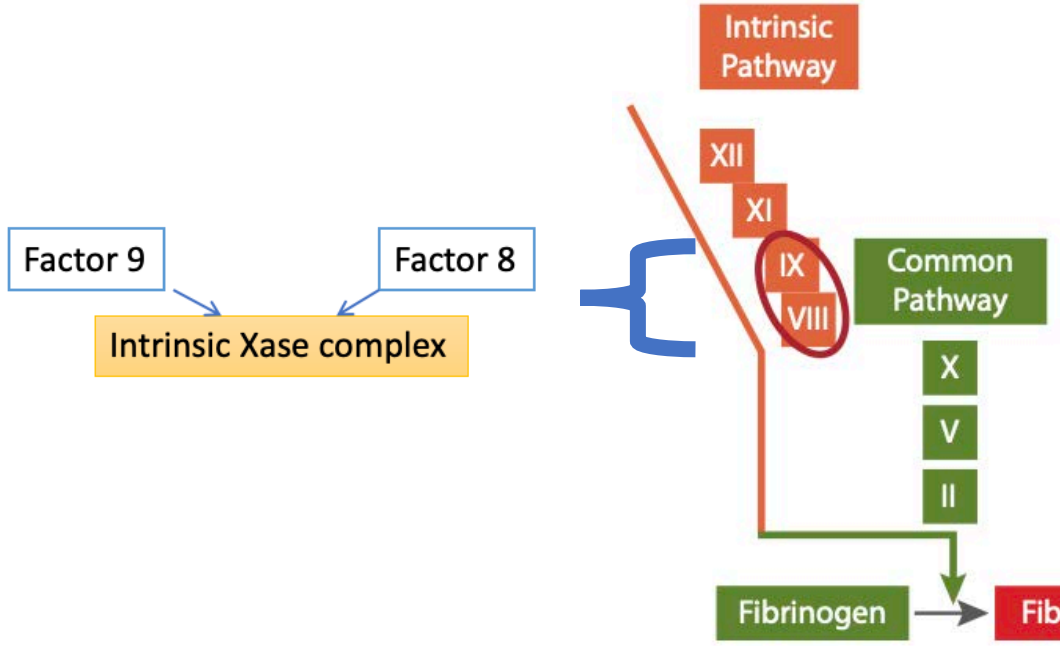
Hemophilias: X-linked recessive disorders

Hemophilia A

- FVIII deficiency
- 1 in 5,000 males

- **Hemophilia B**
- Factor IX deficiency
- 1 in 30,000 males
- “Christmas Disease”

- ~ 4000 in Canada
- No family history in ~30% of cases
- Males predominantly affected
- Female carriers can be symptomatic



Hemostasis Simplified: Hemophilia

Hemophilias

Trauma to the endothelium = TRIGGER

Platelets 1st on the scene

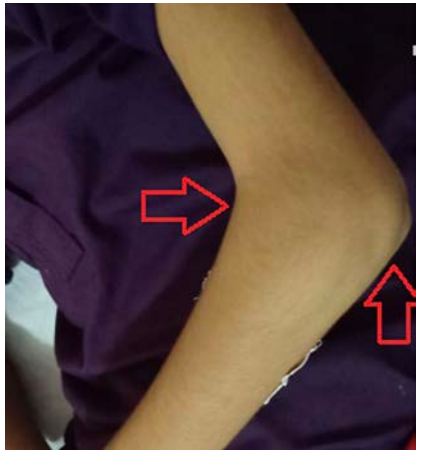
VWF glues platelets to the endothelium

Coagulation factors assemble to make a clot

Additional factors stabilize clot

Fibrinolytic system breaks down clot

Bleeding Symptoms



- Classically, musculoskeletal bleeding
  - Hemarthrosis
  - Intramuscular hematoma
  - Soft tissue hematoma
- Mucosal bleeding: mouth bleeding, epistaxis
- CNS (intracranial) bleeding
- Excessive and prolonged bleeding with trauma, procedures, surgery
- HMB symptomatic carriers

Majid et. al., 2019. Cureus 11(4): e4524. doi:10.7759/cureus.4524

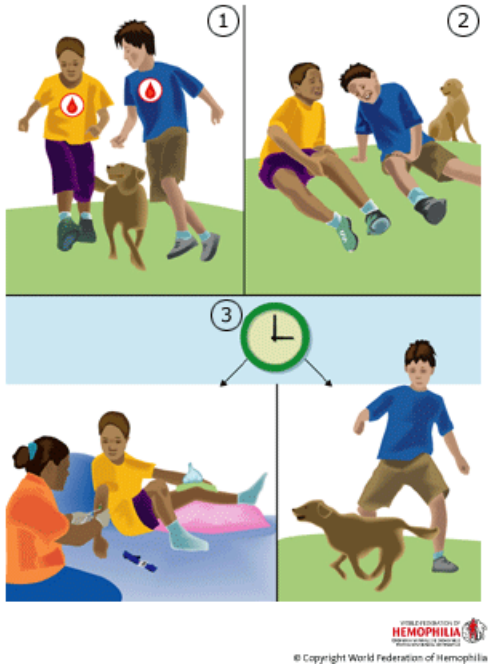
Grades of Severity

Severe <1%	• Spontaneous bleeding into joints/muscles • Severe bleeding with minimal trauma/surgery
Moderate 1-4%	• Occasional spontaneous bleeding • Severe bleeding with trauma/surgery
Mild 5-40%	• Severe bleeding with major trauma/ surgery

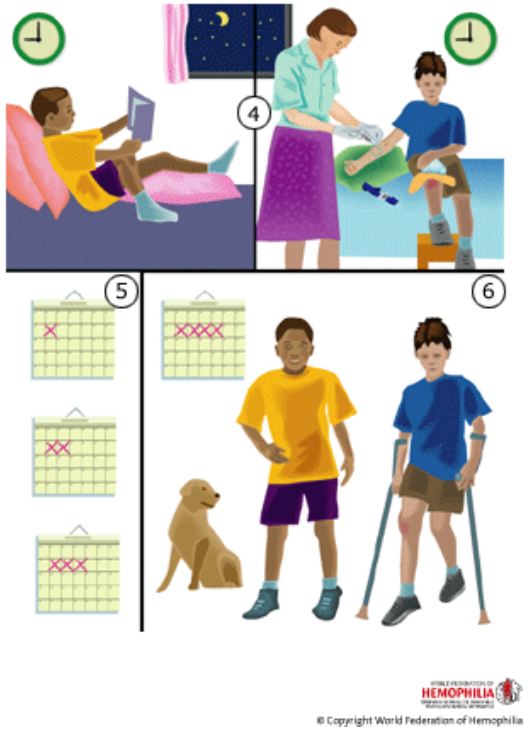
Srivastava A. WFH Guidelines for the management of hemophilia. Haemophilia 2013, 19:e1-e47.

Principles of Bleed Management

1. TREAT FIRST!



2. INVESTIGATE LATER!



Remember...
FactorFirst

PROMPT INFUSION will halt bleeding, minimize long-term complications and can save life. If bleeding persists, follow the guidelines for life or limb-threatening bleeds and call the:

Hemophilia Treatment Centre

Physician: _____

Nurse: _____

Day Phone: _____

Night Phone: _____

Delay in the restoration of hemostasis to the patient with hemophilia or von Willebrand disease may be life or limb-threatening.

- **PROMPT TRIAGE AND ASSESSMENT.**
- Determine the severity of the bleed.
- Recognize that bleeding in the head, spine, abdomen or pelvis may initially be occult and potentially life-threatening.
- **TREAT FIRST AND INVESTIGATE LATER – "FACTOR FIRST".**
- Avoid invasive procedures such as arterial punctures unless the patient has factor replacement.
- **NO** IM injections and **NO** ASA.
- The patient or guardian may be your most important resource, so do ask about specific treatment protocols.
- Contact the patient's Hemophilia Treatment Centre where a hematologist is always on call.
- Provide clear discharge instructions and arrange a follow-up plan or admit to hospital if necessary.

Use Universal Precautions

Patient Information:

Name: _____

Date of Birth: _____

Diagnosis: _____

Severity: _____ Level: _____

Response to desmopressin (DDAVP): ☐ no ☐ yes to _____ %

Inhibitors: ☐ 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:

LIFE OR LIMB-THREATENING BLEEDS

- Head (intracranial) and neck
- Chest, abdomen, pelvis, spine
- Iliopsoas muscle and hip
- Massive vaginal hemorrhage
- Extremity muscle compartments
- Fractures or dislocations
- Any deep laceration
- Any uncontrolled bleeding

MODERATE/MINOR BLEEDS

- Nose (epistaxis)
- Mouth (including gums)
- Joints (hemarthroses)
- Menorrhagia
- Abrasions and superficial lacerations

TREATMENT FOR LIFE OR LIMB-THREATENING BLEEDS

PATIENT MUST RECEIVE PRODUCT URGENTLY

Hemophilia A: (all severities)
Recombinant factor VIII concentrate 40-50 units/kg

Hemophilia B: (all severities)
Recombinant factor IX concentrate 100-120 units/kg >15 yrs
Recombinant factor IX concentrate 135-160 units/kg <15 yrs
The dosage for recombinant factor IX is substantially higher because of its lower recovery, particularly in children.

Von Willebrand Disease:
A VW factor concentrate containing factor VIII such as Humate-P 60-80 Ristocetin cofactor units/kg

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

TREATMENT FOR MODERATE/MINOR BLEEDS

PATIENT MUST RECEIVE PRODUCT WITHIN 30 MINUTES WHENEVER POSSIBLE

Hemophilia A: (severe/moderate)
Recombinant factor VIII concentrate 20-30 units/kg

Hemophilia A: (mild)
Desmopressin (Octostim/DDAVP) 0.3 mcg/kg (max. 20 mcg) –SC/IV

Hemophilia B: (severe/moderate/mild)
Recombinant factor IX concentrate 35-50 units/kg >15 yrs
Recombinant factor IX concentrate 50-70 units/kg <15 yrs
The dosage for recombinant factor IX is substantially higher because of its lower recovery, particularly in children.

Von Willebrand Disease:
Type 1 and Type 2A or 2B known to have used desmopressin safely and effectively – (Octostim/DDAVP) 0.3 mcg/kg (max. 20 mcg) –SC/IV
For patients not responding to desmopressin (such as Type 3 or Type 2B) use a VW factor concentrate containing factor VIII such as Humate-P 60-80 Ristocetin cofactor units/kg

For mucosal bleeds in all above add:
Tranexamic Acid (Cyklokapron) 25 mg/kg po tid 1-7 days (contraindicated if hematuria)

Dosages are patient specific – these are general guidelines only. Round doses up to the nearest vial.
If the products listed are not available, please call the nearest Canadian Blood Services or Héma-Québec Centre.

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

www.hemophilia.ca/emergency

Phone Numbers:

Nurse Coordinator: Phone: 416.864.5129
Fax: 416.864.5310
Pager: 416.685.9404 (enter return number on touch tone phone)

Medical Directors: 416.864.5128

Off-Hours Emergencies: 416.864.5431

Toronto and Central Ontario Comprehensive Hemophilia Program

St. Michael's Hospital
30 Bond Street
4th Floor, Cardinal Carter Wing
Toronto, ON M5B 1W8 Canada
stmichaelshospital.com

St. Michael's
Inspired Care.
Inspiring Science.

Fully affiliated with the University of Toronto.

Name: _____

Diagnosis: _____

Notes: _____

Give replacement therapy **immediately** for obvious or suspected bleeding or major trauma. Treat first, and then investigate.

Recommended Treatment:

Severe Bleed/Major Trauma

Mild/Moderate Bleed

Please contact the clinic for further information

Physician's Name _____

Physician's Signature _____

Treatment Basics – Acute Bleed

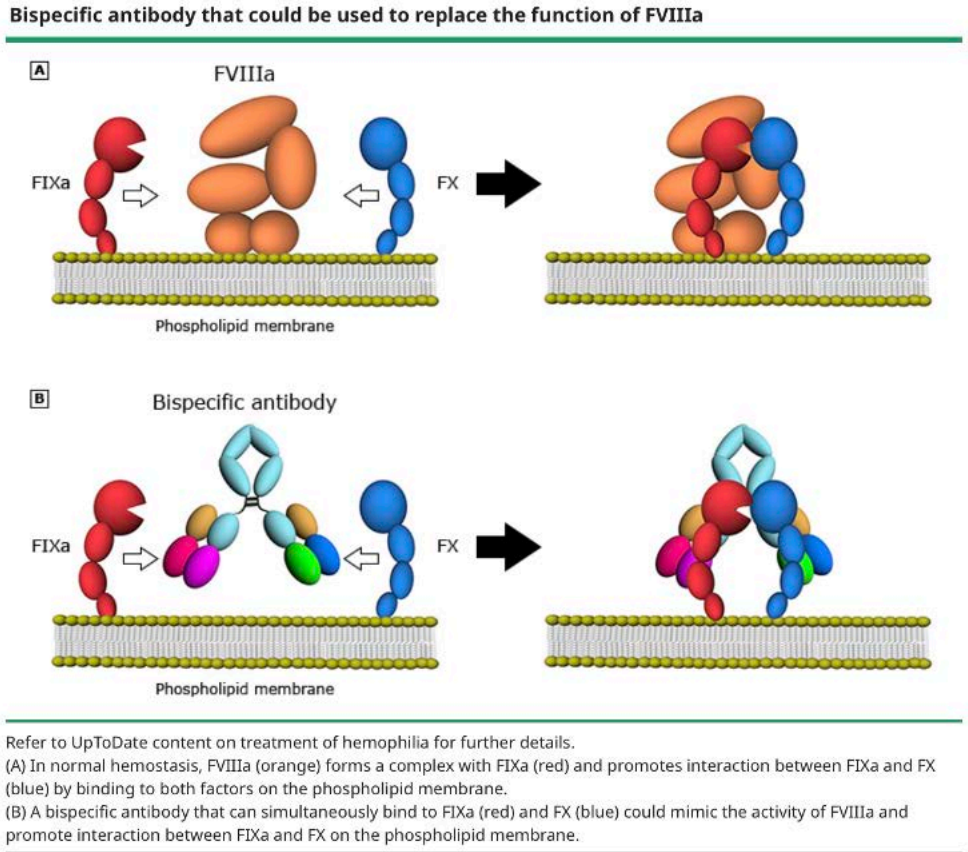
- ***Call Hematology / Transfusion Medicine***

- Increase deficient factor

- Medications:
  - Factor VIII: Xyntha, Kovaltry, Nuwiq, Adynovate, Jivi,
  - Factor IX: Benefix, Rebinyn
  - Adjunctive anti-fibrinolytic agent (TXA)
  - DDAVP (Desmopressin) – mild hemophilia (FVIII>10%)

- Non-factor therapies: Emicizumab
  - Avoid PCC – risk of thrombosis
  - Inhibitor present - rVIIa
  - No inhibitor – FVIII concentrate

- Role for prophylaxis



Treatment Dosing

Treatment of bleeding in hemophilia

	Hemophilia A	Hemophilia B
Major/severe bleeding* Raise factor level to 80 to 100%	Factor VIII dose of approximately 50 units/kg	Factor IX dose of approximately 100 to 120 units/kg
Hemarthrosis Raise factor level to 40 to 50%	Factor VIII dose of approximately 25 units/kg	Factor IX dose of approximately 50 to 60 units/kg

This table is a general guide and does not replace clinical judgment in determining the severity of bleeding, risk of morbidity, factor dosing, and need for other treatments. Mucosal bleeding can be treated with antifibrinolytics or local hemostatic therapies concomitantly with factor infusion. Patients with mild hemophilia A and minor bleeding may be treated with DDAVP if they have previously demonstrated a response. Patients with inhibitors may require a bypassing agent such as recombinant activated factor VII (rFVIIa) or FEIBA. Do not use antifibrinolytics with FEIBA concomitantly. Refer to UpToDate for additional information about management of bleeding in patients with hemophilia.

FEIBA: Factor eight inhibitor bypassing agent.

* Examples of major bleeding include bleeding affecting the central nervous system, airway, hip, deep muscle with neurovascular injury, or abdomen; bleeding that cannot be controlled with local therapies, or bleeding necessitating transfusion.

UpToDate®

FVIII/ FIX Products

Selected available factor VIII products for patients with hemophilia A

Product name	Half-life (hours)*	Characteristics
Standard half-life products¶		
Advate	9 to 12	Recombinant
Hemofil M	15	Plasma-derived; mAb-purified
Kogenate FS	11 to 15	Recombinant
Koate (previously called Koate DVI)	16	Plasma-derived; chromatography purified
Kovaltry	12 to 14	Recombinant
Novoeight	8 to 12	Recombinant
Nuwiq	12 to 17	Recombinant
Recombinate	15Δ	Recombinant
Xyntha	8 to 11	Recombinant
Longer-lasting products		
Adynovate	13 to 16	Recombinant; PEGylated
Afstyla	10 to 14	Recombinant; single chain
Eloctate	13 to 20	Recombinant; Fc fusion
Esperoct	17 to 22	Recombinant, glycoPEGylated
Jivi	17 to 21	Recombinant; PEGylated

This table is intended as a guide for rapid identification of the product the patient is using and its characteristics and should not be used to select a product or calculate dosing. Refer to prescribing information in the product insert and to UpToDate for the use of factor replacement in patients with hemophilia. The plasma-derived products listed here are ultra-high purity (mAb purified) or high purity (chromatography purified).

FS: formulated with sucrose; mAb: monoclonal antibody.

* Half-lives are approximate. Half-lives are generally shorter for children than adults when assessed in pharmacokinetic studies. The half-life of factor VIII products without modifications to extend half-life is considered to be approximately 12 hours. The half-life should be determined for the individual patient. Refer to product information and institutional guidelines for additional dosing and monitoring information.

¶ Monoclate-P was discontinued in early 2018. Helixate FS manufacturing was discontinued in 2018, with supply available through early 2019.

Δ Adults only.

Selected available factor IX products for patients with hemophilia B

Product name	Half-life (hours)*	Characteristics
Standard half-life products		
AlphaNine SD	18¶	Plasma-derived; solvent/detergent treated
BeneFIX	16 to 19	Recombinant
Ixinity	24Δ	Recombinant
Mononine	23¶	Plasma-derived; mAb purified
Rixubis	23 to 26	Recombinant
Longer-lasting products		
Alprolix	54 to 90	Recombinant; Fc fusion
Idelvion	104¶	Recombinant; albumin fusion
Rebinyn	103 to 115	Recombinant; glycoPEGylated

This table is intended as a guide for rapid identification of the product the patient is using and its characteristics. Refer to the product information and to UpToDate for the use of factor replacement in patients with hemophilia.

SD: solvent/detergent treated; mAb: monoclonal antibody.

* Half-lives are **approximate**. Half-lives are generally shorter for children than adults when assessed in pharmacokinetic studies. The half-life of factor IX products without modifications to extend half-life is considered to be approximately 24 hours. The half-life should be determined for the individual patient. Refer to product information and institutional guidelines for additional dosing and monitoring information.

¶ Adults only.

Δ 12 years and older.

MCWBD

Multidisciplinary Clinic
for Women with
Bleeding Disorders

MCWBD
Multidisciplinary Clinic for Women with Bleeding Disorders

RECOMMENDATIONS FOR L&D and POST-PARTUM MANAGEMENT OF MOTHER AND BABY

St. Michael's
Inspired Care.
Inspiring Science.

Demographics:
Name: XXX
DOB: XXX
MRN: XXX

Bleeding Disorder Diagnosis:
Hemophilia A Carrier
Baseline Factor VIII level 69%. Auto-correction (normalization) during pregnancy Factor VIII level 146% on January 25, 2016.

Expected Delivery Date:
June 15, 2016 - Plan for spontaneous vaginal delivery
Carrying a female baby therefore 50% chance of being a carrier and is unlikely to experience bleeding complications at birth.

OB Recommendations:
1. **Avoidance of invasive instrumentation** (forceps, vacuum, scalp electrodes) and prolonged labour.
2. Vaginal delivery as per usual OB indications.

Anesthesia Recommendations:
1. Does not require additional hemostatic coverage prior to any intervention.
2. Provide neuraxial anesthesia as per protocol.

Hematology Recommendations - Care of Mother:
*Mother is at **risk for post-partum hemorrhage** – her factor VIII levels can drop rapidly post-partum*
1. **No** upfront administration of **hemostatic agents needed** (whether C-section or vaginal delivery) →factor VIII level **normal** at **146%** (spontaneous correction of factor deficiency in pregnancy).
2. First dose of post-partum **tranexamic acid** (cyklokapron) to be given **1 hour post-partum** – 1 g PO.
3. Continue post-partum **tranexamic acid** (cyklokapron) at 1 gram PO TID for a total of **10 days.**
4. CBC and Factor VIII activity assay to be drawn daily in the AM.
5. Call hematology on-call during off hours or Dr. Sholzberg directly, during regular hours, at XXX-XXX-XXXX.

Hematology Recommendations - Care of the Newborn:
1. **Pediatrics to attend delivery and perform an immediate physical examination to assess for signs of bleeding.** Given the inheritance pattern of hemophilia in family, a female baby has a 50% chance of being a carrier.
2. Draw **cord blood** for CBC, INR, PTT and factor VIII assay.
3. Should there be any clinical signs of excessive bruising or bleeding, **an urgent head ultrasound should be done.**
4. Avoid any unnecessary instrumentation or blood draws.
5. Vitamin K may be given IM **using a small gauge needle and apply pressure x 5-10 minutes post injection.**
6. Contact SickKids Pediatric Hematology Fellow on-call at XXX-XXX-XXXX in the event you suspect or confirm bleeding in the neonate.

Georgina Floros	Dr. Michelle Sholzberg	Dr. Filomena Meffe	Dr. Rachel Martin	Dr. Jillian Baker
Nurse Coordinator	Adult Hematology	OB/GYN	Anesthesia	Pediatric Hematology

Conclusion

Question

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 most appropriate course of action is the following:

A. Administer recombinant factor VIIa at 90 mcg/kg IV 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 recombinant factor VIII at 30 U/kg IV if positive
C. Infuse Recombinant factor VIII at 50 U/kg IV 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

Helpful Materials

New Guidelines 2021

CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

Nathan T. Connell,[1,*] Veronica H. Flood,[2,*] Romina Brignardello-Petersen,[3] Rezan Abdul-Kadir,[4] Alice Arapshian,[5] Susie Couper,[6] Jean M. Grow,[7] Peter Kouides,[8] Michael Laffan,[9] Michelle Lavin,[10] Frank W. G. Leebeek,[11] Sarah H. O'Brien,[12] Margareth C. Ozelo,[13] Alberto Tosetto,[14] Angela C. Weyand,[15] Paula D. James,[16] Mohamad A. Kalot,[17] Nedaa Husainat,[17] and Reem A. Mustafa[17]

[1]Hematology Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Versiti Blood Research Institute, Medical College of Wisconsin, Milwaukee, WI; [3]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; [4]Department of Obstetrics and Gynaecology and Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Foundation Hospital and Institute for Women's Health, University College London, London, United Kingdom; [5]Middle Village, NY; [6]Maylands, WA, Australia; [7]Department of Strategic Communication, Marquette University, Milwaukee, WI; [8]Mary M. Gooley Hemophilia Treatment Center, University of Rochester, Rochester, NY; [9]Centre for Haematology, Imperial College London, London, United Kingdom; [10]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland and National Coagulation Centre, St James's Hospital, Dublin, Ireland; [11]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands; [12]Division of Hematology/Oncology, Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH; [13]Hemocentro UNICAMP, University of Campinas, Campinas, Brazil; [14]Hemophilia and Thrombosis Center, Hematology Department, S. Bortolo Hospital, Vicenza, Italy; [15]Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI; [16]Department of Medicine, Queen's University, Kingston, ON, Canada; and [17]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

CLINICAL GUIDELINES

blood advances

ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease

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[1]Department of Medicine, Queen's University, Kingston, ON, Canada; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Pharmacology Consulting, Princeton Junction, NJ; [4]Rutgers–Robert Wood Johnson Medical School, New Brunswick, NJ; [5]Department of Pediatrics, Washington University in St. Louis, St. Louis, MO; [6]Division of Thrombosis and Hemostasis, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands; [7]Marseille, France; [8]Diagnostic Laboratories, Versiti Blood Research Institute, Milwaukee, WI; [9]Auburn, ME; [10]Bloodworks Northwest, Seattle, WA; [11]Division of Hematology, University of Washington, Seattle, WA; [12]National Women's Health, Auckland City Hospital, Auckland, New Zealand; [13]Northern Cancer Service, Launceston General Hospital, Launceston, TAS, Australia; [14]Versiti Blood Research Institute, Milwaukee, WI; [15]Irish Centre for Vascular Biology, Royal College of Surgeons in Ireland, Dublin, Ireland; [16]Coraopolis, PA; [17]Aflac Cancer and Blood Disorders, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; [18]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; and [19]Outcomes and Implementation Research Unit, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Von Willebrand Disease

POCKET GUIDES

von Willebrand Disease

Presented by ASH in 2012, adapted from: The diagnosis, evaluation, and management of von Willebrand Disease. National Heart, Lung, and Blood Institute, NIH Pub.No. 08-5832. December, 2007.

Thank you!

- "Principles of Management of Urgent Bleeding in Hemophilia" - developed by Dr. Jerry Teitel

http://www.stmichaelshospital.com/programs/hemophilia/resources-urgent-bleeding.php

- Illustrated Review of Bleeding Assessment Tools and Coagulation tests (Elbaz, Sholzberg)

https://onlinelibrary.wiley.com/doi/full/10.1002/rth2.12339

- World Federation of Hemophilia Guidelines- 3rd Ed. https://elearning.wfh.org/resource/treatment-guidelines/