Introduction to Bleeding Disorders

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HEMATOLOGY-ONCOLOGY CLINICAL RESEARCH GROUP

UNIVERSITY OF TORONTO FACULTY OF MEDICINE

MCWBD

Multidisciplinary Clinic for Women with Bleeding Disorders

Medicine UNIVERSITY OF TORONTO

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Disclaimer

- No relevant conflicts of interest

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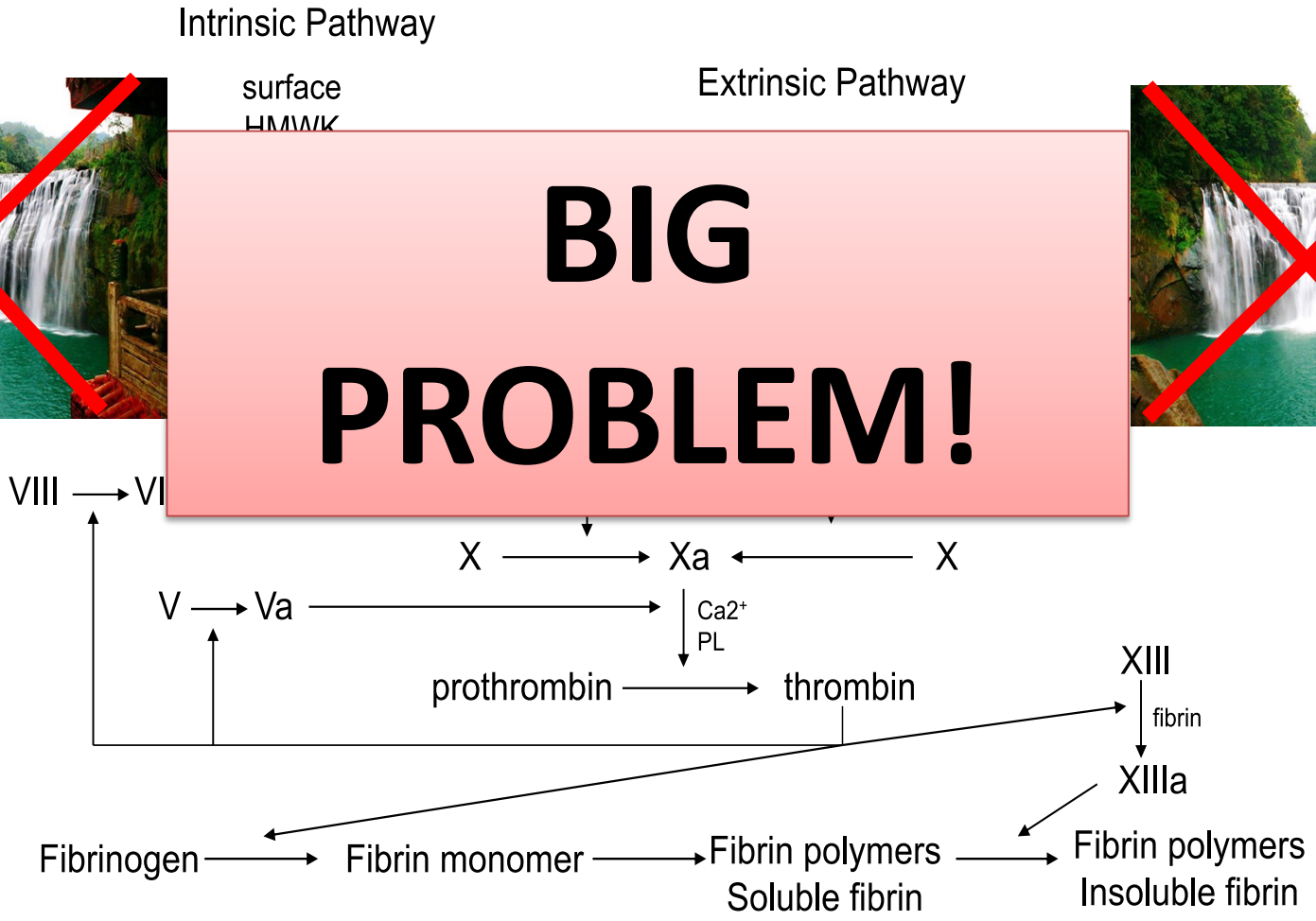
Objectives

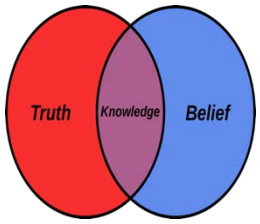
- **Quick review – basics of hemostasis**
- **Quick review – basics of routine coagulation**
- **Review some selected disorders of hemostasis and treatment principles**

Review basics of hemostasis

Updated Coagulation Cascade

BIG PROBLEM!





Walsh PN. Biochemistry 2007,Nov 6; 46(44): 12886-12887

Hemostasis Simplified




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



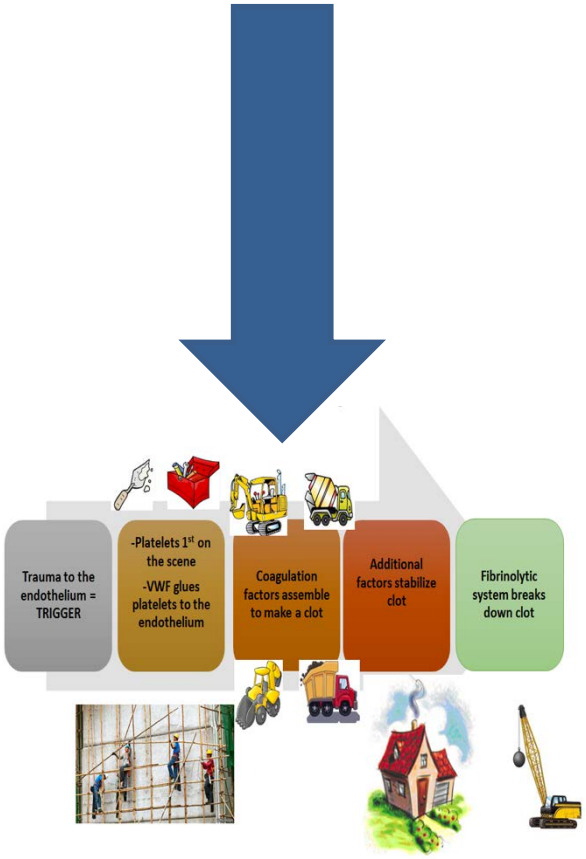


Review basics of routine coagulation tests

Basic Clot Based Tests

- Prothrombin Time (PT)
  - International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (PTT)
- END RESULT = CLOT FORMATION
- **Sensitivity of 1-2% → normal PT/PTT does not R/O a bleeding disorder**

PT/INR & PTT



Hemostasis Simplified: Static Assays

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

PTT
PT/INR

How important is the bleeding history?

Understand the utility of Bleeding Assessment Tools (BATs)

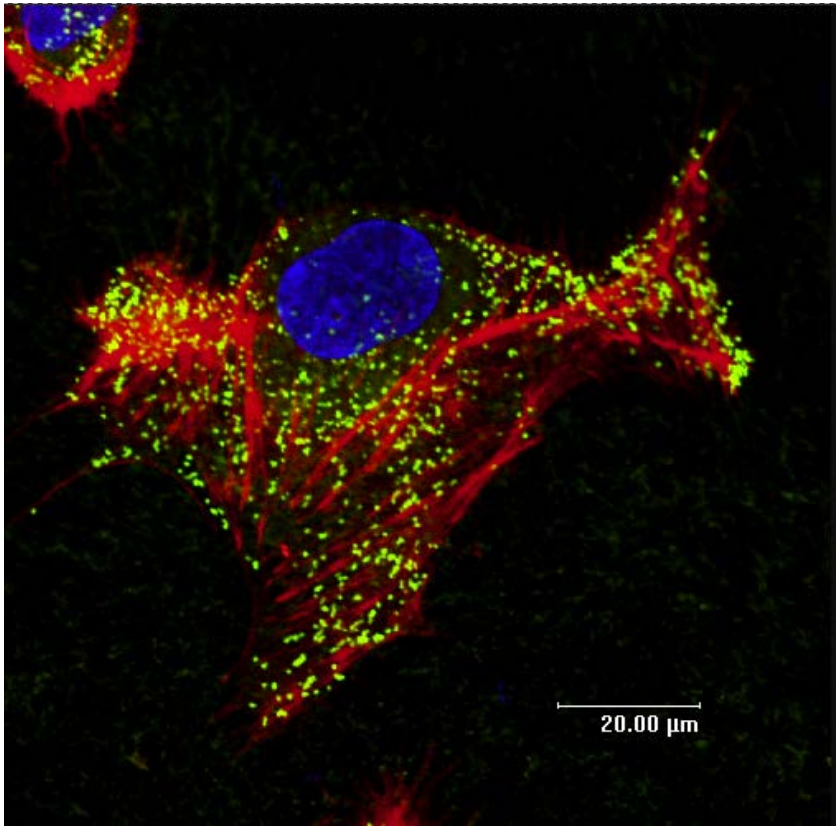
The Bleeding History is the most Important Test of Hemostasis

Hemostasis Simplified: BAT

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

Review some disorders of hemostasis
1) Von Willebrand disease
2) Hemophilia

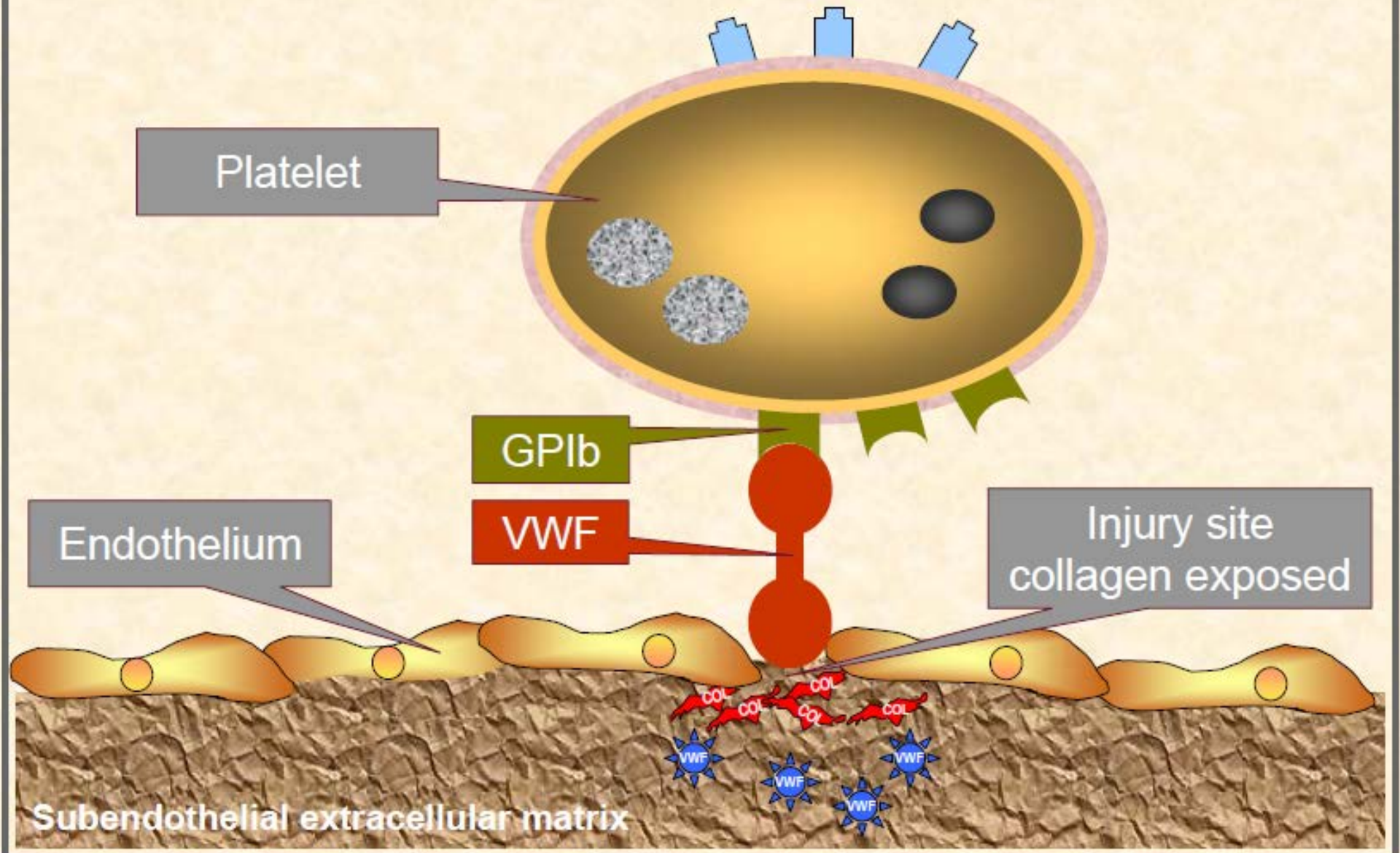
Von Willebrand Factor



- synthesized by endothelial cells and megakaryocytes
- stored in Weibel-Palade bodies (endothelial cells) and alpha granules (platelets)
- platelet adhesion and aggregation
- chaperones FVIII

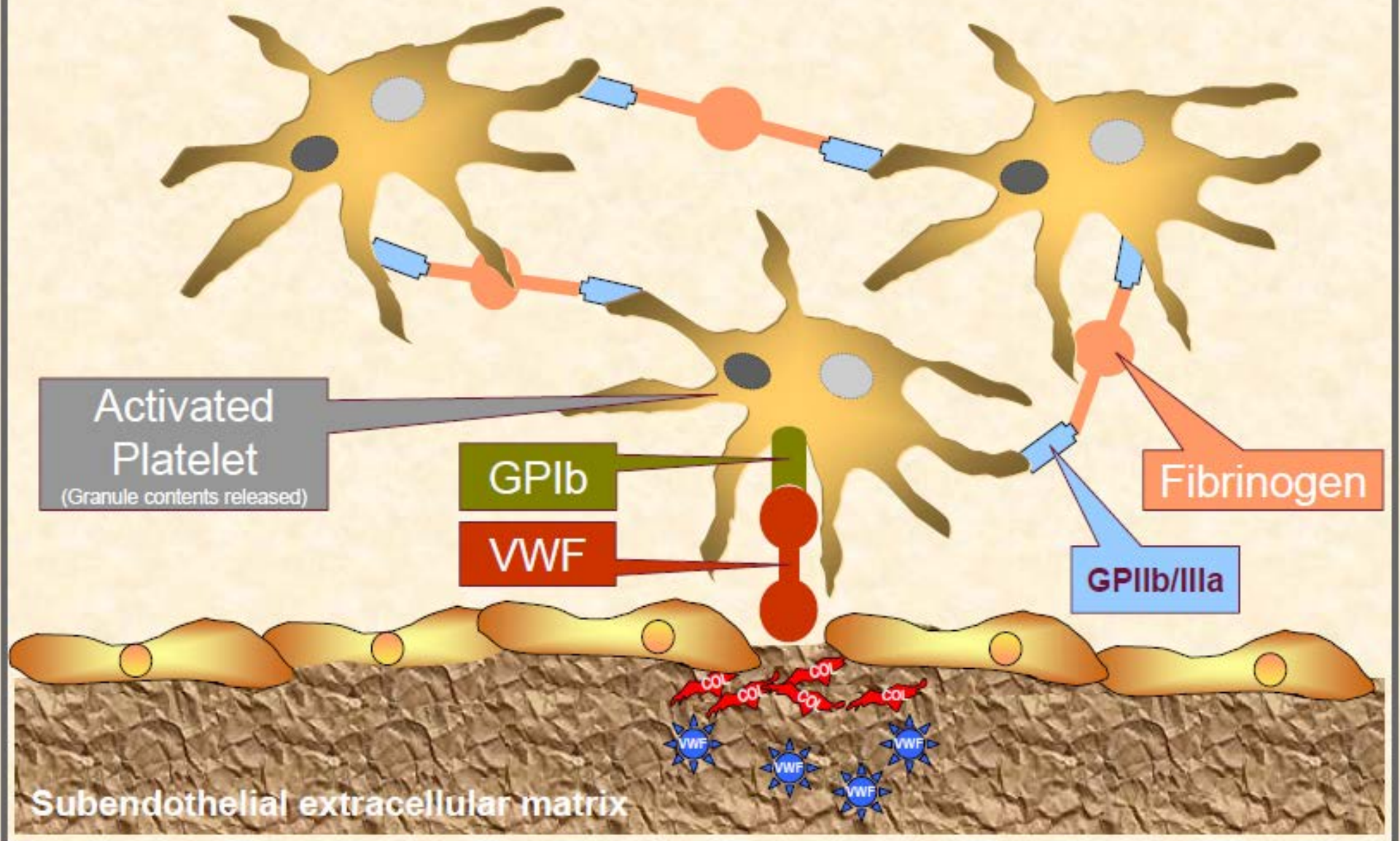
CLOT-ED

Platelet Adhesion

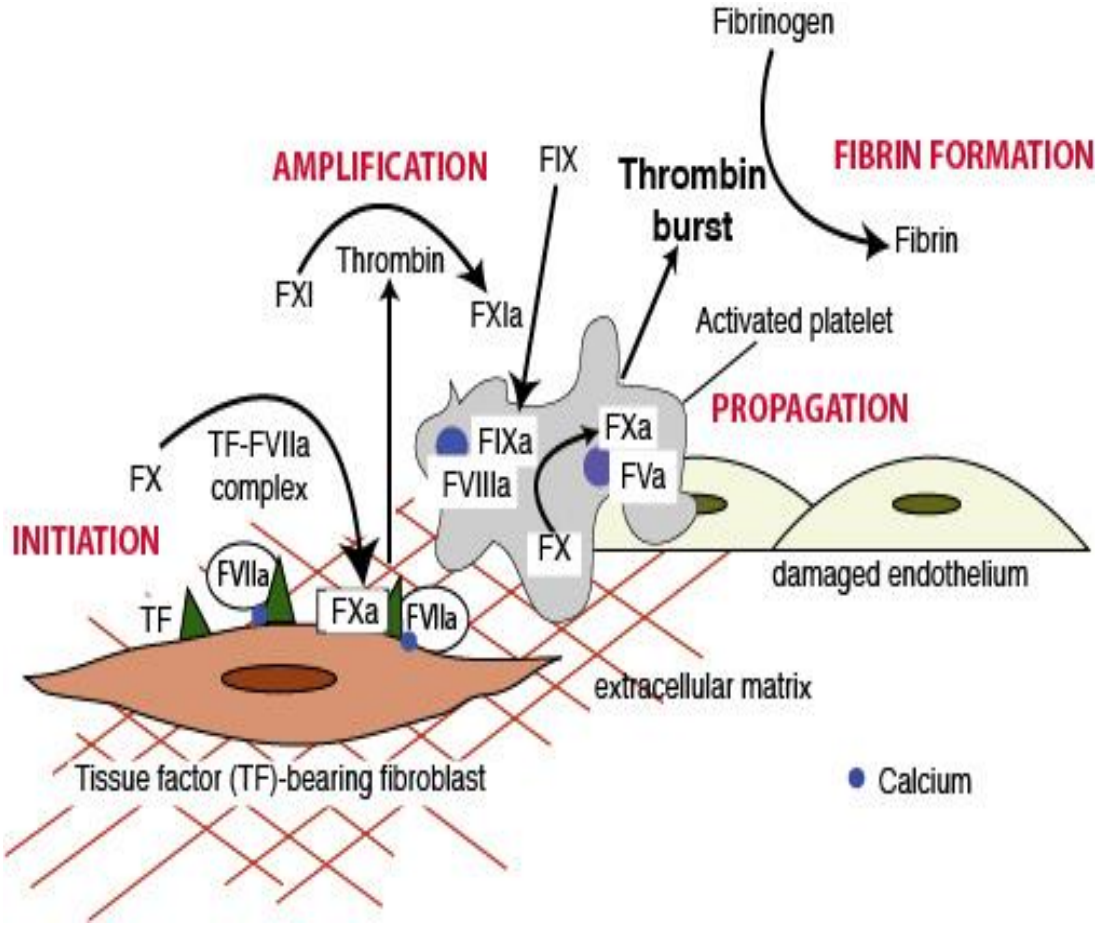


CLOT-ED

Platelet Aggregation



Von Willebrand Factor: Secondary Hemostasis



Slide courtesy of Dr. Khandelwal

Hemostasis Simplified

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



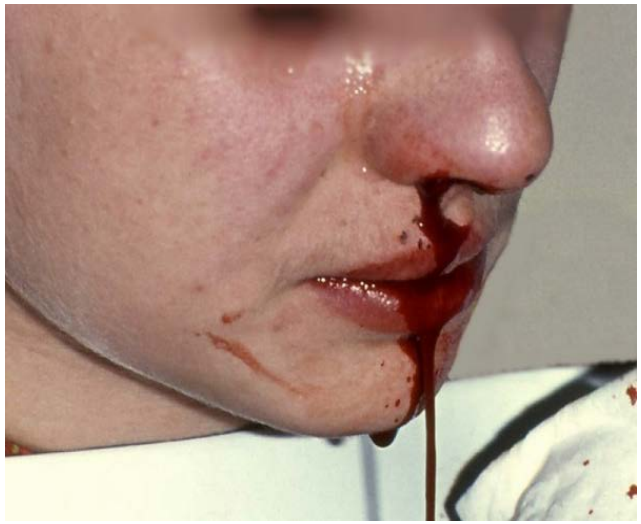


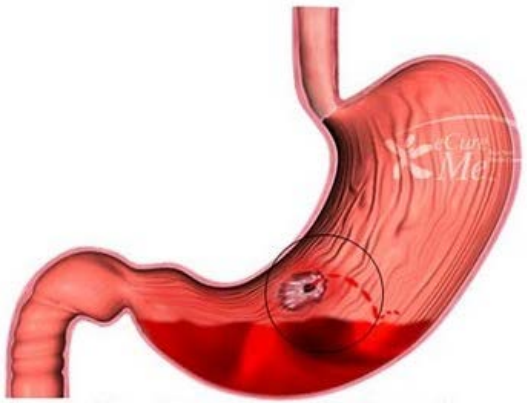
The Diagnosis of von Willebrand Disease:
3 Clinical Components

1. Bleeding symptoms
2. +/- Family history
3. Laboratory results

Bleeding Symptoms

- **Mucocutaneous**
  - Menorrhagia
  - Epistaxis
  - Bruising
  - Excessive bleeding from minor wounds
  - GI bleeding
  - Oral cavity/post-dental procedure
  - Post-operative
  - Post-partum
- **Musculoskeletal (Type 3 VWD)**
  - Hemarthrosis
  - Soft tissue, muscle hematomas



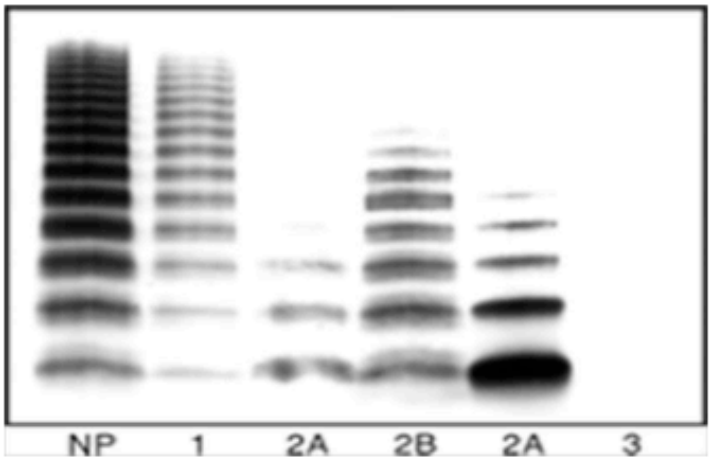


Laboratory Tests

- 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**

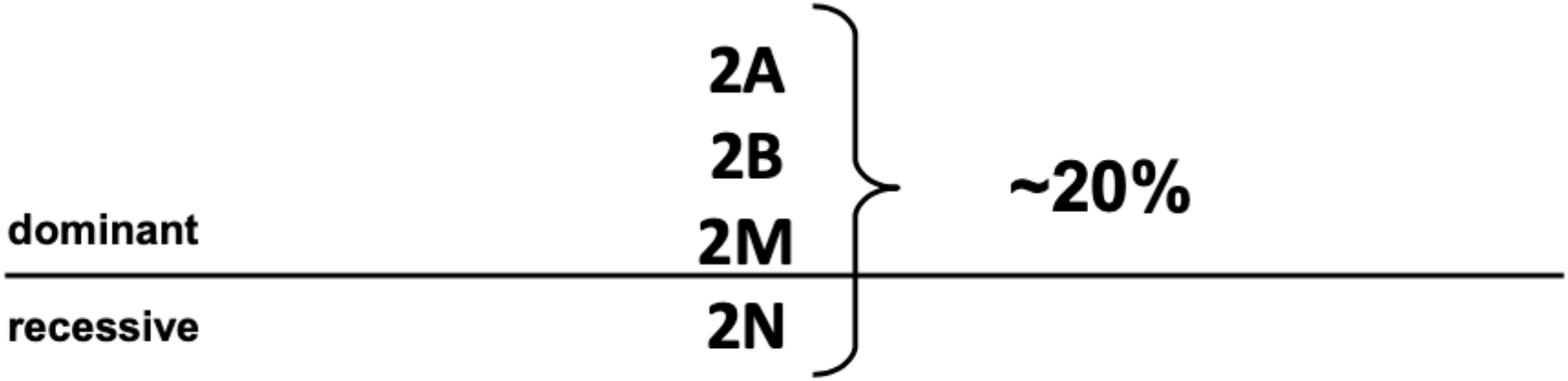
- Multimers
- Ristocetin Induced Platelet Agglutination (2B)
- VWF:FVIII binding activity
- VWF:Collagen binding activity
- VWF propeptide antigen
- Genetic testing – Types 2 and 3



ISTH VWD Classification

Type 1 - Mild/moderate **Quantitative** trait ~80%

Type 2 - **Qualitative** traits

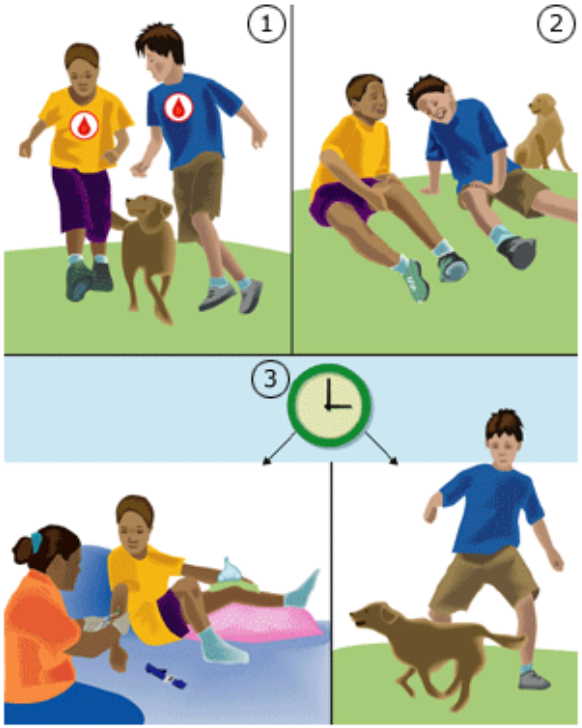


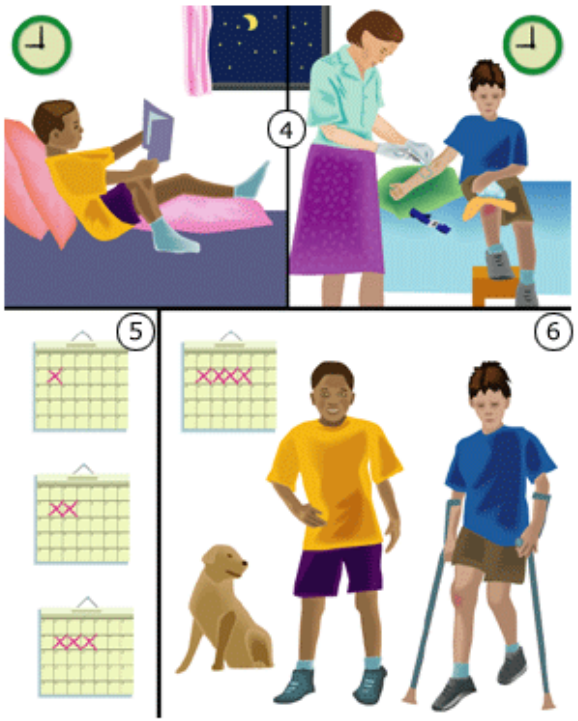
Type 3 - Severe **Quantitative** trait ~ 1 per million

Sadler et al JTH 2006

Principles of Bleed Management

- **Treat first**
- **Investigate later**



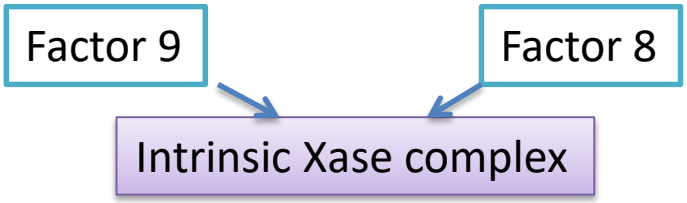


Treatment

CALL HEMATOLOGY/TRANSFUSION MED

- DDAVP (Desmopressin)
- Anti-fibrinolytic agents (TXA)
- Transfusion based – VWF:FVIII concentrate
  - Humate-P or Wilate
- Consider prophylactic care

The Hemophilias: X linked



Hemophilia B

- Factor IX deficiency
- 1 in 30,000 males

Hemophilia A

- Factor VIII deficiency
- 1 in 5,000 males

~4000 in Canada

No family history
In 30% of cases

Hemostasis Simplified

Hemophilias




Trauma to the endothelium = TRIGGER

-Platelets 1st on the scene

-VWF glues platelets to the endothelium

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Clinical Manifestations

- Musculoskeletal bleeding
  - Hemarthrosis
  - Intra-muscular hematoma
- Mouth bleeding, epistaxis
- Intracranial bleeding
- Bleeding with trauma, procedures, surgery
- Menorrhagia (symptomatic carriers)

Clinical Manifestations:
Bleeding Severity α Factor Levels

- **Severe < 0.01 U/mL (<1%)**
  - frequent, spontaneous, life-threatening with trauma or surgery

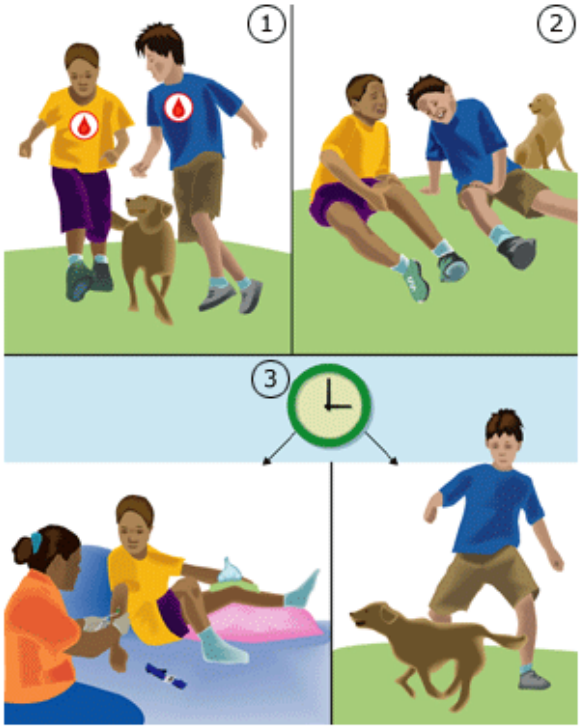
- **Moderate 0.01 - 0.05 U/mL (1-5%)**
  - provoked by minor trauma, serious with trauma or surgery

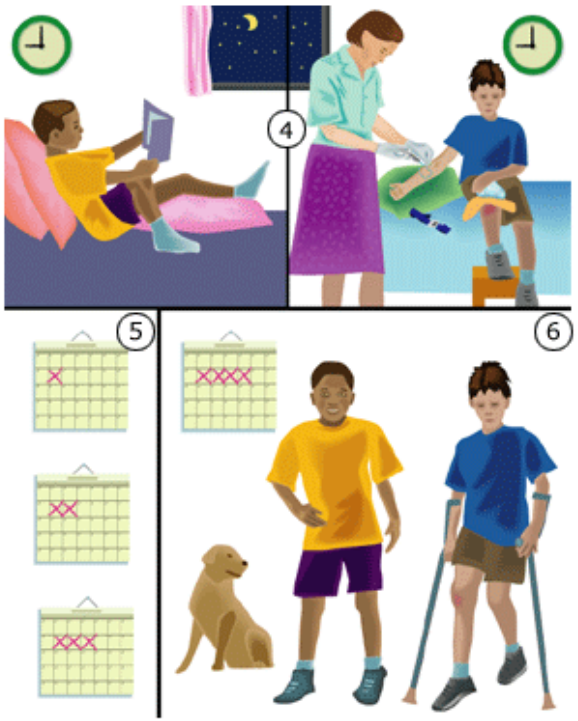
- **Mild > 0.05 U/mL (>5%)**
  - mild symptoms, can be asymptomatic aside from trauma or surgery

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

Principles of Bleed Management

- **Treat first**
- **Investigate later**





Treatment

CALL HEMATOLOGY/TRANSFUSION MED

- Anti-fibrinolytic agents (TXA)
- Transfusion based – specific factor concentrate
  - Factor VIII: Xyntha, Kovaltry, Nuwiq, Adynovate, Jivi
  - Factor IX: Benefix, Rebinyn
- DDAVP/Desmopressin – for mild hemophilia A (FVIII >10%)
- Consider prophylactic care (Emicizumab)

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:

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

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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 _____

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Multidisciplinary Clinic for Women with Bleeding Disorders

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

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

Conclusions

- Clinical management requires understanding of disease mechanisms and therapeutic properties
- The PT and aPTT are NOT the be all, end all
- Consider baseline and surgical bleeding risk
- Do not delay treatment in patients with bleeding disorders – BELIEVE THEM
- **Consult hematology/transfusion medicine**

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:
  1. Administer recombinant factor VIIa at 90 mcg/kg IV and arrange for a CT scan of the head to rule out intracranial bleed
  2. Arrange for a CT scan to rule out intracranial bleed and infuse recombinant factor VIII at 30 U/kg IV if positive
  3. Infuse Recombinant factor VIII at 50 U/kg IV and arrange for a CT head thereafter to rule out intracranial bleed
  4. Draw blood for factor VIII activity level and treat with factor VIII based on the result when obtained

Helpful Materials

Target: Outpatient Setting

BLEEDING ASSESSMENT TOOL (BAT): HOW TO ADMINISTER AND INTERPRET

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BACKGROUND

- BATs are good screening tests for bleeding disorders
- The Condensed MCMDM-1* BAT is the one used at St. Michael's hospital
- Validated for use in von Willebrand disease, platelet disorders, hemophilia carriers, and other mild bleeding disorders (sensitivity: 85-100%, NPV: 0.92-1.0)[1-5]

ADMINISTRATION

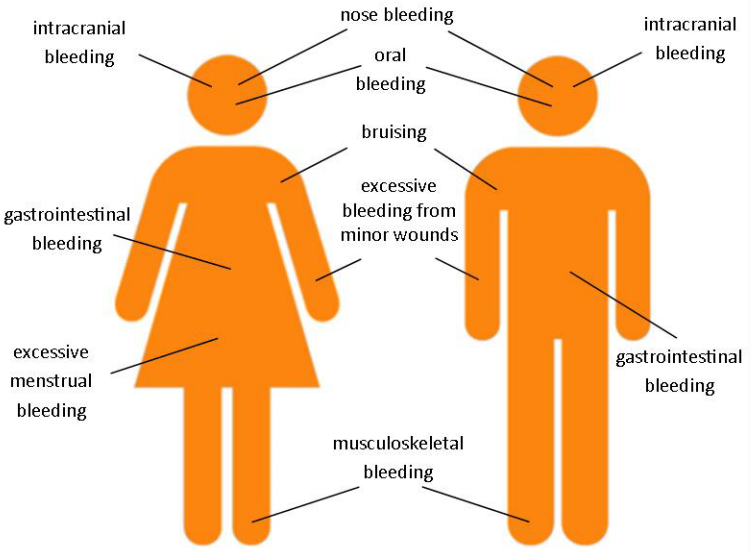
- Time to complete: 5-10 minutes
- Expert administered (MD, NP, or RN)

INTERPRETATION

- Negative BAT score (<4 for adults, <2 for children) AND negative family history of bleeding
  - ⇒ no additional hemostatic evaluation required
- Positive BAT score (≥4 for adults, ≥2 for children) AND/OR positive family history of excessive bleeding
  - ⇒ **Hematology referral suggested**

BLEEDING SYMPTOM CATEGORIES

1. Spontaneous Bleeding



2. Bleeding with Challenges

- Surgery
- Dental Extraction
- Childbirth

*MCMDM-1 = Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand disease

1. Bowman et al. (2008) 2. Tosetto et al. (2011) 3. Azzam et al. (2012) 4. Rydz and James (2012) 5. Paroskie et al. (2015)

Target: Acute Care Setting

WHEN TO ORDER COAGULATION TESTS (PT/INR & aPTT)

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PT = Prothrombin Time
INR = International Normalized Ratio
aPTT = Activated Partial Thromboplastin Time

- Warfarin therapy
- Liver disease
- Risk factor for vitamin K deficiency (e.g. malnutrition, fat soluble vitamin malabsorption, cholestasis, prolonged antibiotics)

CONSIDER PT/INR

- IV heparin monitoring
- IV argatroban monitoring
- Suspected hemophilia A/B, Factor XI deficiency, severe von Willebrand disease

CONSIDER aPTT

- Bleeding patient
- Suspected severe DIC
- Active trauma patient (Trauma panel)
- Patient requiring a Massive Transfusion Protocol (MTP or MTP-Trauma panel)
- Patient who will receive thrombolytic therapy

CONSIDER BOTH PT/INR & aPTT

TOP 5 REASONS NOT to ORDER PT/INR or aPTT

1. As routine blood work.
2. As a routine pre-op screen in a patient without a personal/family bleeding history.
3. For monitoring of direct oral anticoagulant (DOAC) therapy (e.g. dabigatran, rivaroxaban, apixaban).
4. For monitoring of low molecular weight heparin (LMWH) therapy (e.g. dalteparin, enoxaparin, tinzaparin, fondaparinux).
5. For monitoring of thromboprophylaxis (e.g. heparin 5000 U SC BID; dalteparin 5000 U SC QD).

Form No. XXXXX Dev. 02/2016

ED, ICU

Target: Inpatient Care Setting

WHEN TO ORDER COAGULATION TESTS

(PT/INR & aPTT)

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- Bleeding patient

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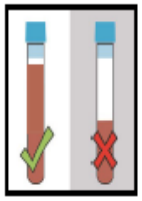
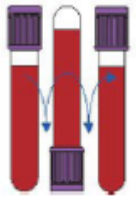
ORDER OF DRAW

Tube Closure Color	Collection Tube	Mix by Inverting	Min. Clot Time
	Blood Cultures – SPS	8 to 10 times	N/A
	Citrate Tube (Light Blue)	3 to 4 times	N/A
	Serum Separator Tubes (Gold and Tiger)	5 times	30 minutes
	Serum Tube (Red)	5 times (plastic) None (glass)	60 minutes
	Rapid Serum Tube (Orange)	5 to 6 times	5 minutes
	Plasma Separator Tube	8 to 10 times	N/A
	Heparin Tube (Green)	8 to 10 times	N/A
	EDTA Tube (Lavender)	8 to 10 times	N/A
	PPT Separator Tube (Pearl)	8 to 10 times	N/A
	Fluoride Tube (Gray)	8 to 10 times	N/A

BLOOD DRAW REMINDERS



1. Draw a discard tube first.
2. Fill the entire tube.
3. Invert the tube several times.
4. DO NOT draw from an IV.



http://www.bd.com/resource.aspx?IDX=1157

Thank you!

michelle.sholzberg@unityhealth.to
Twitter: @sholzberg

Illustrated Review of Bleeding Assessment Tools and Coagulation tests (Elbaz, Sholzberg) https://onlinelibrary.wiley.com/doi/full/10.1002/rth2.12339

"Principles of Management of Urgent Bleeding in Hemophilia" - developed by Dr. Jerry Teitel http://www.stmichaelshospital.com/programs/hemophilia/resources-urgent-bleeding.php

http://thrombosiscanada.ca