Introduction to Congenital Bleeding Disorders

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Medicine
UNIVERSITY OF TORONTO

St. Michael's
Inspired Care. Inspiring Science.

Disclosures

- No relevant conflicts of interest.

- Acknowledgement
  - Dr. Michelle Sholzberg – adaptation of her slides.

Objectives

1

Review the basics of hemostasis

2

Review the basics of routine coagulation

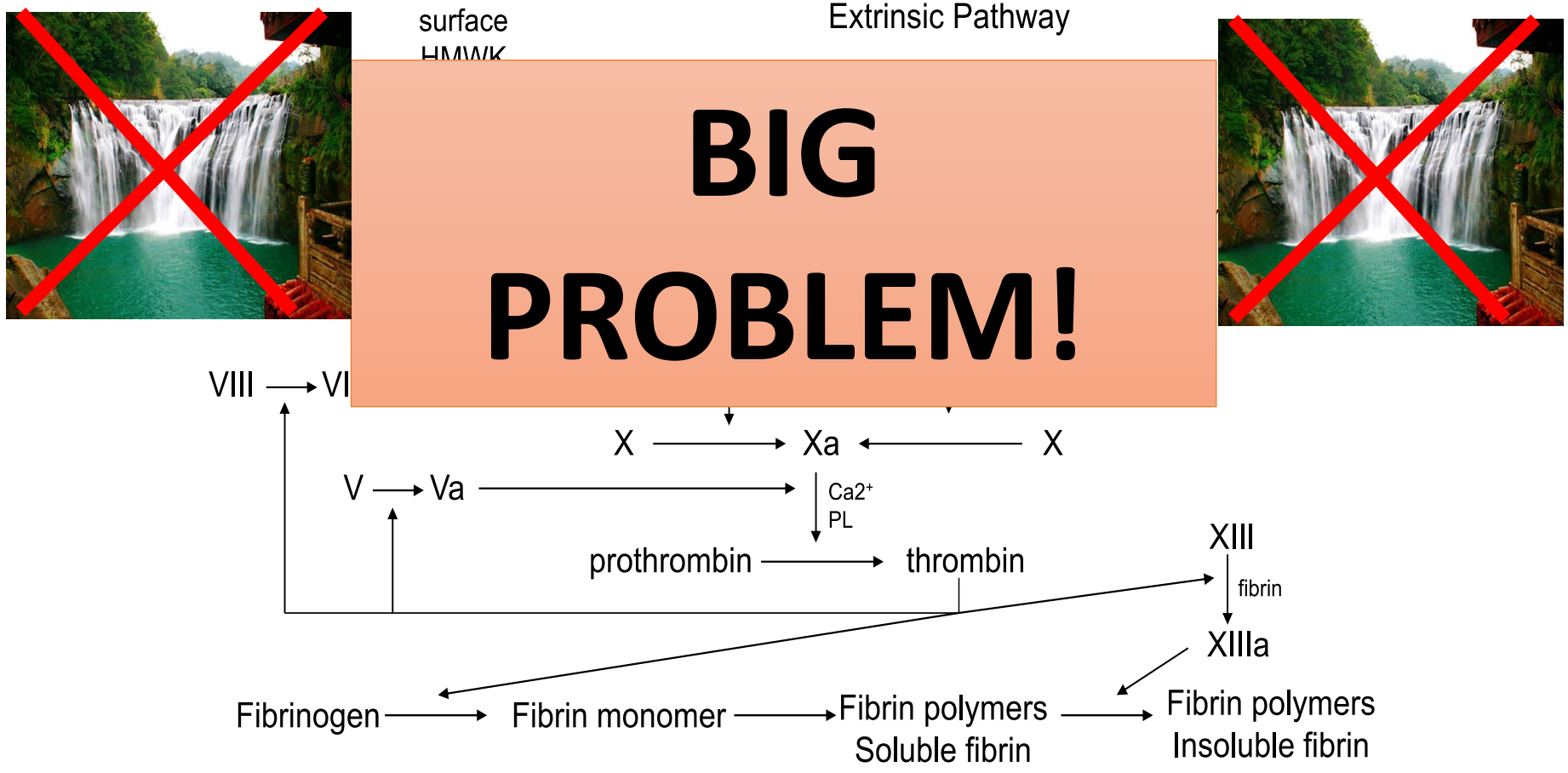
3

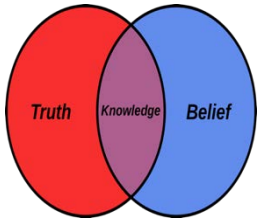
Review selected disorders of hemostasis and the treatment principles

- Von Willebrand Disease
- Hemophilia A and B

Basics of Hemostasis

Updated Coagulation Cascade





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

Basics of Routine Coagulation Tests

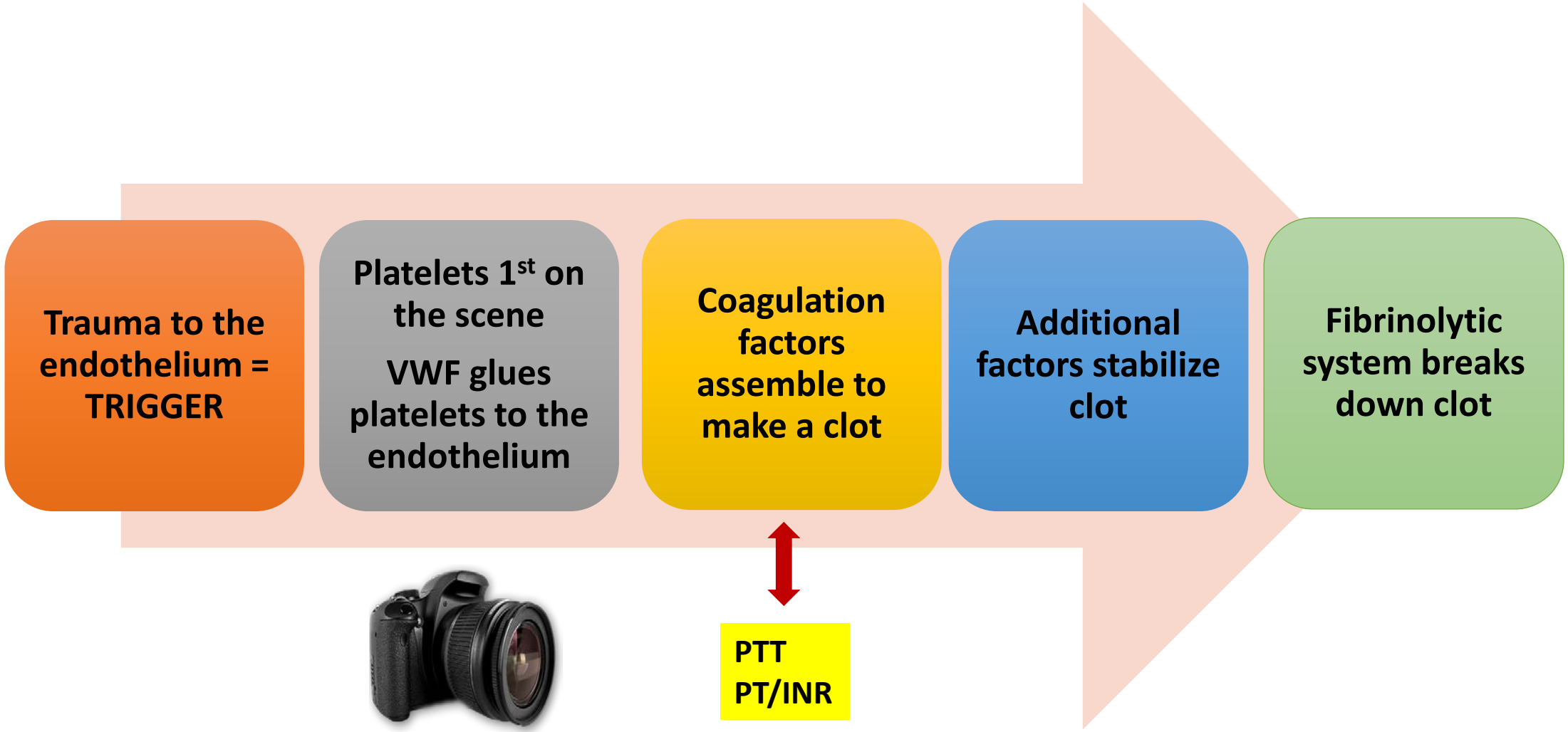
Basic Clot-Based Tests

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

END RESULT – CLOT FORMATION

Sensitivity of 1-2% → normal PT/PTT 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*

Trauma to the endothelium = TRIGGER

BAT

Platelets 1st on the scene

VWF glues platelets to the endothelium

BAT

Coagulation factors assemble to make a clot

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Additional factors stabilize clot

BAT

Fibrinolytic system breaks down clot

BAT

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

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

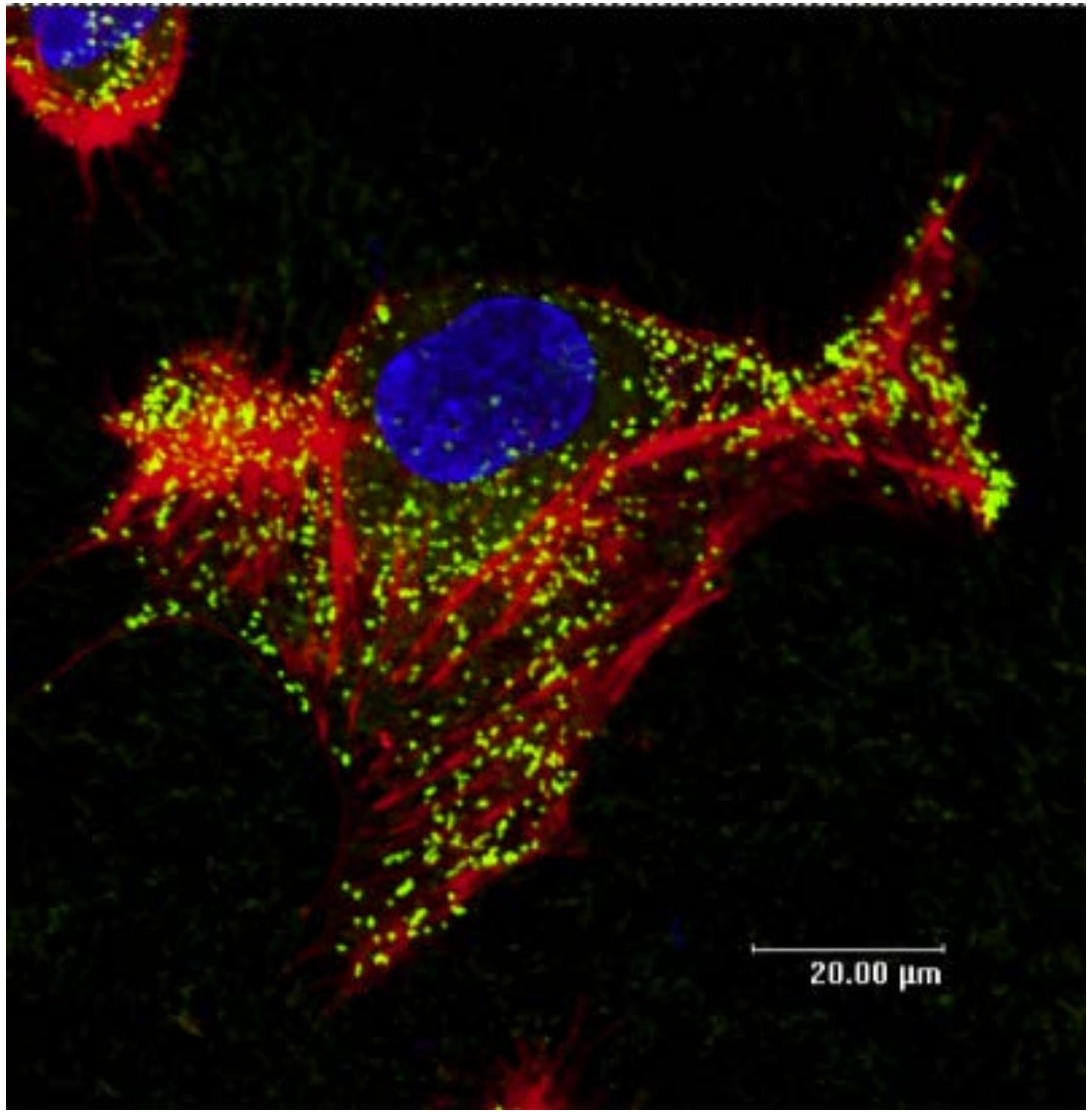
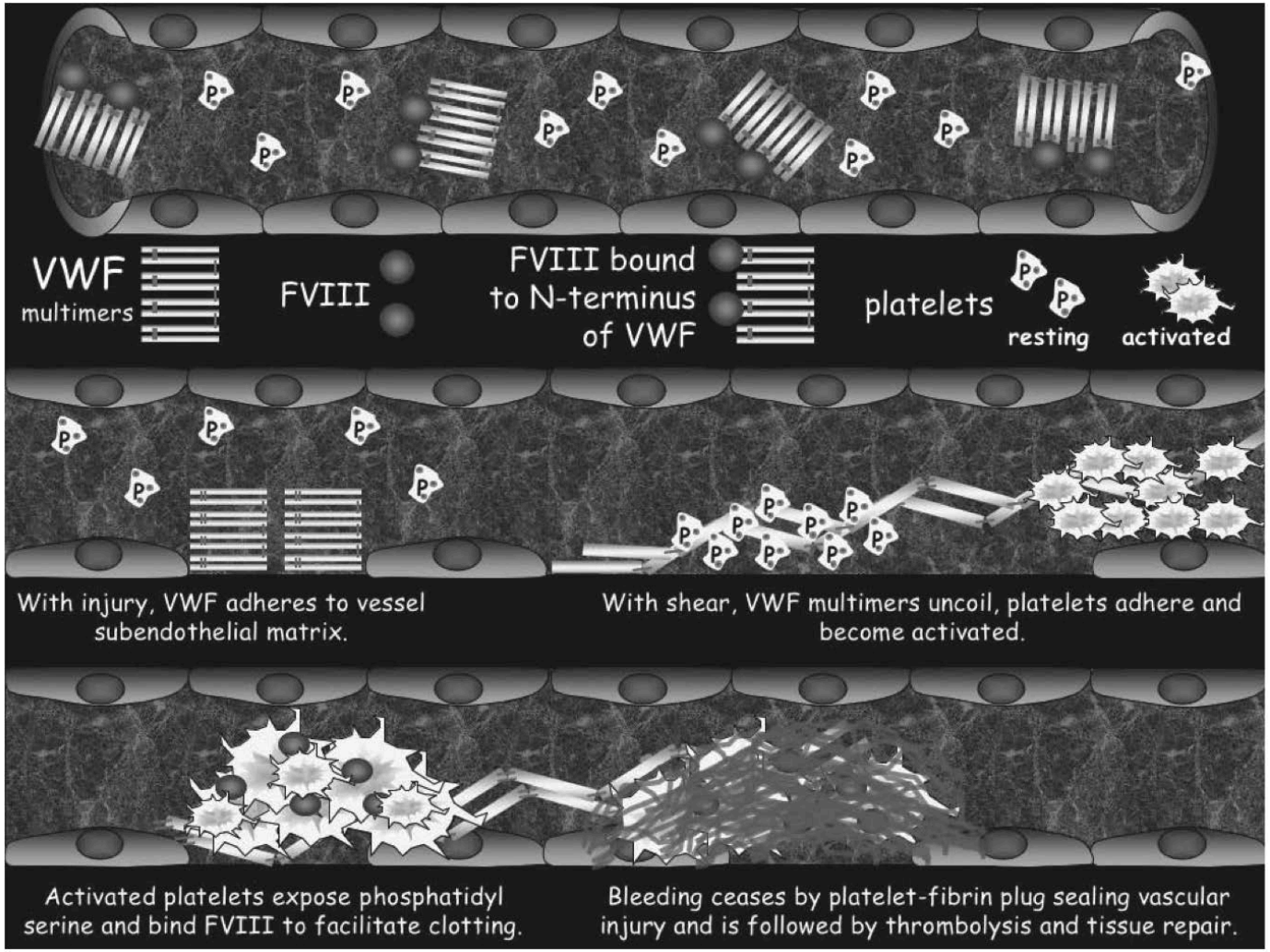


Image courtesy of Dr. Paula James

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

Hemostasis Simplified: VWD

VWD

Trauma to the endothelium = TRIGGER

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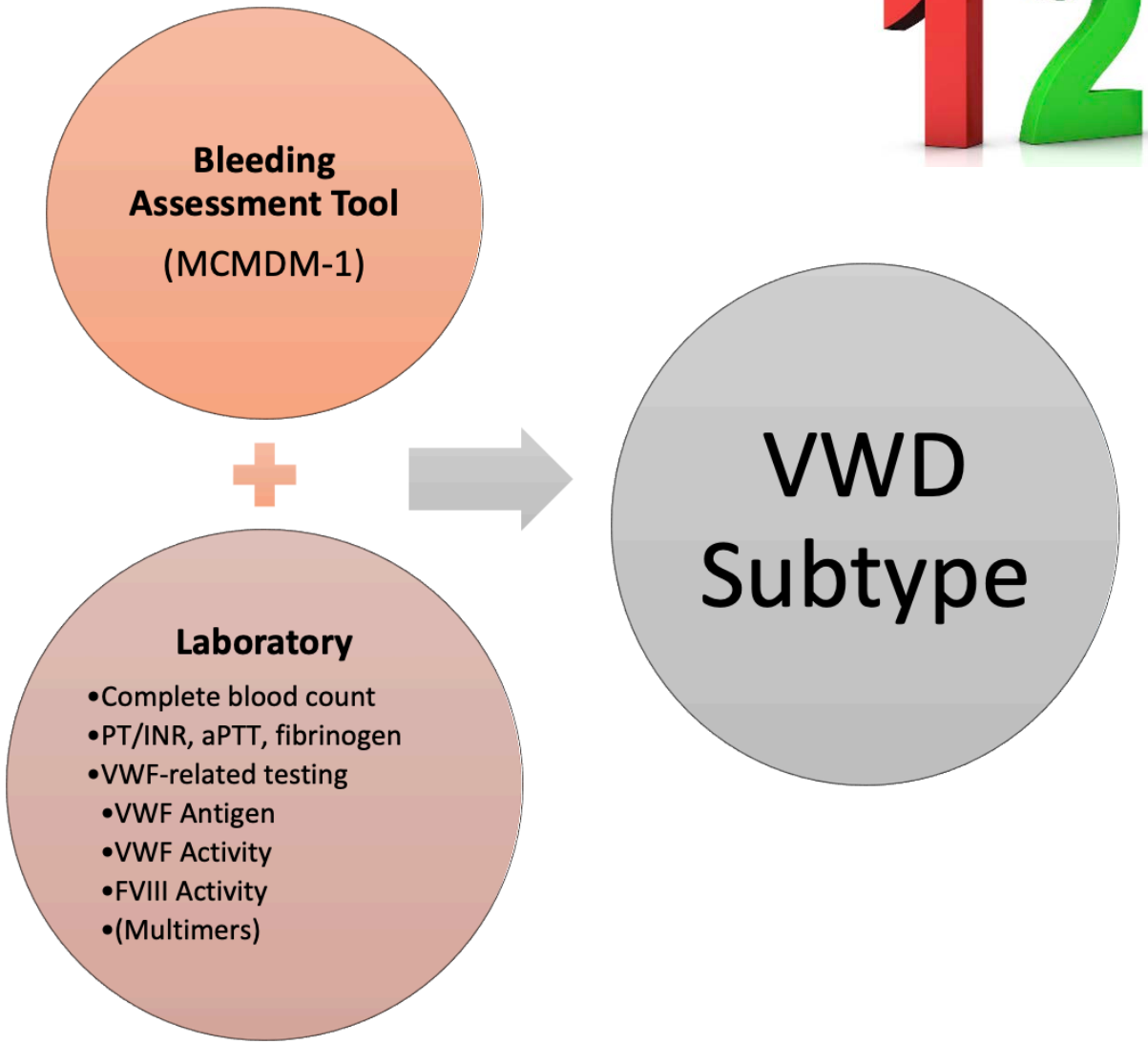
Diagnoses

- 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

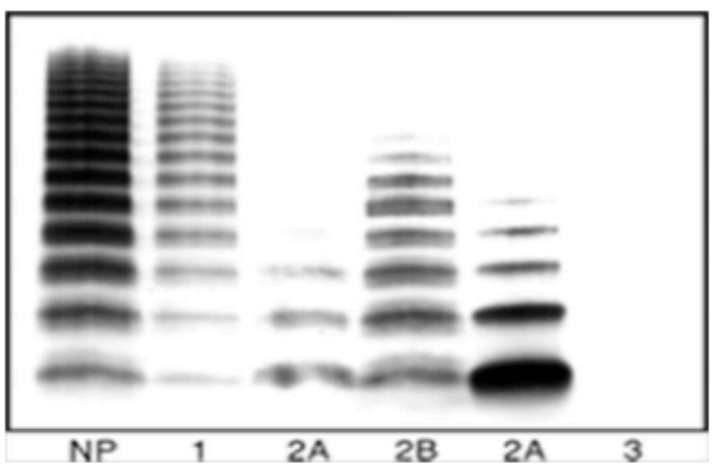
- SURGERY
- POST PARTUM HEMORRHAGE
- DENTAL EXTRACTION

Laboratory Tests

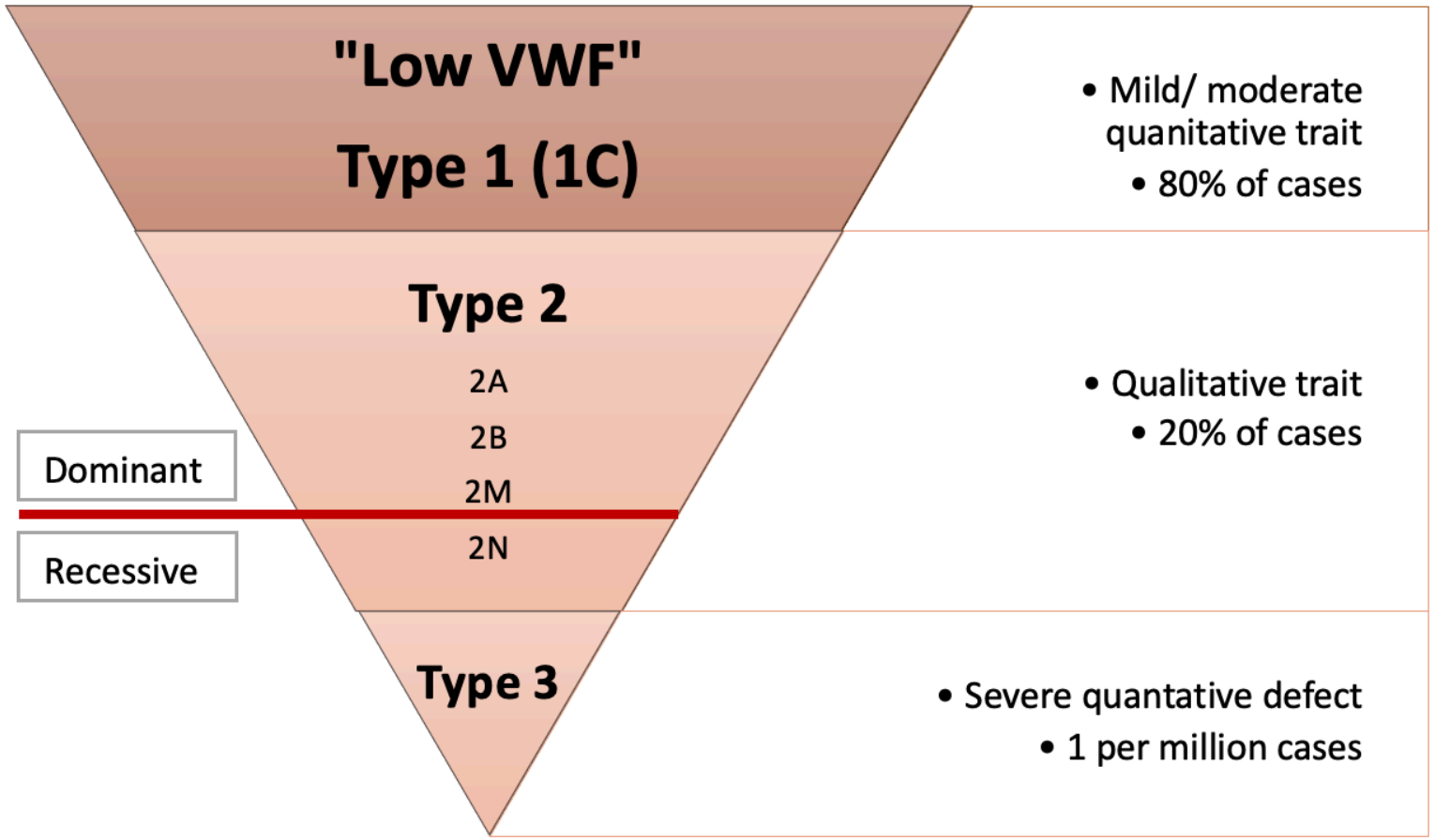
- CBC, INR normal, PTT often normal

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



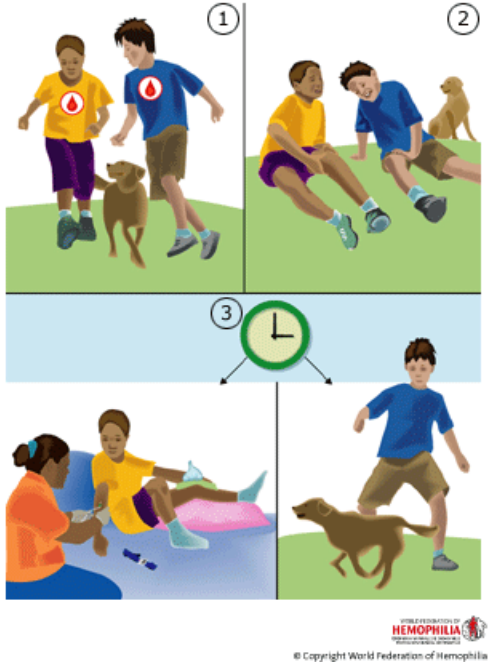
ISTH VWD Classification



Sadler et al JTH 2006

Principles of Bleed Management

1. TREAT FIRST!



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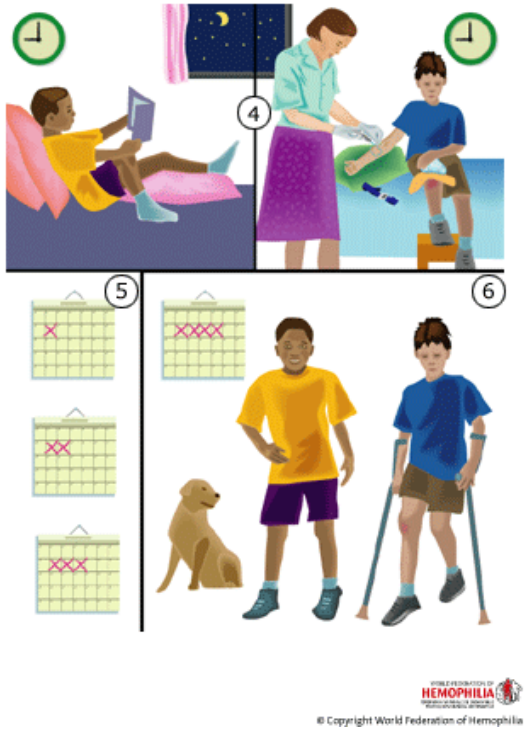

Remember…
FactorFirst

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

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Recombinant factor IX concentrate 35-50 units/kg >15 yrs
Recombinant factor IX concentrate 50-70 units/kg <15 yrs
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Von Willebrand Disease:
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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

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Help Stop the Bleeding

AHCDC Association of Hemophilia Clinic Directors of Canada

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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 _____

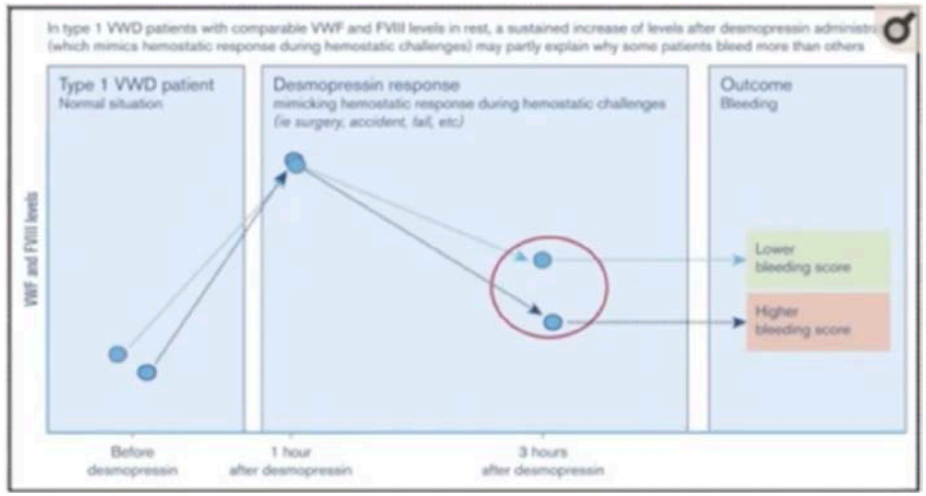
Treatment Basics – Acute Bleed

- ***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



Hemophilias: X-linked

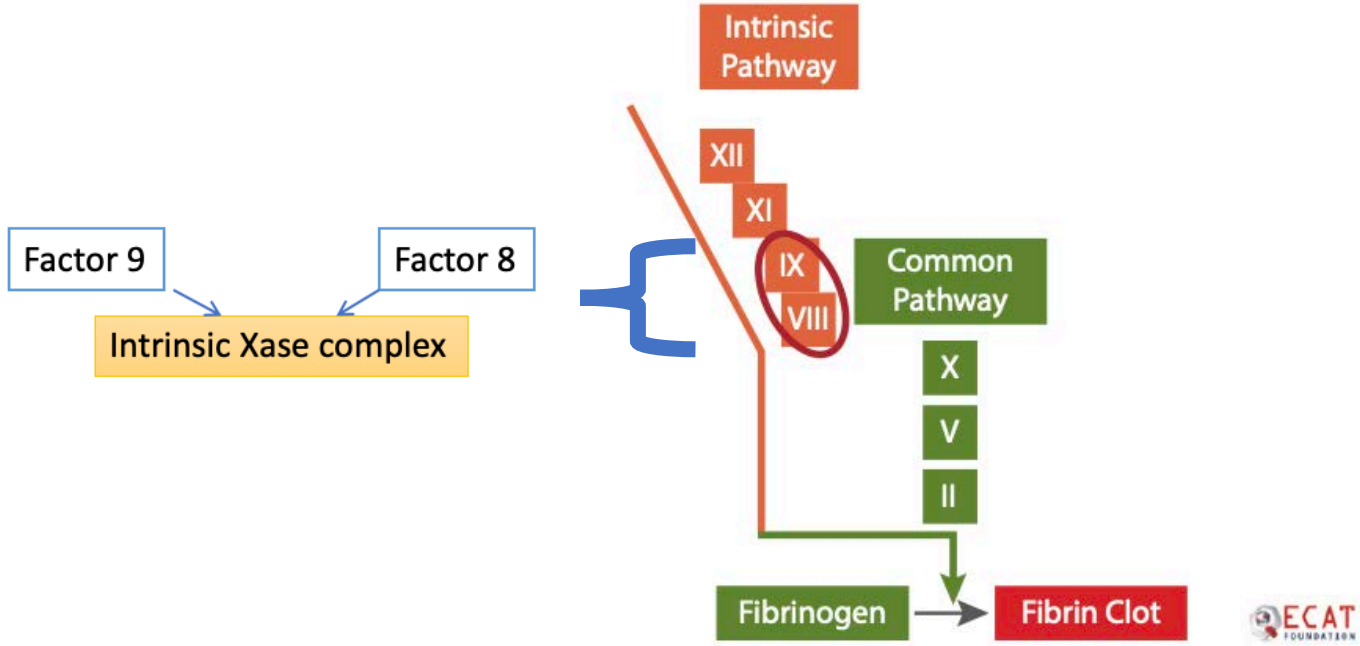
Hemophilia A

- FVIII deficiency
- 1 in 30,000 males

Hemophilia B

- Factor IX deficiency
- 1 in 5000 males

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



Hemostasis Simplified: Hemophilia

Hemophilias

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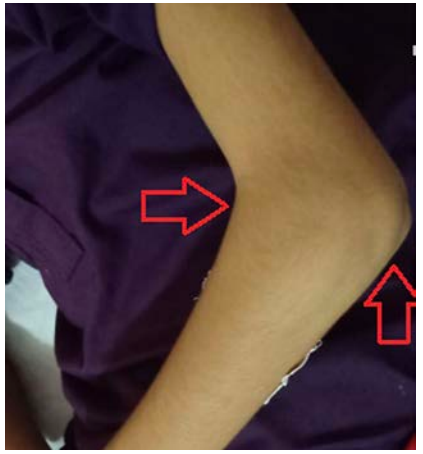
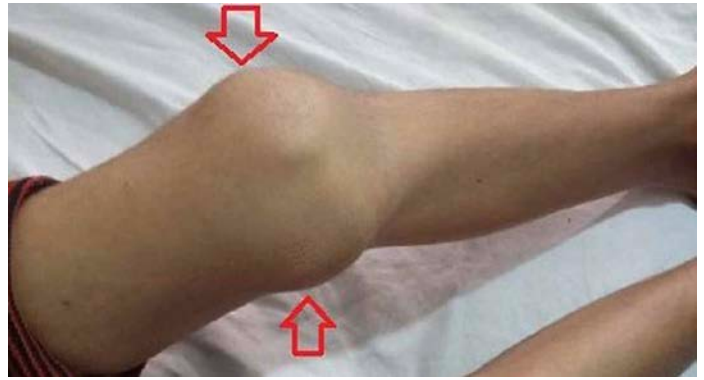
Bleeding Symptoms





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

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

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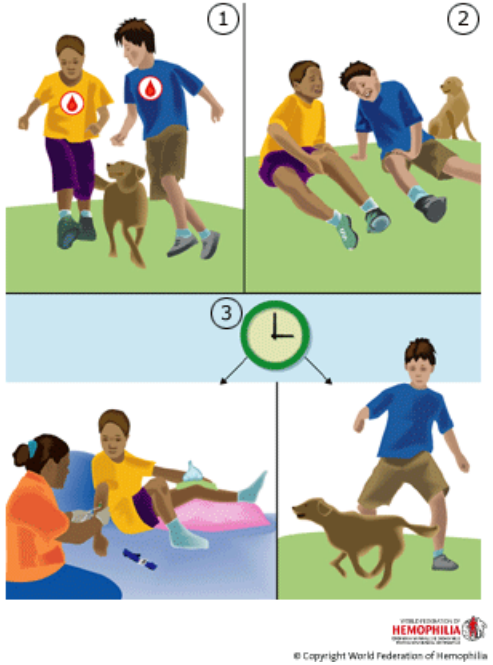

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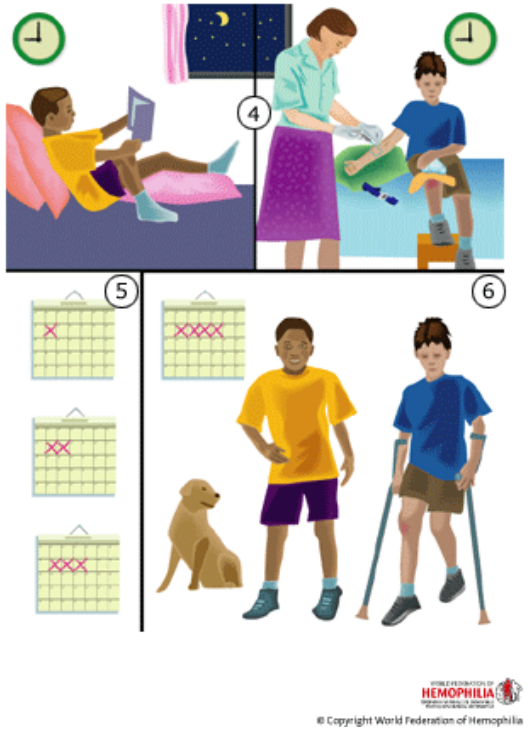
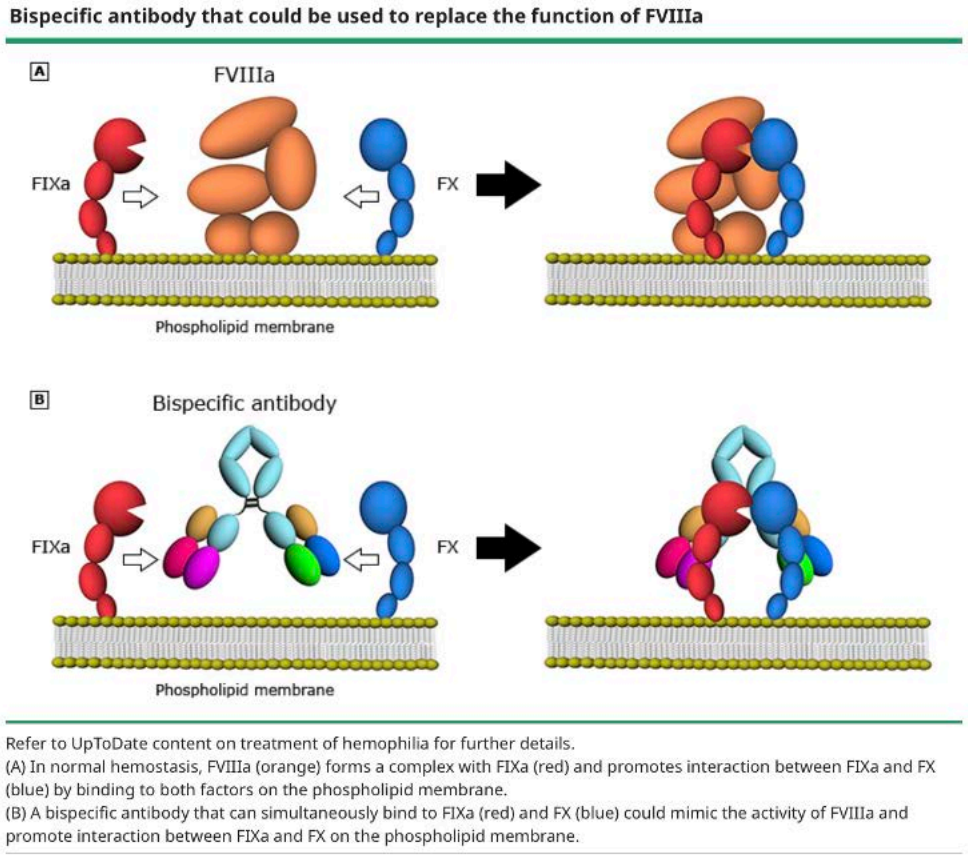


Treatment Basics – Acute Bleed

- ***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



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Severity: _____ Level: _____

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Inhibitors: ☐ no ☐ yes

Other Medical Information: _____

Date of Recommendation: ____/____/____

Signature of Physician _____

Recommended Treatment:

Product and Dose/kg for Life or Limb-threatening Bleeds:

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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 _____

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

Conclusion

Routine coagulation tests **(PT and aPTT)** have a **very poor sensitivity** for assessing bleeding risk

Diagnosis of a bleeding disorder largely hinges on the bleeding history using a **validated BAT**

Clinical **management** requires an **understanding of disease mechanisms** and therapeutic properties

Treat first! Investigate Later!

Do not delay treatment in patients with bleeding disorders. **BELIEVE THEM.**

Consult hematology/transfusion medicine and consider transferring to a HTC

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

St. Michael's
Inspired Care.
Inspiring Science.

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

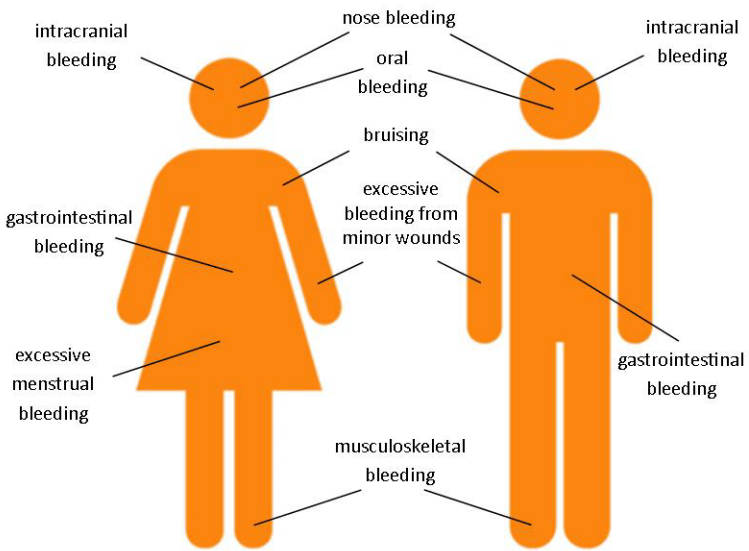
- Time to complete: 5-10 minutes
- Expert administered (MD, NP, or RN)

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



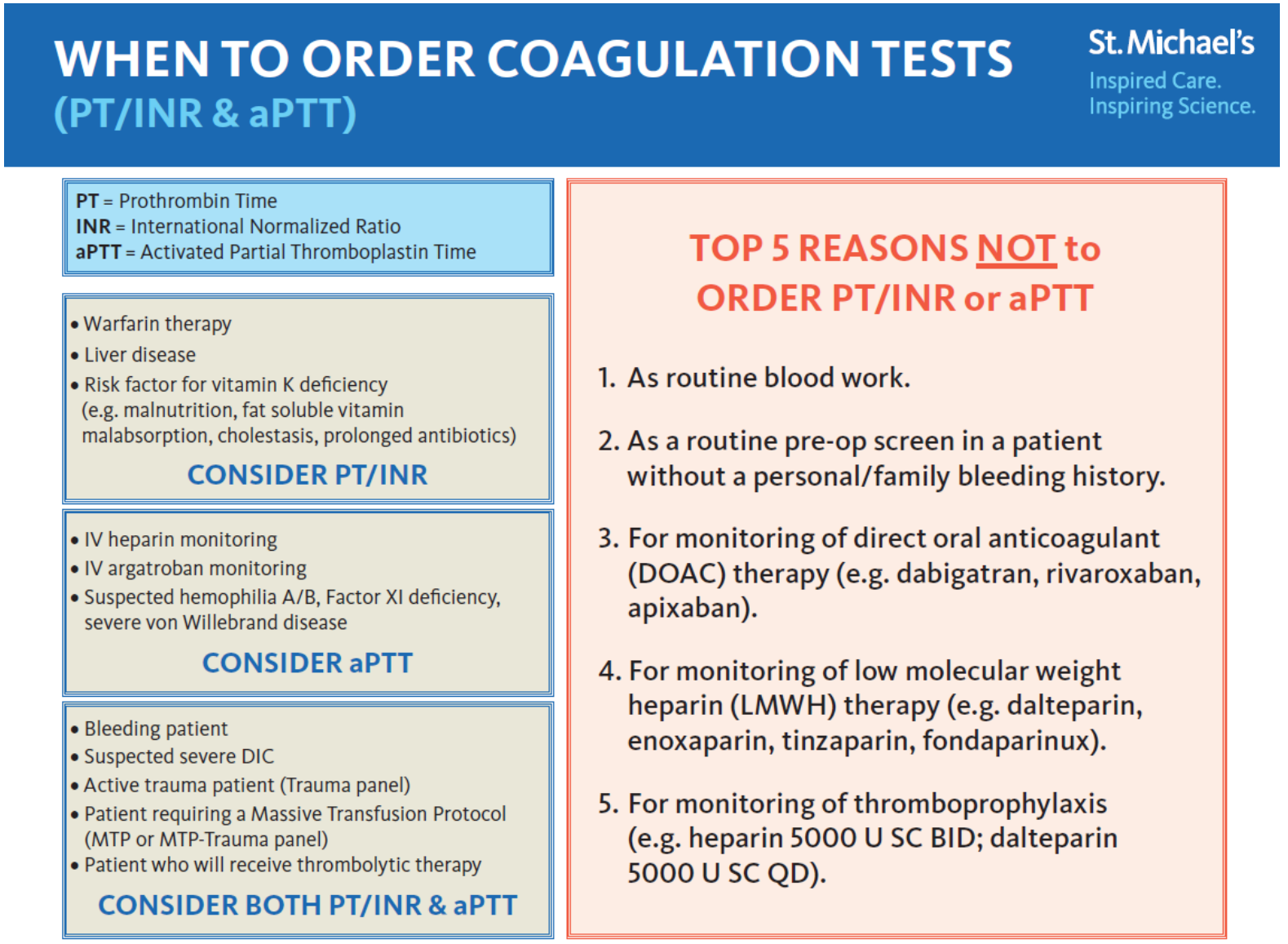
2. Bleeding with Challenges

- 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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Inspiring Science.

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

Form No. XXXXX Dev. 02/2016

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).

ED, ICU

Target: Inpatient Care Setting

WHEN TO ORDER COAGULATION TESTS

(PT/INR & aPTT)

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- Warfarin Therapy
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CONSIDER PT/INR

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

CONSIDER aPTT

- Bleeding patient

CONSIDER BOTH PT/INR & aPTT

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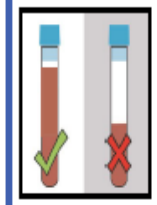
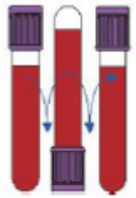
ORDER OF DRAW

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!

- "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