

Bleeding Assessment and Approach to Coagulation Testing



Zach Liederman, MD, FRCPC, MScCH
University Health Network & University of Toronto

Disclosure

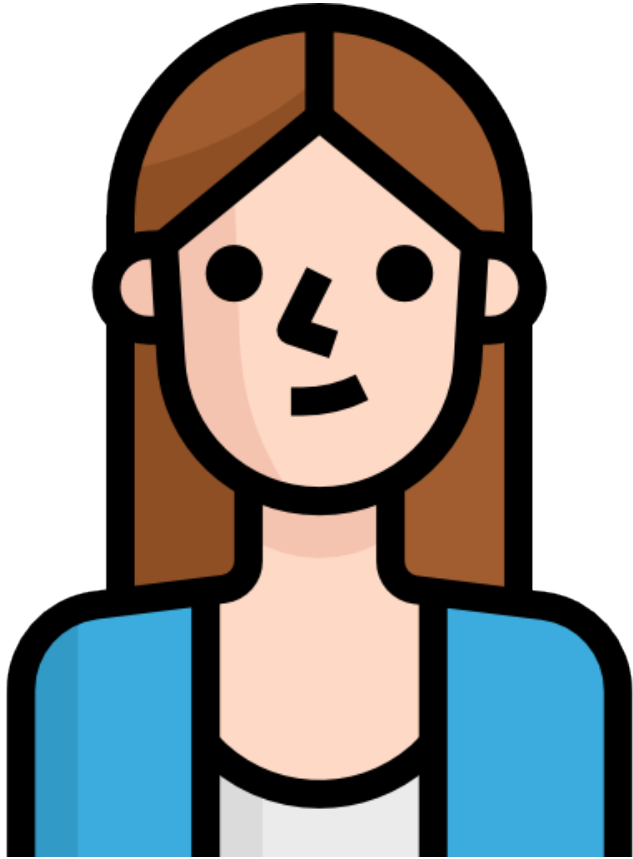
I have no conflicts of interest to declare with regards to the presentation of this topic



Why Bleeding Assessment Matters Hemostasis & Geopolitics



Why Bleeding Assessment Matters

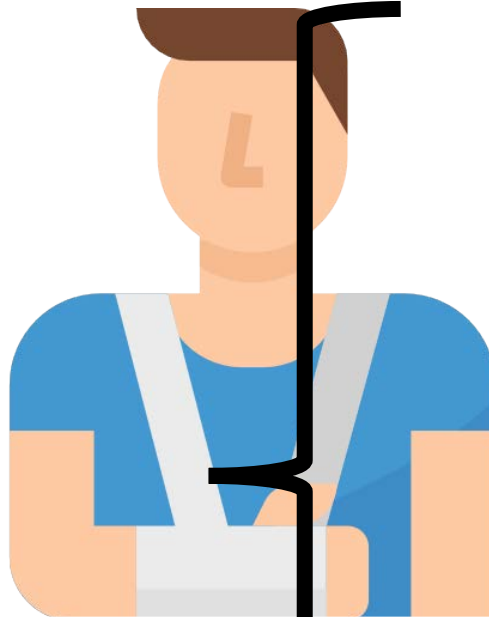


26 year old woman seen for preoperative assessment prior to tonsillectomy. PT/INR and PTT normal. Assessed by resident and approved for OR.

+++ bleeding. Requires 6 units pRBC, ICU admission and 2 return trips to the OR

On further review, history of heavy menstrual bleeding and severe post partum hemorrhage. Ultimately diagnosed with Von Willebrand Disease.

Learning Objectives



Screen for bleeding disorders

Establish a diagnosis/ provide perioperative treatment

Use and Limitations of:

Bleeding History

Laboratory Investigations

- Primary Hemostasis (platelet plug)
 - Von Willebrand Disease (VWD)
 - Platelet Function
- Secondary Hemostasis (fibrin formation)
 - Global screens (PT/PTT)
 - Specialized tests

Extracurricular reading

Practical-Haemostasis.com

A PRACTICAL GUIDE TO HAEMOSTASIS



**Thromboelastography [TEG] &
Rotational Thromboelastometry [ROTEM]**

NAVIGATION

Screening Tests

Factor & Inhibitor Assays

Platelet Function Testing

"TEG talk": expanding clinical roles for thromboelastography and rotational thromboelastometry

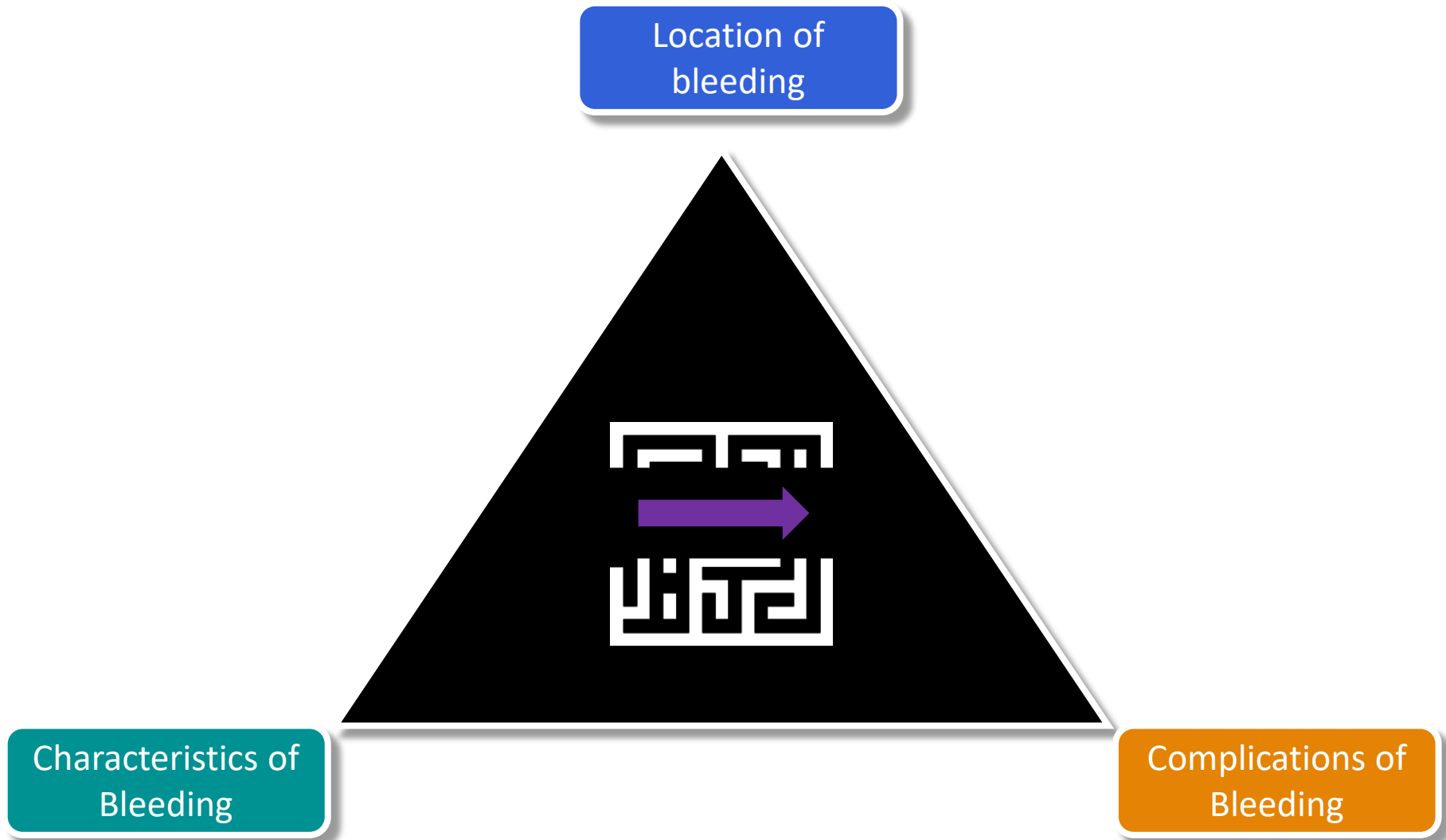
Rita Selby

Department of Laboratory Medicine and Pathobiology and Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Tool Box

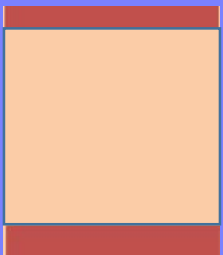


Bleeding History is the most important clinical part of hemostasis

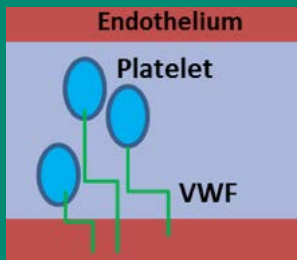


Hemostasis

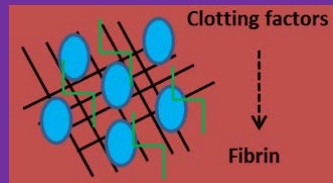
Blood
Vessel/
Connective
Tissue



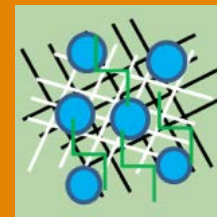
Platelet
Plug (VWF)



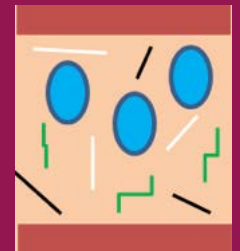
Fibrin
Formation



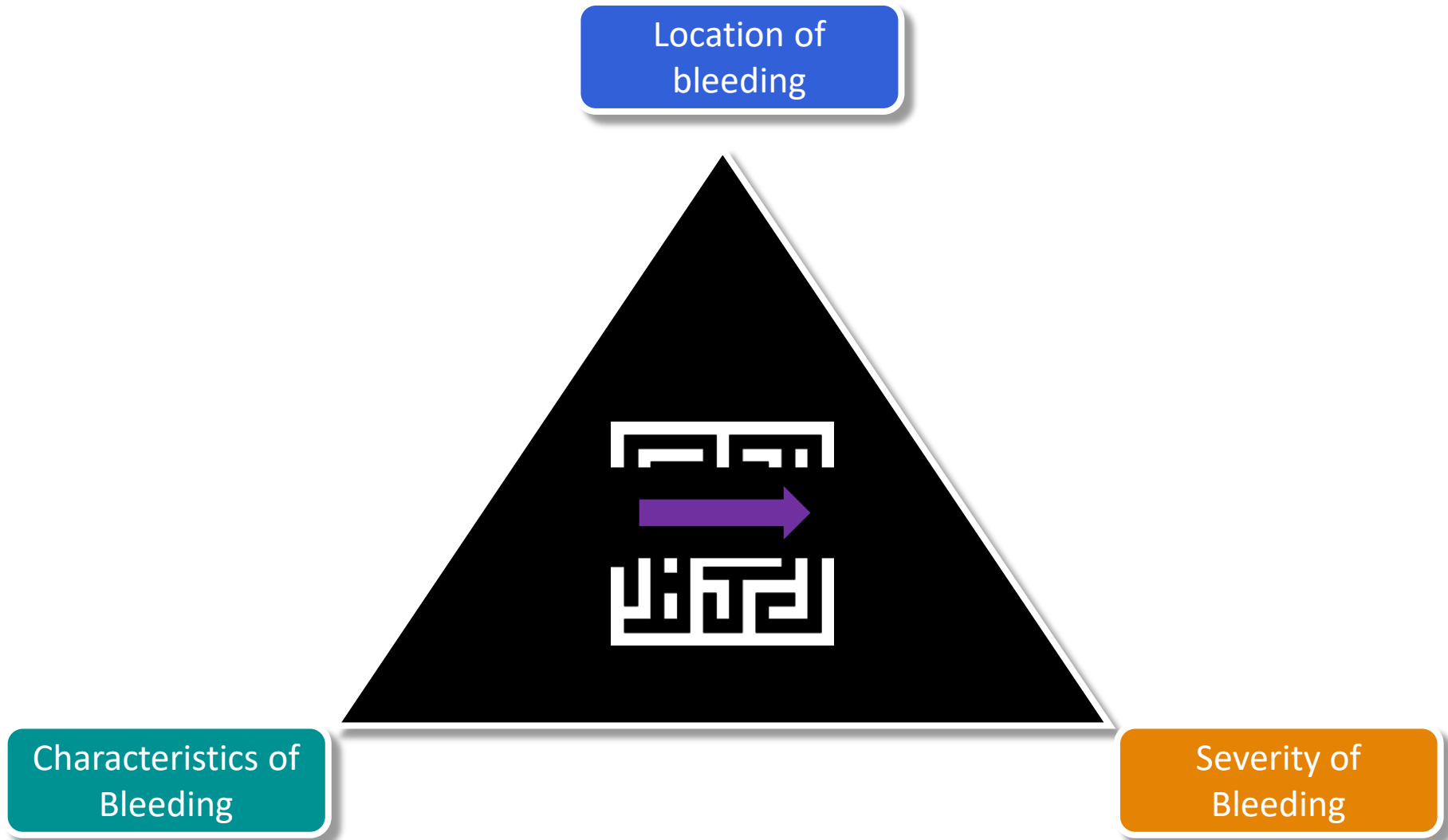
Clot
stabilization



Fibrinolysis



Bleeding History is the most important clinical part of hemostasis

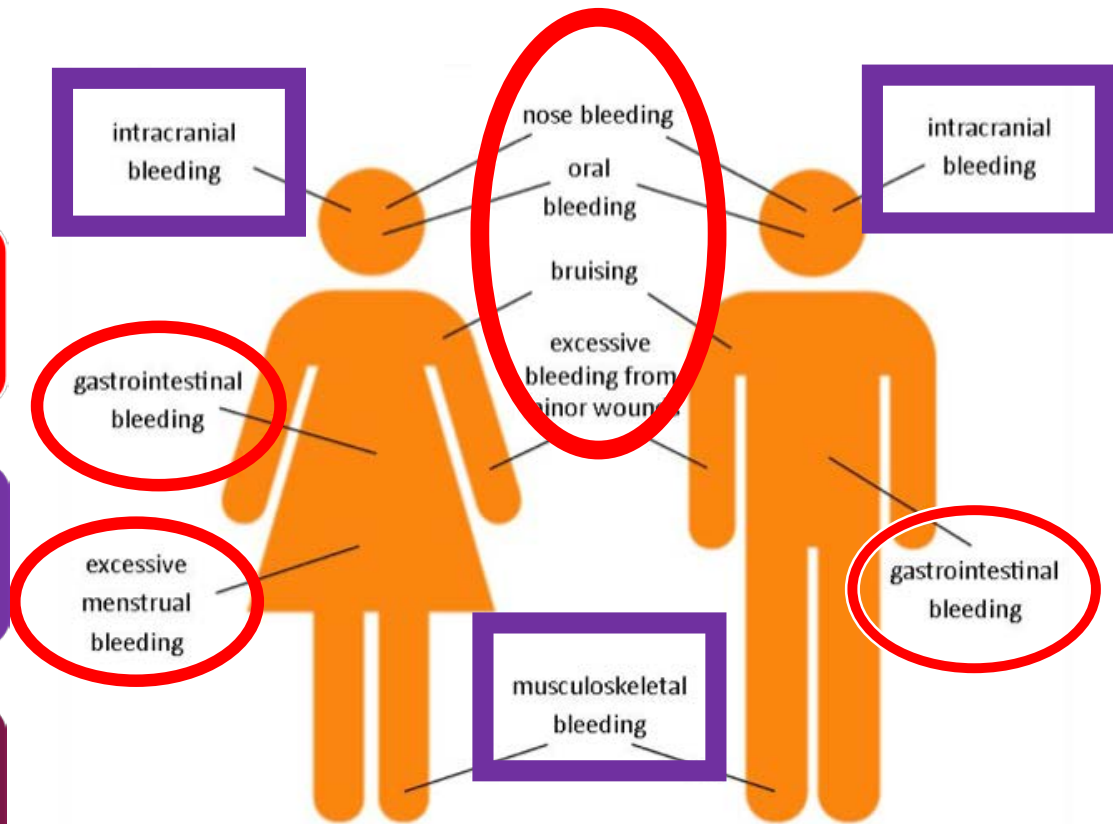


Location of Bleeding

Mucocutaneous Bleeding

“Deep”
Bleeding

“Delayed”
Bleeding



Location of Bleeding

Mucocutaneous bleeding

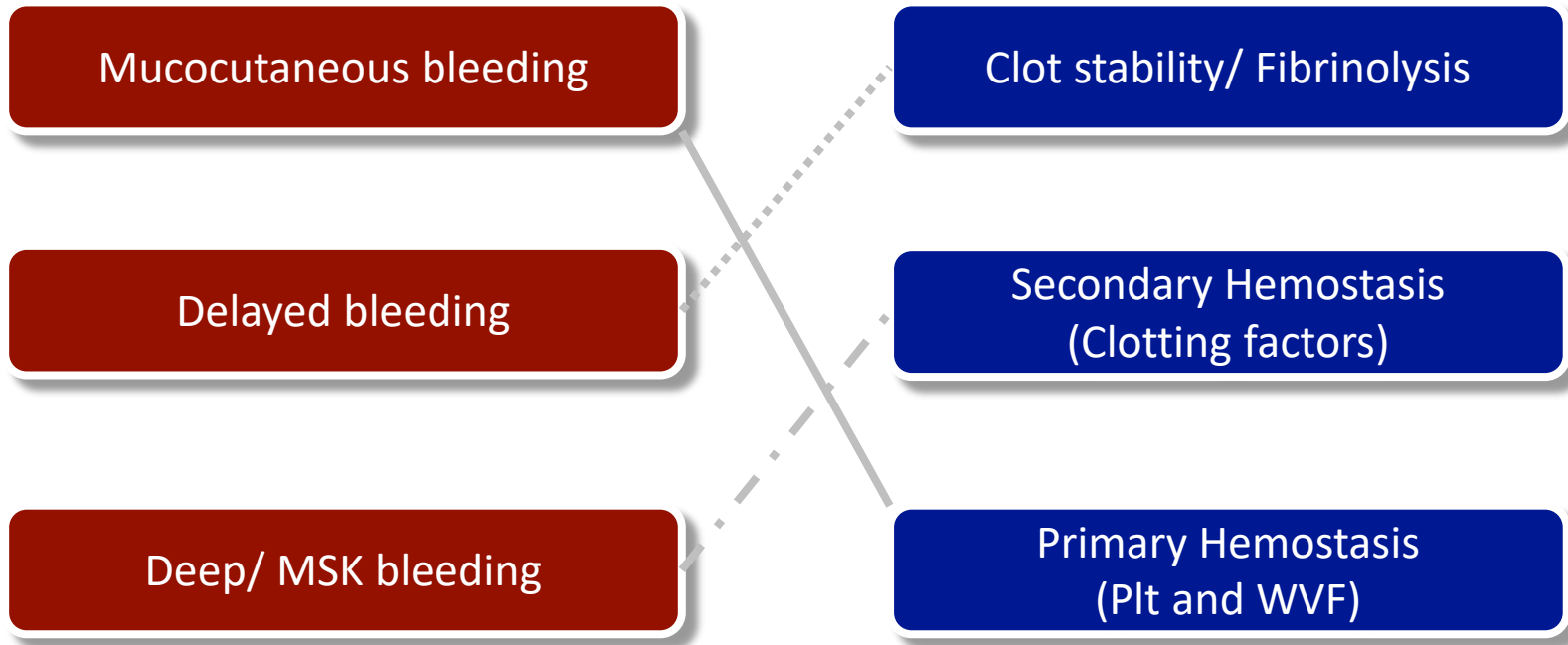
Delayed bleeding

Deep/ MSK bleeding

Clot stability/ Fibrinolysis

Secondary Hemostasis
(Clotting factors)

Primary Hemostasis
(Plt and WVF)



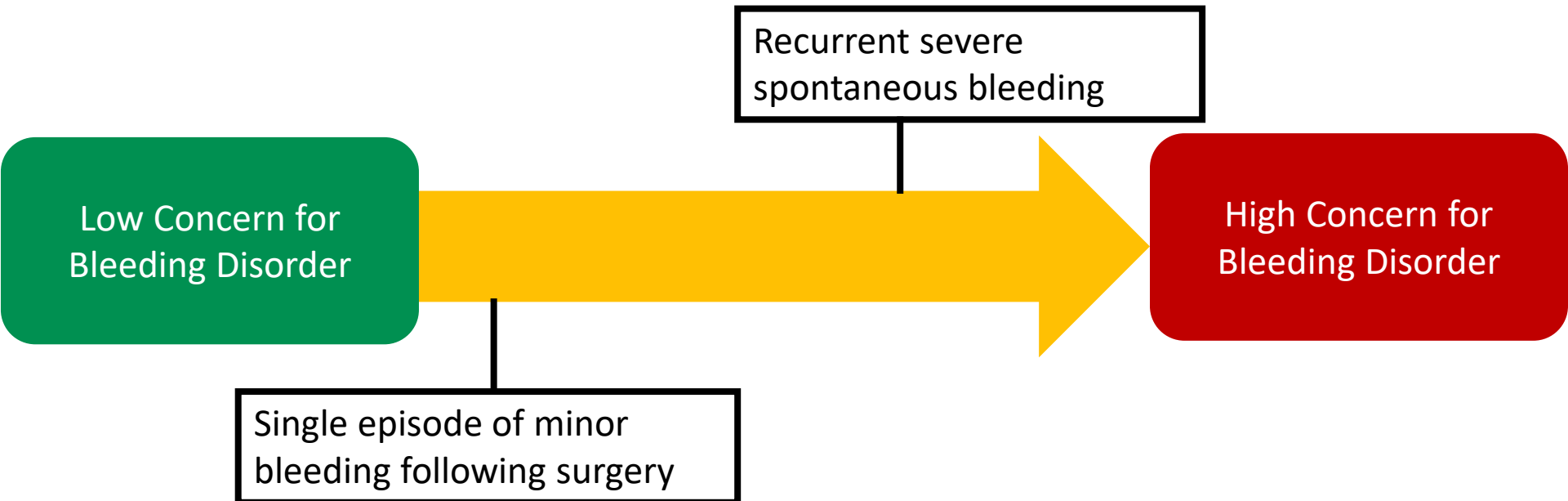
Timing of Bleeding

1. Frequency and onset

- Chronic vs. acute
- Duration

2. Inciting factors

- Spontaneous vs. traumatic



Severity of Bleeding

1. Amount

- Be specific

2. Treatment Required

- Iron infusions, blood transfusions, surgery

3. Complications

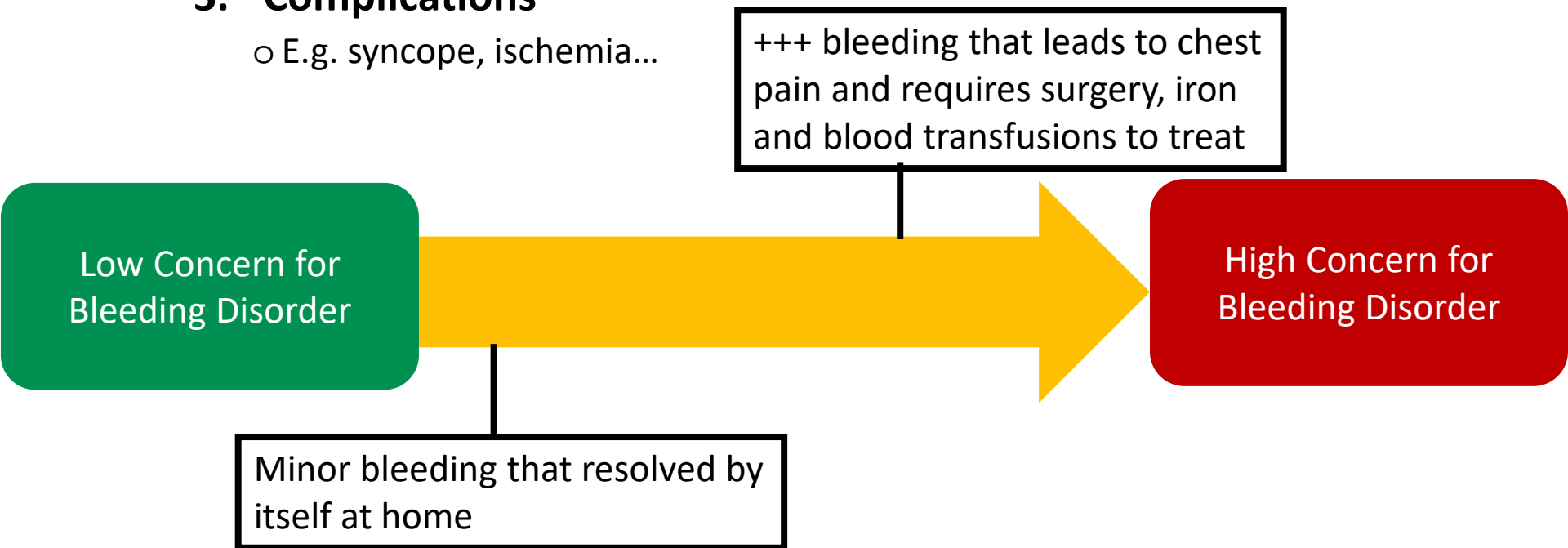
- E.g. syncope, ischemia...

+++ bleeding that leads to chest pain and requires surgery, iron and blood transfusions to treat

Low Concern for Bleeding Disorder

High Concern for Bleeding Disorder

Minor bleeding that resolved by itself at home



Condensed MCMDM-1 VWD 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
Cutaneous	--	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	Referred, 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	None done 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

bloody easy

Coagulation

Simplified...

Second Edition

Lesley Black, Rita Selby
University Health Network

Elena Brnjac, Yulia Lin, Rita Selby
Sunnybrook Health Sciences Centre

Carolyn Elbaz
University of Toronto

Paula James
Kingston General Hospital

Karen Moffat
Hamilton Regional Laboratory Medicine Program

Michelle Sholzberg
St. Michael's Hospital

Editors: Yulia Lin and Rita Selby

Published by



QUICK REFERENCE

**2012* Clinical Practice
Guideline on the
Evaluation and
Management of
von Willebrand Disease
(VWD)**

Presented by the
American Society of Hematology,
adapted from: *The Diagnosis,
Evaluation, and Management of von
Willebrand Disease*. National Heart,
Lung, and Blood Institute, NIH Pub.
No. 08-5832. December, 2007.

*This quick reference guide was
revised in 2012.



Bleeding history/ BAT's (bleeding assessment tools) most helpful as **rule out tests**

BAT score < 4 in an adult = unlikely to have bleeding disorder

But.... some limitations

- **Less sensitive if few bleeding challenges (young, male)**
- **Static**
- **Does not include family history**
- **Poorly captures new acquired bleeding disorders**
- **Scores influenced by available medical resources**
- **Only validated in certain settings**

Take Home Point 1

The Bleeding History is the most important test of hemostasis

Effective rule out test but may miss:

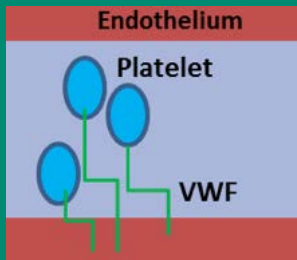
- recently acquired bleeding disorder
- patients with few bleeding challenges

Investigations

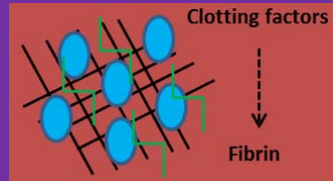
Blood
Vessel/
Connective
Tissue



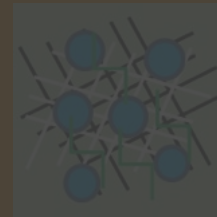
Platelet
Plug (VWF)



Fibrin
Formation



Clot
stabilization



Fibrinolysis



Primary Hemostasis Investigations

Hematologist

Low platelet counts

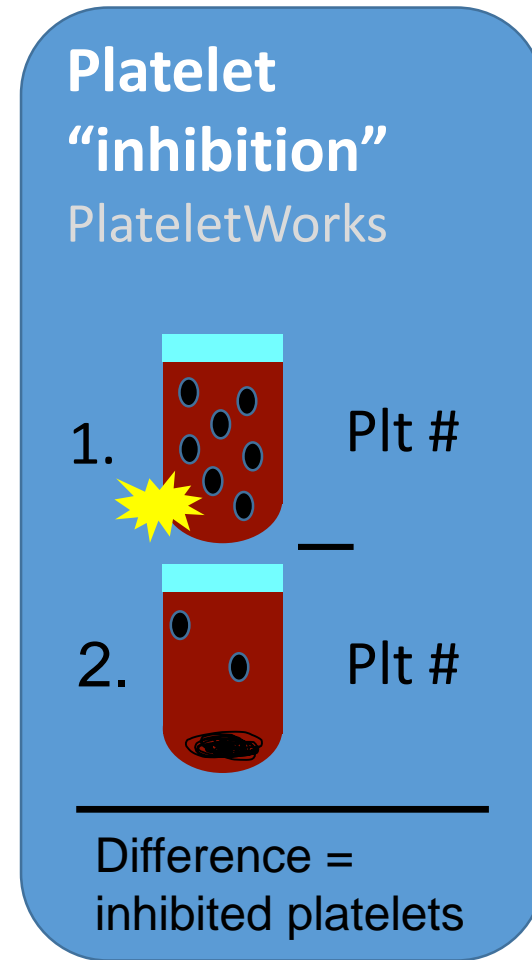
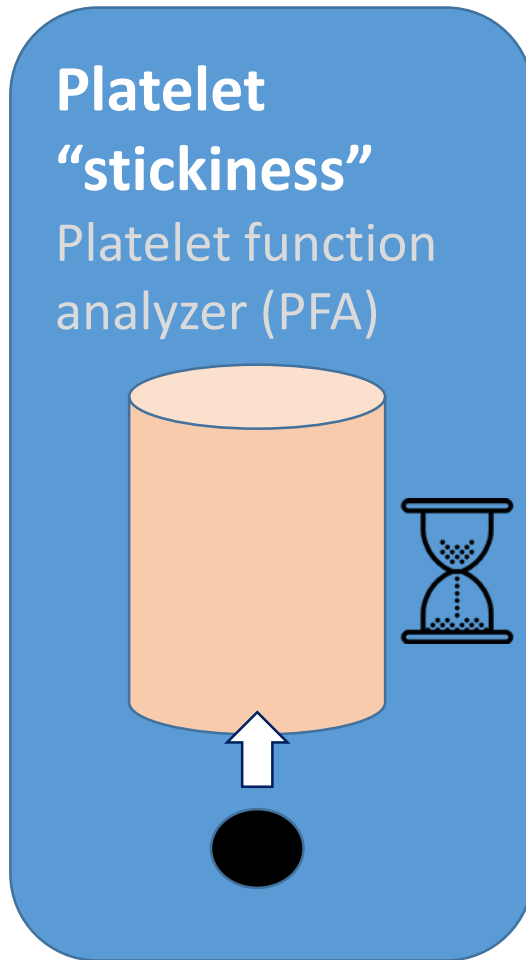
- CBC

Dysfunctional platelets

- Drug history (ex. ASA)

- Platelet function tests
- Blood film

Measuring Platelet Function – Screening Tests



Measuring Platelet Function – Confirmation

Platelet “reactiveness”

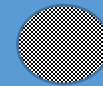
Platelet
aggregometry

Agonists



Platelet “appearance”

Electron
microscopy



Primary Hemostasis Investigations

Hematologist

Low platelet counts

- CBC
- Blood film

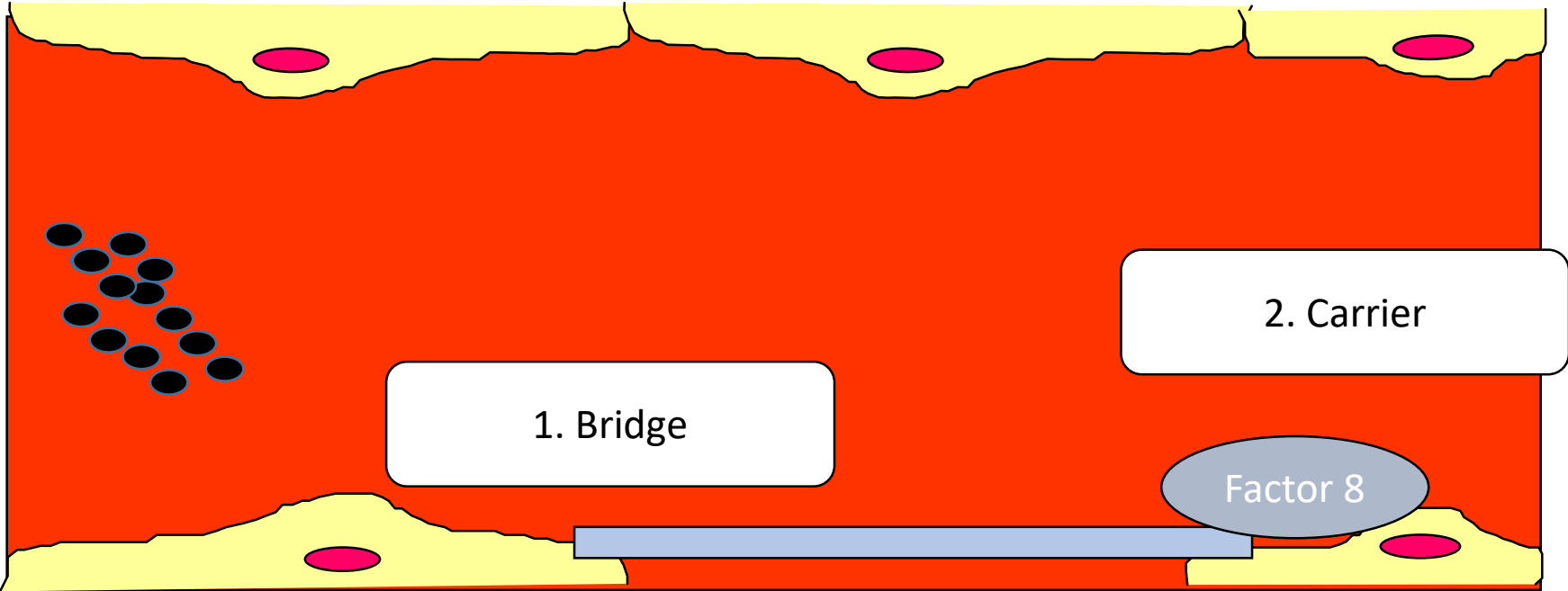
Dysfunctional platelets

- Drug history (ex. ASA)
- Blood film
- Platelet function tests
- Blood film

Von Willebrand Disease

- VWF antigen
- VWF ristocetin
- Factor VIII

Von Willebrand Disease



Von Willebrand Disease Testing

What to test (the basics):



Decreased level	Abnormal function
<ul style="list-style-type: none">VWF antigen level	<ul style="list-style-type: none">Ability to bind to platelets – VWF Activity (Ristocetin Cofactor Assay)Ability to carry Factor 8 – Factor 8 level
<ul style="list-style-type: none">PFA 100/200	

Testing Caveats:

Elevated Values (false negative)	Decreased Values (false positive)
<ul style="list-style-type: none">High estrogen states (e.g. pregnancy)Increased stress (e.g. postop)Interference (e.g. rheumatoid factor)	<ul style="list-style-type: none">Group O bloodOutside lab

Von Willebrand Disease Classification

Activity
Antigen

~1:1 Type 1 - mild/moderate quantitative trait ~80%

< 0.6

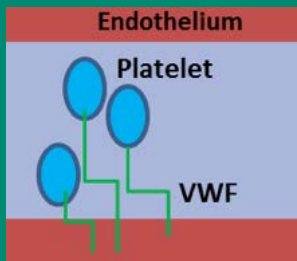
~1:1 Type 3 - severe quantitative trait ~ 1 per million

Investigations

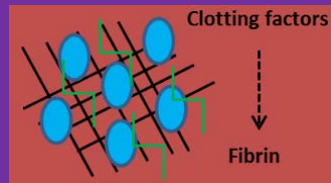
Blood
Vessel/
Connective
Tissue



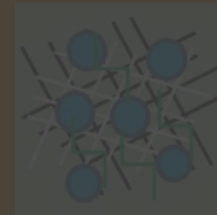
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Plug (VWF)



Fibrin
Formation



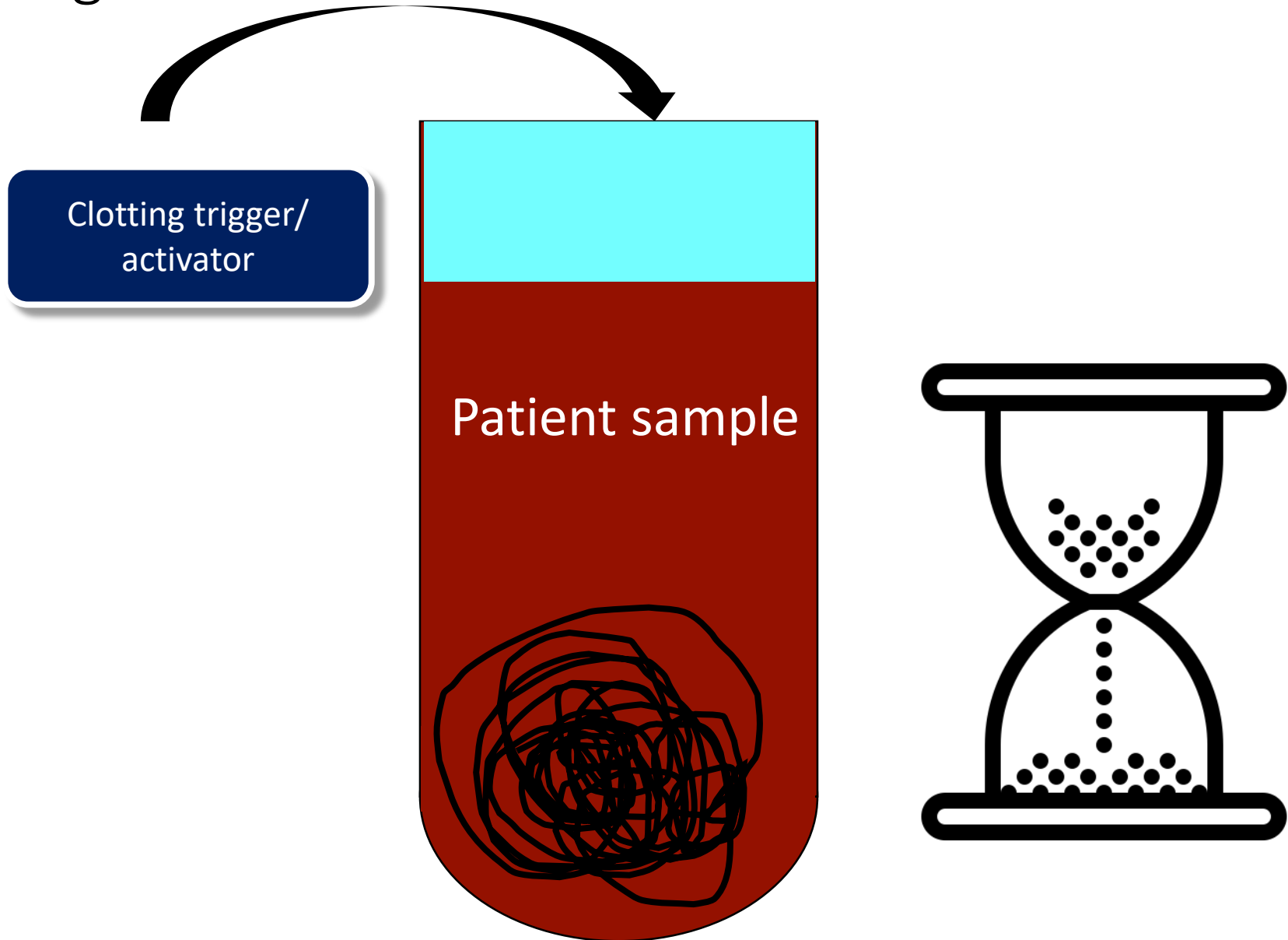
Clot
stabilization



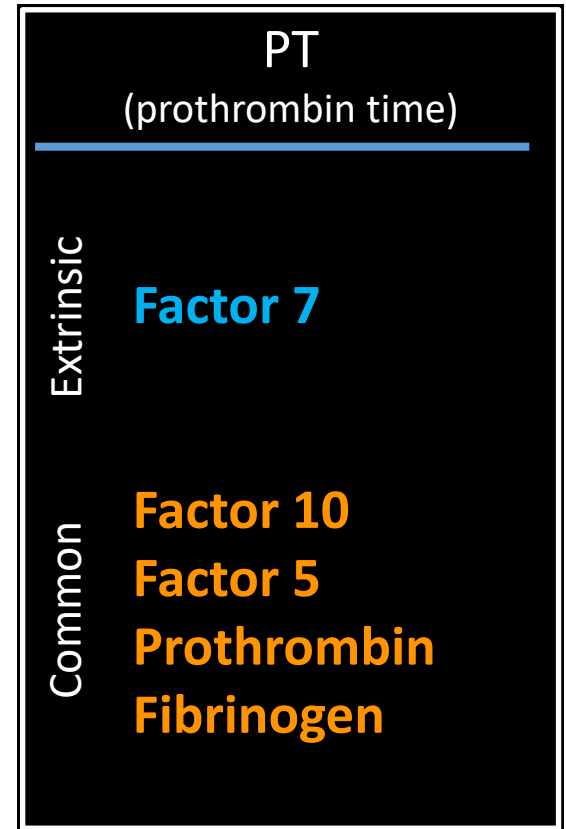
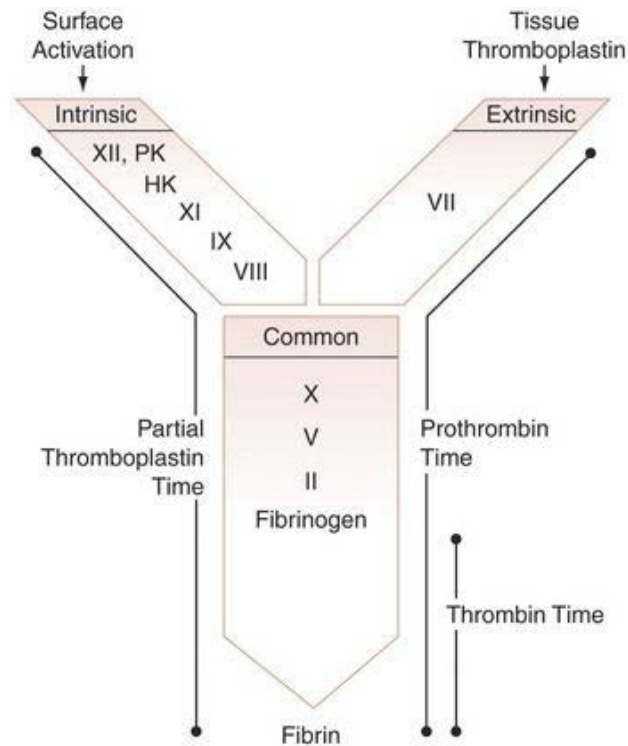
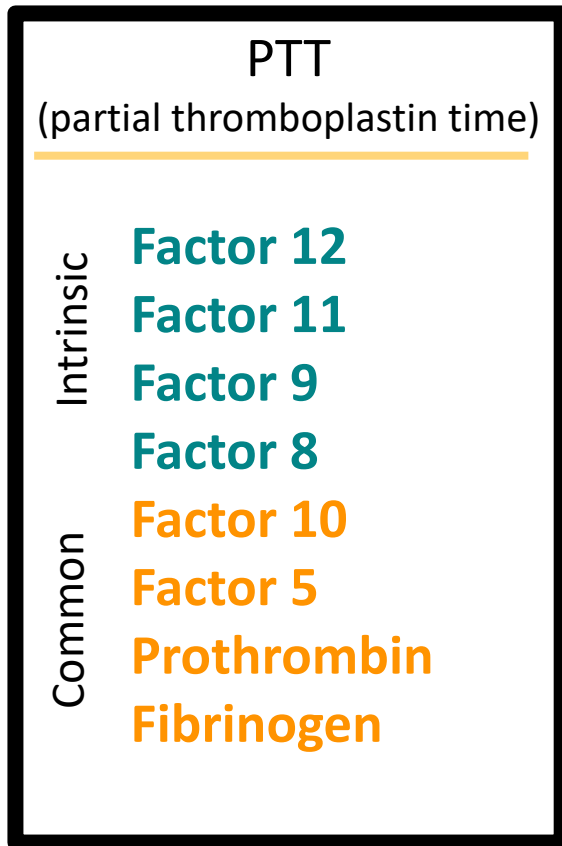
Fibrinolysis



Coagulation test basics



What does each test measure:



BLD0156 Describe drug targets and drug classes that can affect blood coagulation

BLD0165 Understand common coagulation tests used to assess hemostasis e.g., PT and PTT

Secondary Hemostatic Disorders

Clotting factors are missing

Congenital

Acquired

Not
produced

Destroyed

Clotting factors are inhibited/
dysfunctional

Acquired

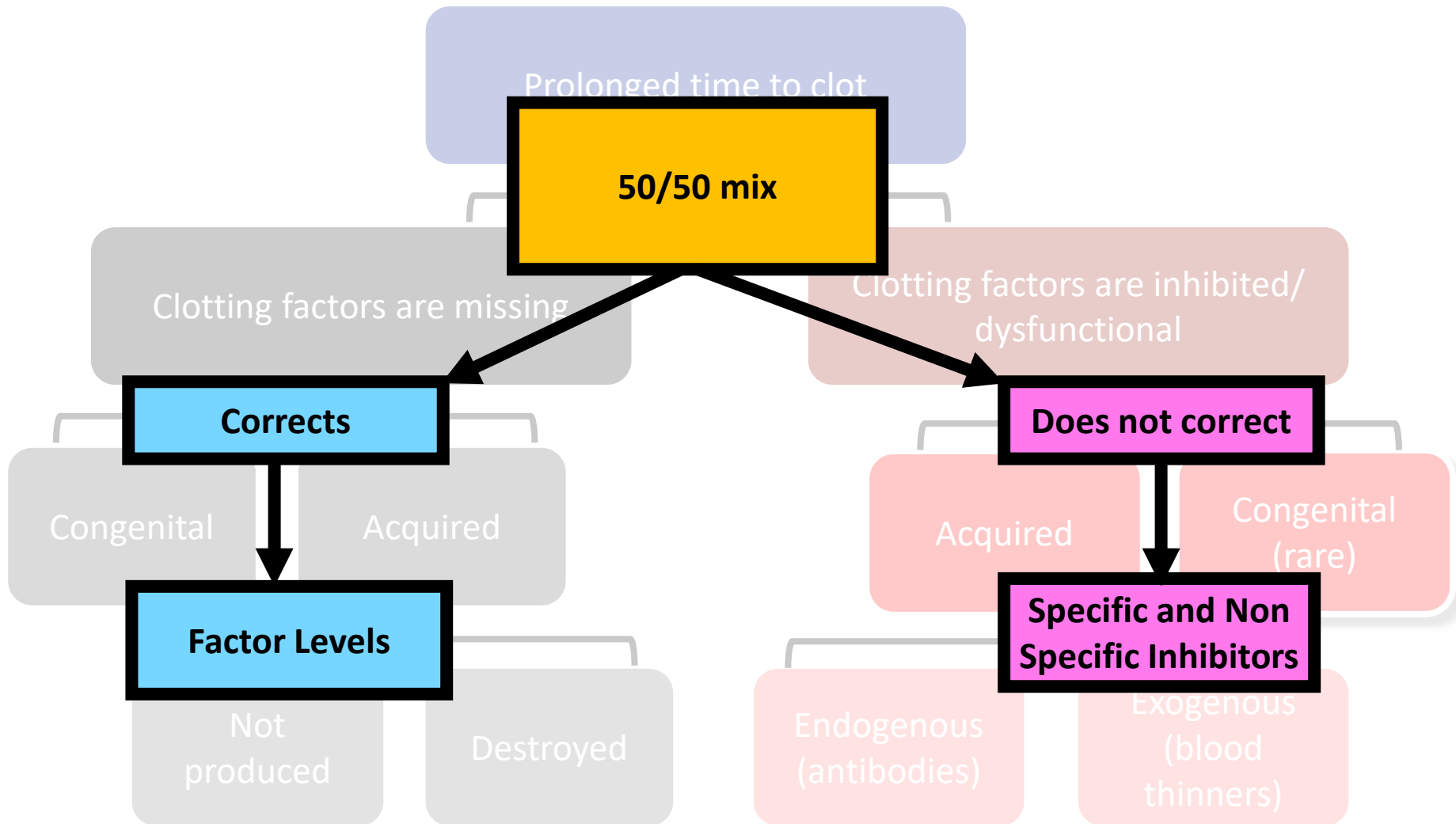
Congenital
(rare)

Endogenous
(antibodies)

Exogenous
(blood
thinners)

Not all of these cause bleeding!!!

Confirming a diagnosis: Factor Levels and Inhibitors



Non Specific vs. Specific Inhibitors

Specific Inhibitors:

- Directed against single clotting factor
- Alloimmune (Hemophilia patients receiving factor replacement) vs. Autoimmune
- **Associated with bleeding**

Non –Specific Inhibitors (lupus anticoagulant):

- Anti-phospholipid antibodies
- **Associated with thrombosis**

INR/PT & PTT Limitations

■ PT

- Effective at determining the amount of warfarin that is present in steady state

■ PTT

- Historically designed to screen for inherited hemophilia pre-operatively in high risk patients
- Subsequently validated to monitor unfractionated heparin therapy

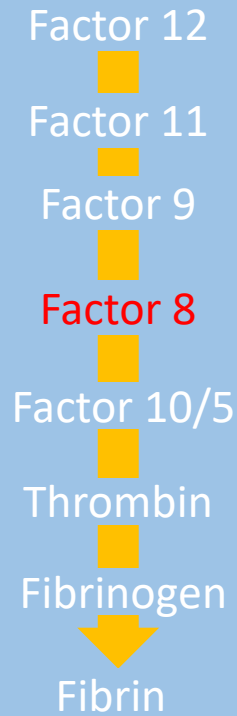
These tests were never designed nor validated to screen for hemostatic defects in unselected patients!

INR/PT & PTT Pitfalls: 1) Variable Sensitivity

Drug Class	DOAC	Conventional Coagulation Testing		
		PT	APTT	TT
Direct Thrombin Inhibitor	Dabigatran	↑/↔	↑	↑
Factor Xa Inhibitor	Rivaroxaban	↑/↔	↑/↔	N/A
	Apixaban	↑/↔	↑/↔	N/A
	Edoxaban	↑/↔	↑/↔	N/A

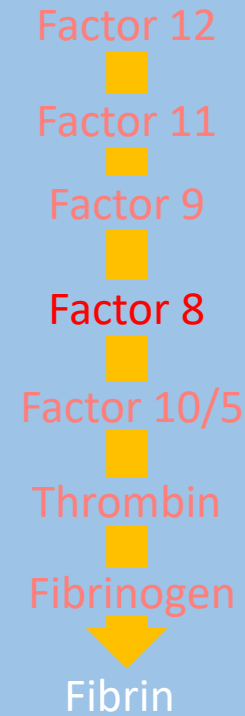
INR/PT & PTT Pitfalls: 2) Clotting factors are connected

Healthy Hemophilia A Patient



Elevated PTT reflects Factor 8 deficiency

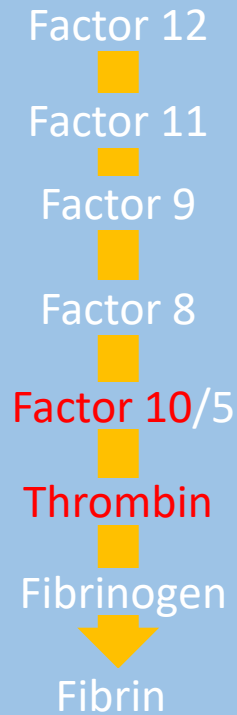
Hemophilia A Patient with Cirrhosis



Elevated PTT is no longer only dependent on Factor 8

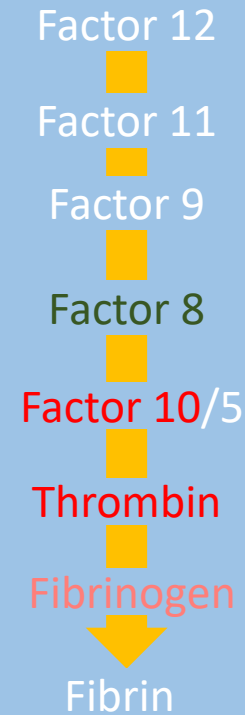
INR/PT & PTT Pitfalls: 2) Clotting factors are connected

Ward patient on IV UFH



Elevated PTT reflects
heparin level

Complex ICU patient on IV UFH



Elevated PTT is no longer only
dependent on heparin level

Take Home Point 2

Abnormal coagulation tests ~~=~~ bleeding risk

Normal coagulation tests ~~=~~ no bleeding risk

Clinical Assessment

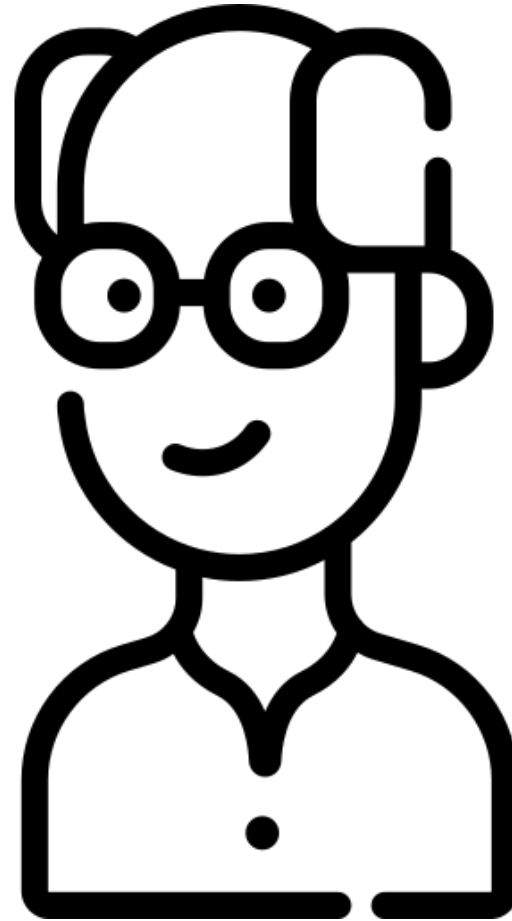


Case 1

72 year old male for
cholecystectomy.

PMHx: HTN

Medications:
Amlodipine



Approach to Bleeding Assessment

1) Screen for bleeding risk

- Comprehensive bleeding history

*PTT & PT/INR for high risk surgeries or limited bleeding challenges

Bleeding Score = 7

1. History of epistaxis since childhood, requiring cauterization
2. Easy bruising
3. Bleeding following tooth extraction requiring packing

Decision for OR – General Rule

+ bleeding history		Red
∅ bleeding history but limitations or high risk procedure	abnormal coag testing	Red
	normal coag testing	Cyan
∅ bleeding history		Cyan

Approach to Bleeding Assessment

2) Determine bleeding phenotype:

- Clues from bleeding history
- Global hemostatic assays
 - CBC
 - PT/INR & PTT

- Predominately mucocutaneous bleeding (? congenital)
- Hb 118, Plt 180, WBC 7.2
- INR 1.1, PTT 36 s

**Mild factor deficiency vs. VWD vs.
Platelet disorder**

Approach to Bleeding Assessment

3) Confirm a Diagnosis :

- Involve Hematology
- Guided by global assays and clinical suspicion
 1. PFA, platelet aggregation
 2. VWD profile
 3. Factor levels
 4. Factor Inhibitors

- Abnormal PFA, no specific pattern with aggregation
- VWF antigen 0.62, VWF activity 0.65
- F8 0.81, F9 0.74, F11 0.88

Bleeding Disorder NYD

Take Home Points

- 1) The Bleeding History is the most important test of hemostasis
- 2) Coagulation tests can help clarify risk of bleeding/ direct treatment in patients who have suspicious histories and physicals
- 3) INR/PT and PTT have wide DDX and variable sensitivity/ specificity

Appendix

Isolated ↑ PTT

Prolonged time to clot

Clotting factors are missing

Clotting factors are inhibited/
dysfunctional

Congenital

**FVIII (+/- VWD),
FIX, FXII, FXI**

Acquired

Not produced

Destroyed

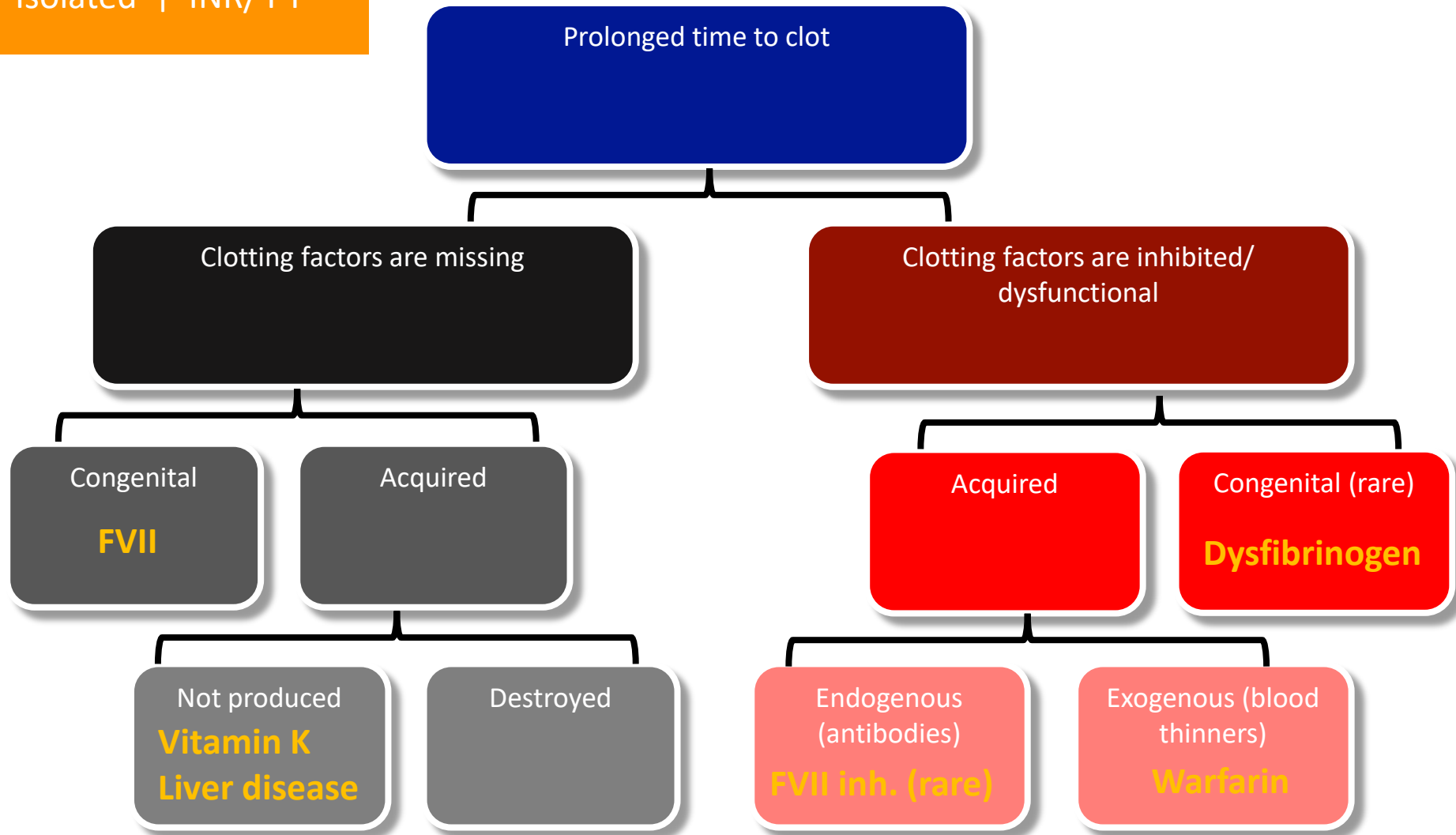
Acquired

Endogenous
(antibodies)
**FVIII antibodies
APLA**

Congenital (rare)

Exogenous (blood
thinners)
**Heparins,
Argatroban**

Isolated \uparrow INR/ PT



Target: Outpatient Setting

MAKING THE BEST USE OF COAGULATION TESTS AND TOOLS

St. Michael's
Inspired Care.
Inspiring Science.

BAT = Bleeding Assessment Tool
PT = Prothrombin Time
INR = International Normalized Ratio
aPTT = Activated Partial Thromboplastin Time

- Suspected bleeding disorder (e.g. recurrent epistaxis, excessive post-operative bleeding, menorrhagia, post partum hemorrhage)

CONSIDER BAT

(aPTT is rarely useful in the outpatient setting)

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

CONSIDER PT/INR

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).

MOST COMMON BLEEDING DISORDERS IN ORDER OF PREVALENCE:

- 1) Von Willebrand Disease
- 2) Platelet Function Disorders
- 3) Hemophilia A (FVIII) and B (FIX)
- 4) Factor XI Deficiency

Target: Inpatient Setting

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

St. Michael's

Inspired Care.
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

TOP 5 REASONS NOT to ORDER PT/INR or aPTT

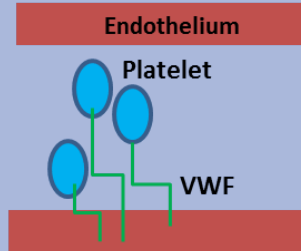
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HEMOSTASIS SIMPLIFIED

St. Michael's
Inspired Care.
Inspiring Science.

HEMOSTASIS PHYSIOLOGY

Primary hemostasis =
formation of platelet plug



COMMON BLEEDING DISORDERS

- Von Willebrand Disease
- Platelet Function Disorders

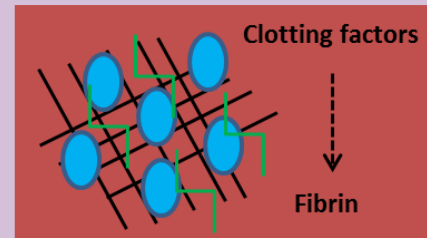
ROUTINE TESTS

CBC

- Assesses platelet count but not function



Secondary hemostasis =
formation of fibrin rich clot



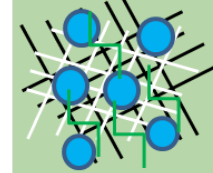
- Hemophilia A and B
- FXI Deficiency

PT/INR and aPTT

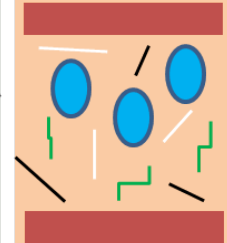
- **ONLY** test secondary hemostasis
- Reagents are attuned to detect a single factor deficiency **ONLY** if it is < 30% of normal function
- Do **NOT** assess primary hemostasis (VWD* and platelet disorders = the most common bleeding disorders)



Clot
stabilization =
formation of
strong clot



Fibrinolysis =
clot
breakdown



BLEEDING ASSESSMENT TOOL (BAT)

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

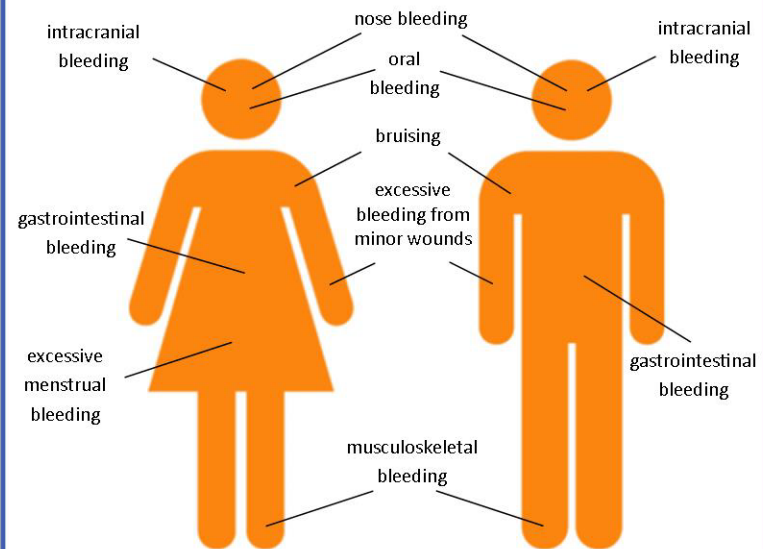
- Time to complete: 5-10 minutes
- Expert administered (MD, NP, or RN)

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)

Slide courtesy M. Sholzberg