Easy bruising vs Coagulopathy

Sept. 19, 2015

Lakehead Summer School

Chris Hillis, MD MSc FRCPC

hillis@hhsc.ca

@HemeHillis

Northern Ontario School of Medicine

École de médecine du Nord de l'Ontario

CEPD continuing education and professional development

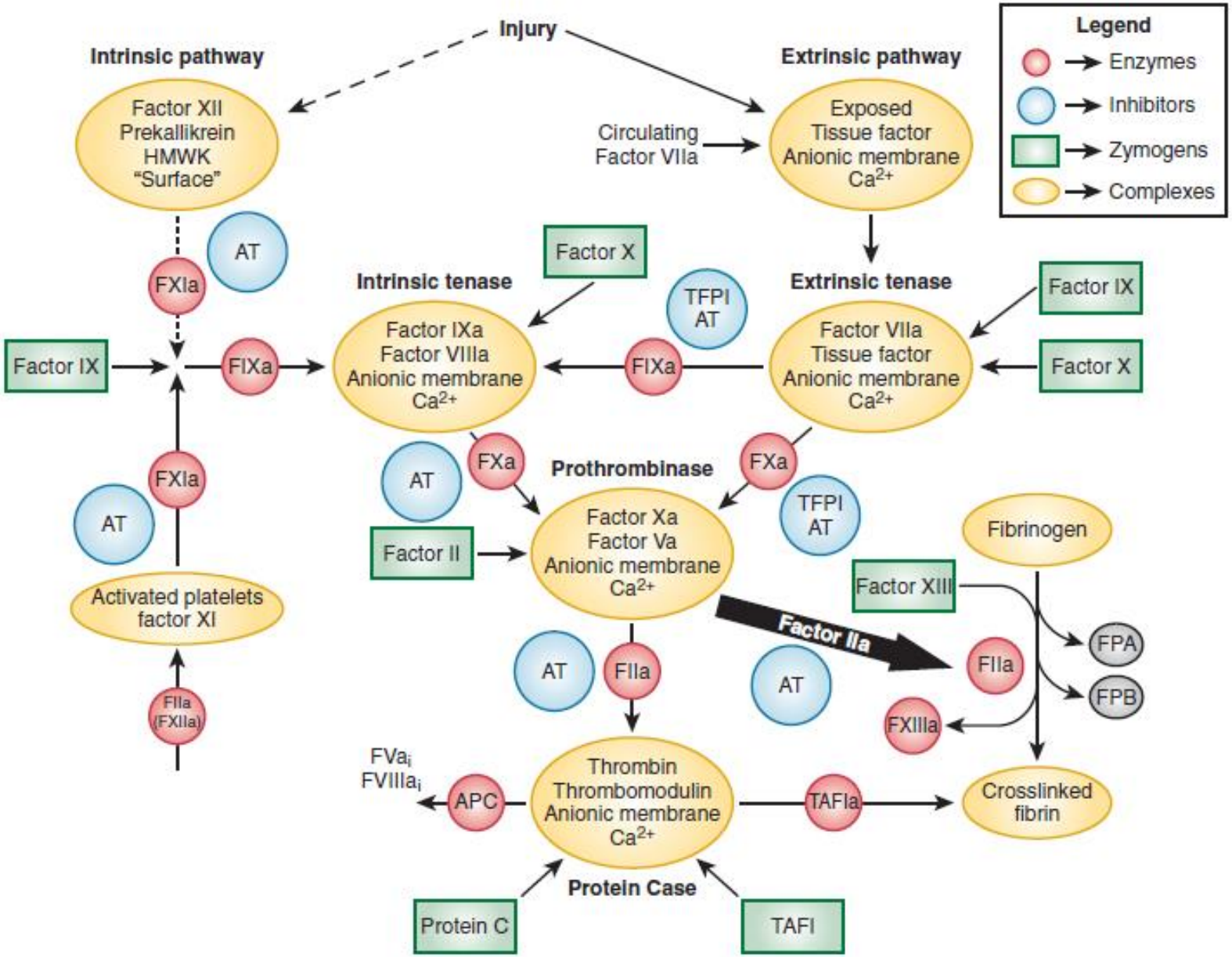
Conflict of Interest Declaration: Nothing to Disclose

Presenter: C. Hillis

I have no financial or personal relationships to disclose

Aim & Objectives

- Aim: To increase comfort in detecting non-pathologic bleeding & bruising.
- Objectives:
  - Discuss pearls on bleeding history
  - DDx of easy bruising and bleeding
  - Care and mgmt of vWD


Injury
Intrinsic pathway
Extrinsic pathway
Legend
Enzymes
Inhibitors
Zymogens
Complexes
Factor XII
Prekallikrein
HMWK
"Surface"
Circulating
Factor VIIa
Exposed
Tissue factor
Anionic membrane
Ca2+
AT
FXIa
Factor X
Intrinsic tenase
TFPI
AT
Extrinsic tenase
Factor IX
Factor IXa
Factor VIIIa
Anionic membrane
Ca2+
FIXa
Factor VIIa
Tissue factor
Anionic membrane
Ca2+
Factor X
FXa
Prothrombinase
Factor II
Factor Xa
Factor Va
Anionic membrane
Ca2+
Fibrinogen
Factor XIII
Activated platelets
factor XI
Factor IIa
FIIa
FPA
FPB
FXIIIa
FIIa
(FXIIa)
FVai
FVIIIai
APC
Thrombin
Thrombomodulin
Anionic membrane
Ca2+
TAFIa
Crosslinked
fibrin
Protein Case
Protein C
TAFI

Let's start with a differential

Phase	Defect
Blood vessel injury	Vascular disorders; Ehlers-Danlos; Amyloid
Platelet plug	Thombocytopenia; VWD; platelet function defect
Fibrin clot	Coagulation defect (hemophilia); liver disease; vit K deficiency; DIC; factor inhibitor
Clot stabilization	FXIII deficiency
Clot lysis	Fibrinolysis; Quebec platelet disorder

Pearls on history

- Unreliable (unfortunately)
- Bruising:
  - Size & location
  - Move?
- Bleeding complicating a procedure:
  - Procedure details
  - Laboratory evaluation
  - Timing
  - Poor wound healing / bruising
- Obstetrical bleeding history:
  - SAs? Infertility
  - Most commonly: abruption, accreta / atony, laceration, retained placenta
  - Don't forget DIC!
  - vWD not ruled-out

Pearls on history

- Menstrual history:
  - No known uterine abnormalities
  - Severe IDA; need for transfusion or hysterectomy
  - 23-44% of non-coagulopathic women experience menorrhagia
  - # of 'heavy' days; length; flooding; pad + tampon, etc..
- Exaggerated bleeding / bruising:
  - Even adults pick their noses
  - ¼ habitual nose-bleeders have a coagulopathy
  - Hemarthrosis, retroperitoneal hematoma, soft tissue hematoma
  - Spontaneous hemorrhage – are you sure?

Pearls on history

- Medical History:
  - SLE / autoimmune conditions (LA)
  - Renal failure
  - Hepatic dysfunction (factor deficiencies; thrombocytopenia; low-grade DIC)
  - Amyloid
  - Hypothyroidism

Pearls on history

- Family history – may help

Sex-Linked Recessive
Hemophilia A/B
Wiskott-Aldrich

Autosomal Dominant
Von Willebrand
HHT
Dysfibrinogenemias

Autosomal Recessive
FII, FV, FVII, FX, FXI, FXIII deficiencies
Alpha2-plasmin inhibitor deficiency
Bernard-Soulier
Glanzmann
Gray platelet syndrome
A/hypo-fibrinogenemia
Type 3 - vWD

Pearls on history

- Medications:
  - Anticoagulants / antiplatelets
  - NSAIDs
  - SSRIs
  - Herbals

Symptoms	Assigned score	
Epistaxis	0 = no or trivial 1 = present	2 = packing, cauterization, 3= transfusion, replacement
Cutaneous symptoms	0 = no or trivial 1 = petechiae or bruises	2 = hematomas 3 = medical consultation
Minor wounds	0 = no or trivial 1 = present (1-5 episodes/year)	2 = medical attention 3 = surgery / blood transfusion
Oral cavity bleeding	0 = no or trivial 1 = present	2 = medical attention 3 = surgery / blood transfusion
Gastrointestinal bleeding	0 = no or trivial 1 = present	2 = medical attention 3 = surgery / blood transfusion
Post-partum hemorrhage	0 = no or trivial 1 = present, iron therapy	2 = blood transfusion, dilatation-curettage, suturing 3 = hysterectomy
Muscle hematomas or hemarthrosis	0 = no or trivial 1 = present	2 = medical attention 3 = transfusion, intervention
Tooth extraction (most severe episode)	0 = no or trivial 1 = present	2 = suturing or packing 3 = transfusion
Surgery (most severe episode)	0 = no or trivial 1 = present	2 = suturing or resurgery 3 = transfusion
Menorrhagia	0 = no or trivial 1 = present	2 = consultation, pill use, iron therapy 3 =transfusion, hysterectomy, dilatation-curettage, replacement therapy

"Ok, so I took a history now what?"

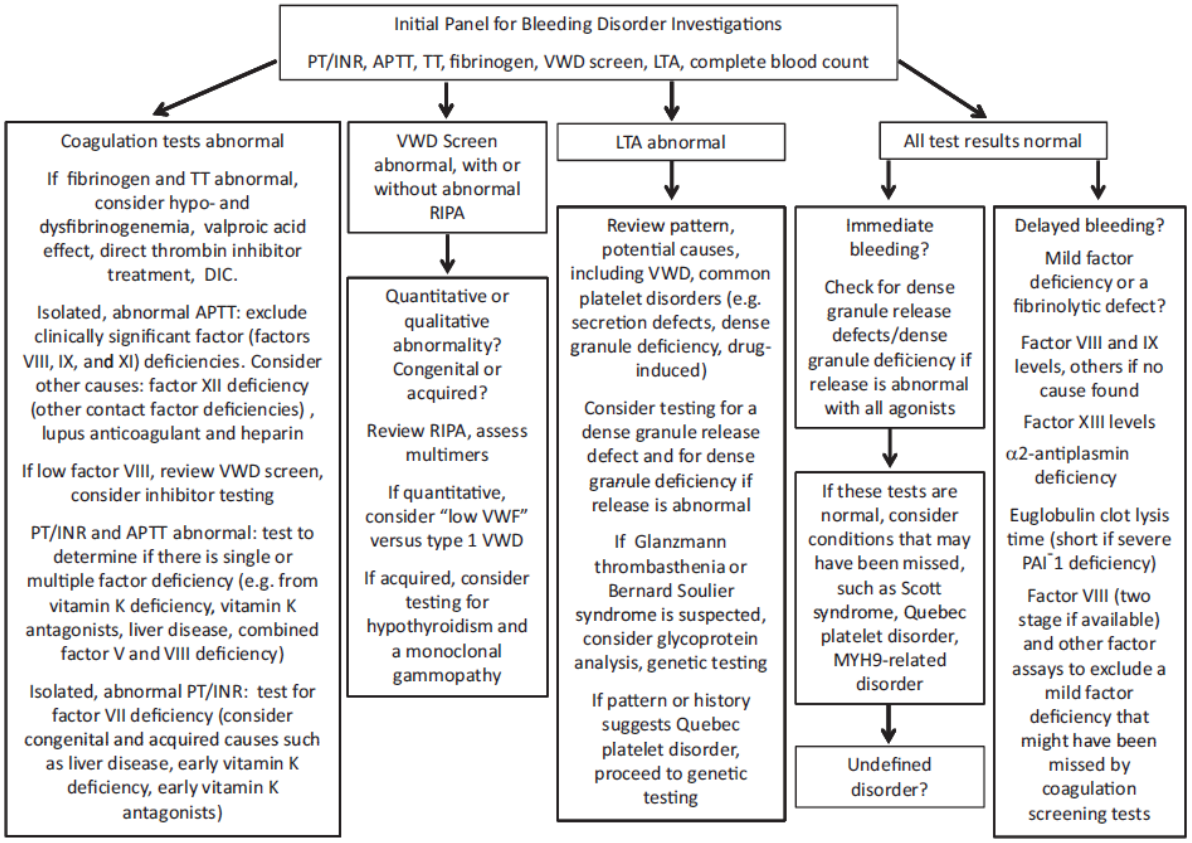


Fig. 1 Proposed laboratory scheme to investigate bleeding disorders, using an initial bleeding disorder panel that optimizes detection of common disorders. APTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; LTA, light transmission platelet aggregometry; MYH9, myosin heavy chain 9, non-muscle; PAI-1, plasminogen activator inhibitor-1; PT/INR, prothrombin time/international normalized ratio; RIPA, ristocetin-induced platelet aggregation; TT, thrombin time; VWD, von Willebrand disease; VWF, von Willebrand factor.

CBC	Platelet count
Peripheral smear	Platelet morphology (?MDS)
aPTT	Factors I, II, V, VIII, IX, XI, XII (intrinsic and common pathway)
PT	Factors I, II, V, **VII**, X (extrinsic and common pathway)
mixing studies	Performed when aPTT/PT is prolonged; patient plasma and normal plasma is mixed 1:1, then aPTT/PT repeated. If aPTT/PT corrects, there is a factor deficiency; if not, there is an inhibitor.
PFA-100 screen	Primary hemostasis (platelets, vWF)
Thrombin time	Fibrinogen
vWF panel	vWF antigen (amount of vWF)
	Ristocetin cofactor activity (function of vWF)
	Factor VIII activity
	vWF multimer analysis (distribution of multimers)
Platelet aggregation studies	Platelet function; patient platelets are exposed to agonists and the degree of aggregation and pattern of the response is unique for various qualitative platelet disorders.

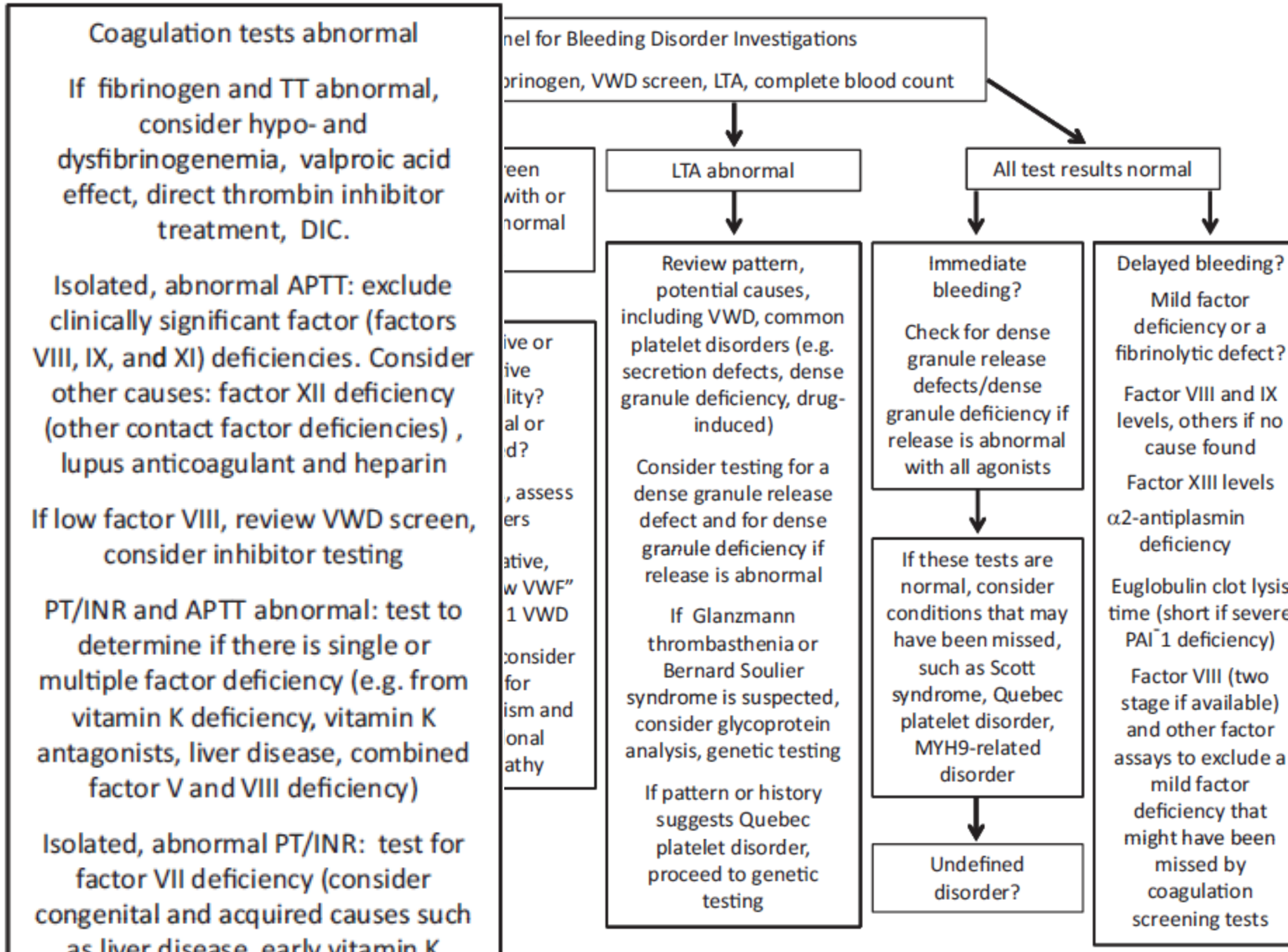


Fig. ng disorders, using an initial bleeding disorder panel that optimizes detection of com

Table 1 Causes of coagulation screening test abnormalities among the cohort of 800 patients

Test(s)	Proportion abnormal (% abnormal)	Type of abnormalities	
		Clinically significant	Other
APTT only	64/800 (8.0%)	• FVIII deficiency from hemophilia or VWD: $n = 18$ (28%) • FXI deficiency: $n = 4$ (6%)	• Prolonged APTT, clinically important factor deficiencies excluded: $n = 18$ (28%), 8 from FXII deficiency; 1 from suspected contact factor deficiency • Lupus anticoagulant positive: $n = 2$ (3%) • Lupus anticoagulant negative: $n = 2$ (3%) • Not investigated/confirmed/normal FVIII level: $n = 18$ (28%) • Unable to locate more records: $n = 2$ (3%)
PT/INR only	3/800 (0.4%)	• None	• Not confirmed on repeat: $n = 3$ (100%)
PT/INR and APTT	12/800 (1.5%)	• Warfarin therapy: $n = 6$ (50%) • Multiple factor deficiencies: $n = 1$ (8%)	• Lupus anticoagulant: $n = 2$ (17%) • Borderline abnormality: $n = 2$ (17%) • Not confirmed on repeat: $n = 1$ (8%)
APTT and TT	2/800 (0.3%)	• Heparin therapy: $n = 1$ (50%)	• Heparin contamination: $n = 1$ (50%)
TT only	4/800 (0.5%)	• None	• Valproic acid therapy: $n = 2$ (50%) • Suspected false positives: $n = 2$ (50%)
TT and fibrinogen	3/800 (0.4%)	• Hypofibrinogenemia: $n = 1$ (33%) • Dysfibrinogenemia: $n = 1$ (33%)	• Mild fibrinogen reduction (1.4 g/L), considered insignificant: $n = 1$ (33%)
All tests combined	88/800 (11%)	32/88 (36%)	56/88 (64%) with exclusively other abnormalities

Abbreviations: APTT, activated partial thromboplastin time; FVIII, factor VIII; FXI, factor XI; FXII, factor XII; PT/INR, prothrombin time/international normalized ratio; TT, thrombin time; VWD, von Willebrand disease.

Cases

Case # 1 - Kate

- 26F with menorrhagia seen pre-operatively for elective cholecystectomy
- aPTT > 100 all other tests WNL
  - ~~I, II, V~~
  - ?VIII, IX, XI, XII
  - ?vWD
- Diagnosis: severe FXII deficiency
- Treatment: patient* education

*Doctor

Case # 2 - Jean

- 19y.o. Male - Returned to OR after wisdom teeth extraction for bleeding
- Immediate: vascular or plt abnormality
- Delayed and/or re-bleeding: coagulation factor deficiency
- Poor or delayed wound healing: FXIII deficiency, dysfibrinogenemia, Ehlers-Danlos
  - Don't forget: DM, Cushing's, steroid use, Zinc deficiency

Case # 2 - Jean

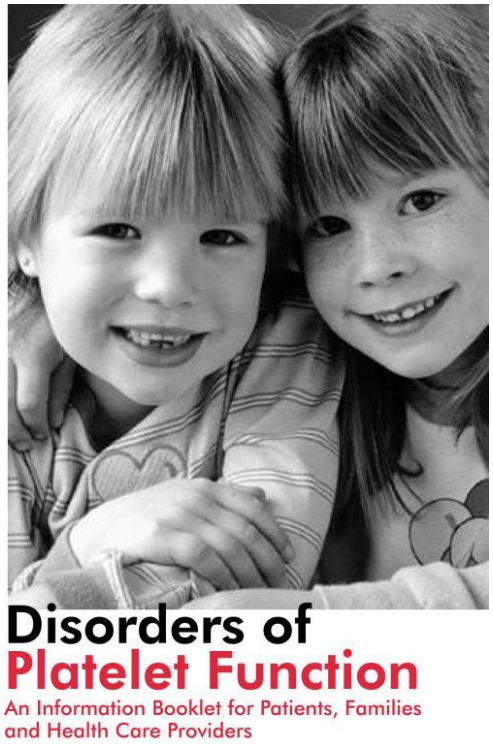
- 19y.o. Male - Returned to OR after wisdom teeth extraction for bleeding
  - 24hrs later - required suture and packing
- All tests normal!

They bleed but all tests are normal!!!

- The knife
- senile purpura
- Factor XIII deficiency
- alpha-2-antiplasmin deficiency
- mild factor deficiency
- vascular disorders
- Hereditary hemorrhagic telangiectasia
- the un-diagnosable fibrinolytic defect
- Amyloidosis; Scurvy; Cushing's

Case # 2 - Jean

- Diagnosed with Quebec Platelet Disorder
  - large amounts of the fibrinolytic enzyme urokinase-type plasminogen activator (u-PA) in platelets
  - Rx = **Tranexamic acid**



C

- 8

TABLE 131.1 Disorders and Conditions Associated with AvWS

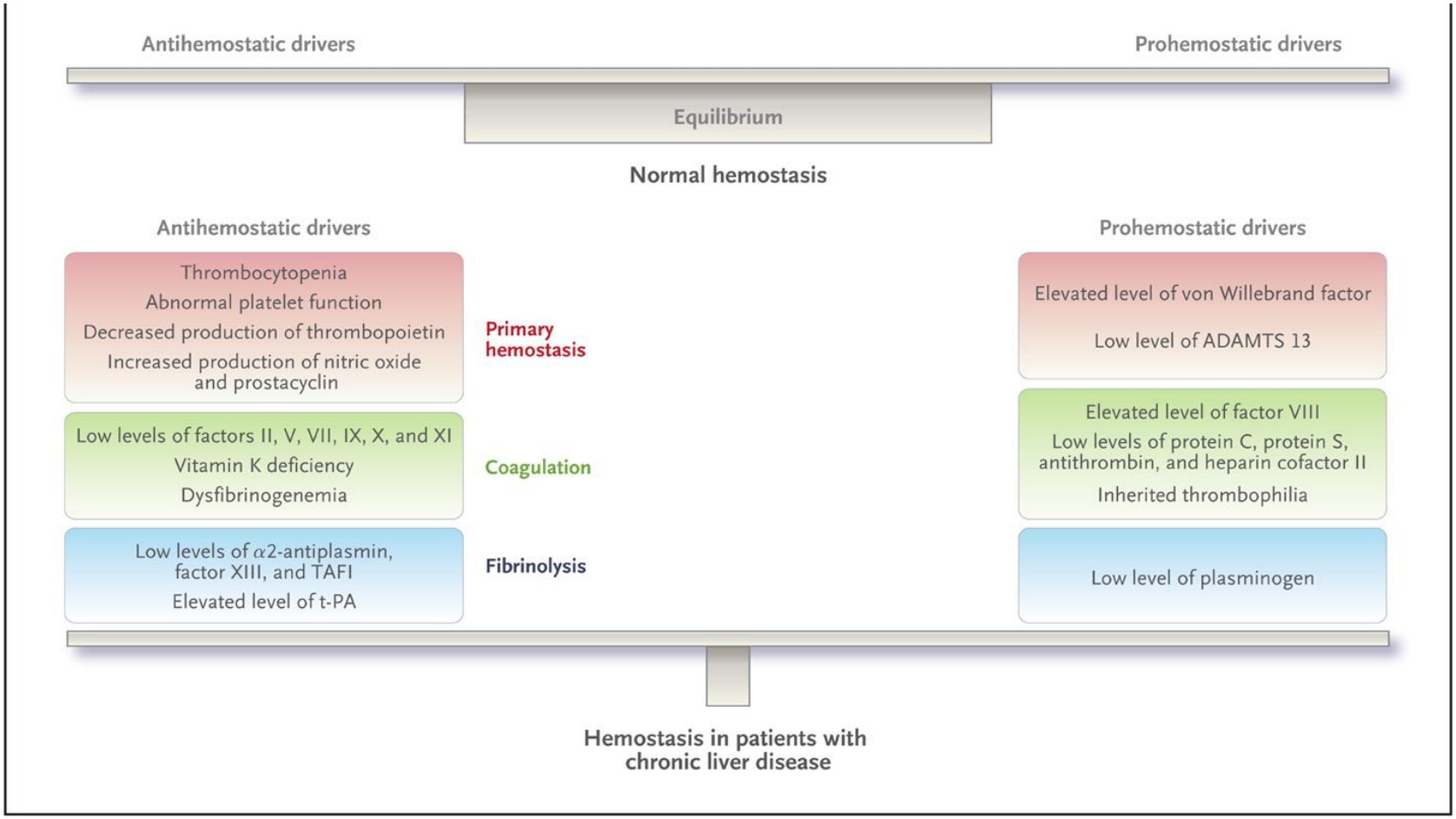
Lymphoproliferative disorders	Monoclonal gammopathy of undetermined significance, multiple myeloma, non-Hodgkin lymphoma, hairy cell leukemia, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, acute lymphocytic leukemia
Myeloproliferative disorders	Polycythemia vera, chronic myeloid leukemia, essential thrombocythemia, myelofibrosis, chronic granulocytic leukemia
Neoplastic disorders	Wilms tumor (nephroblastoma), peripheral neuroectodermal tumor, adrenocortical carcinoma, gastric carcinoma, acute lymphoblastic leukemia, lung cancer, acute myeloid leukemia
Autoimmune disorders	Systemic lupus erythematosus, scleroderma, mixed connective tissue disease, Ehlers Danlos syndrome, autoimmune hemolytic anemia, Felty syndrome
Endocrine disorders	Hypothyroidism, diabetes mellitus
Cardiovascular diseases	Cardiac defects (VSD, ASD), aortic stenosis, angiodysplasia, mitral valve prolapse, patent ductus arteriosus, hypertrophic obstructive cardiomyopathy, left ventricular assist device, primary pulmonary hypertension
Infectious diseases	Epstein-Barr virus, hydatid cyst
Drugs	Ciprofloxacin, valproic acid, griseofulvin, hydroxyethyl starch
Other	Uremia, hemoglobinopathies, reactive thrombocytosis, pesticide ingestion, glycogen storage disease, sarcoidosis, telangectasis, ulcerative colitis, bone marrow transplant, graft-versus-host disease, transplacental transfer of maternal antibodies

ASD = aortic septal defect; VSD = ventricular septal defect

“Warfarin only causes bleeding if fired at you from a gun.”

Dr. M. Crowther

Balance of Antihemostatic and Prohemostatic Drivers in the Different Phases of Hemostasis.

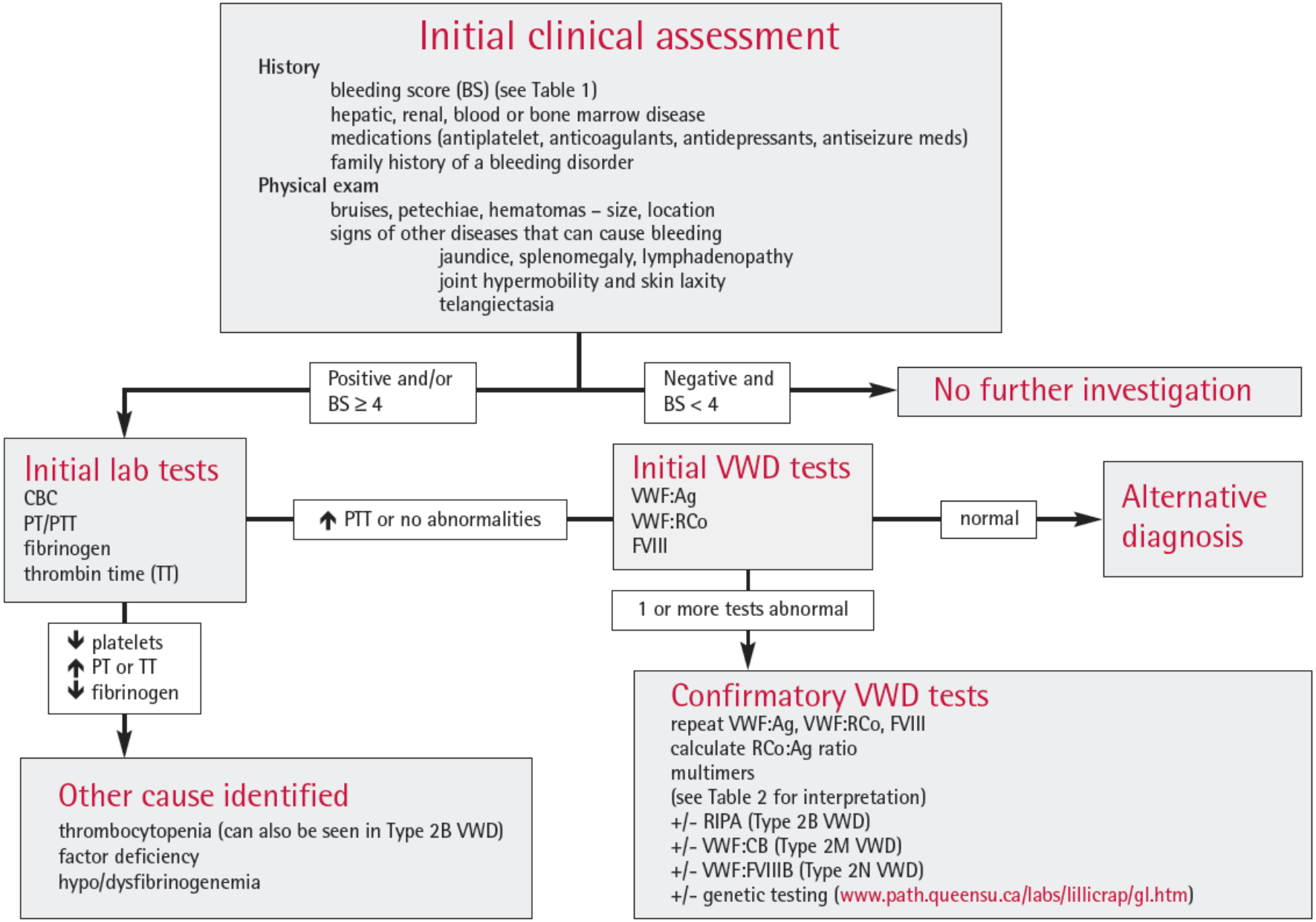


Treatment Options

Tool Kit

- Surgery / interventional radiology
- Source (OCP, D&C, etc…)
- Factor first!
- Tranexamic acid
- DDAVP (with caution)
- PCC
- FVIIa
- Plasma

von Willebrand Disease


Initial clinical assessment
History
bleeding score (BS) (see Table 1)
hepatic, renal, blood or bone marrow disease
medications (antiplatelet, anticoagulants, antidepressants, antiseizure meds)
family history of a bleeding disorder
Physical exam
bruises, petechiae, hematomas – size, location
signs of other diseases that can cause bleeding
jaundice, splenomegaly, lymphadenopathy
joint hypermobility and skin laxity
telangiectasia
Positive and/or BS ≥ 4
Negative and BS < 4
No further investigation
Initial lab tests
CBC
PT/PTT
fibrinogen
thrombin time (TT)
↑ PTT or no abnormalities
Initial VWD tests
VWF:Ag
VWF:RCo
FVIII
normal
Alternative diagnosis
1 or more tests abnormal
↓ platelets
↑ PT or TT
↓ fibrinogen
Other cause identified
thrombocytopenia (can also be seen in Type 2B VWD)
factor deficiency
hypo/dysfibrinogenemia
Confirmatory VWD tests
repeat VWF:Ag, VWF:RCo, FVIII
calculate RCo:Ag ratio
multimers
(see Table 2 for interpretation)
+/- RIPA (Type 2B VWD)
+/- VWF:CB (Type 2M VWD)
+/- VWF:FVIIIB (Type 2N VWD)
+/- genetic testing (www.path.queensu.ca/labs/lillicrap/gl.htm)

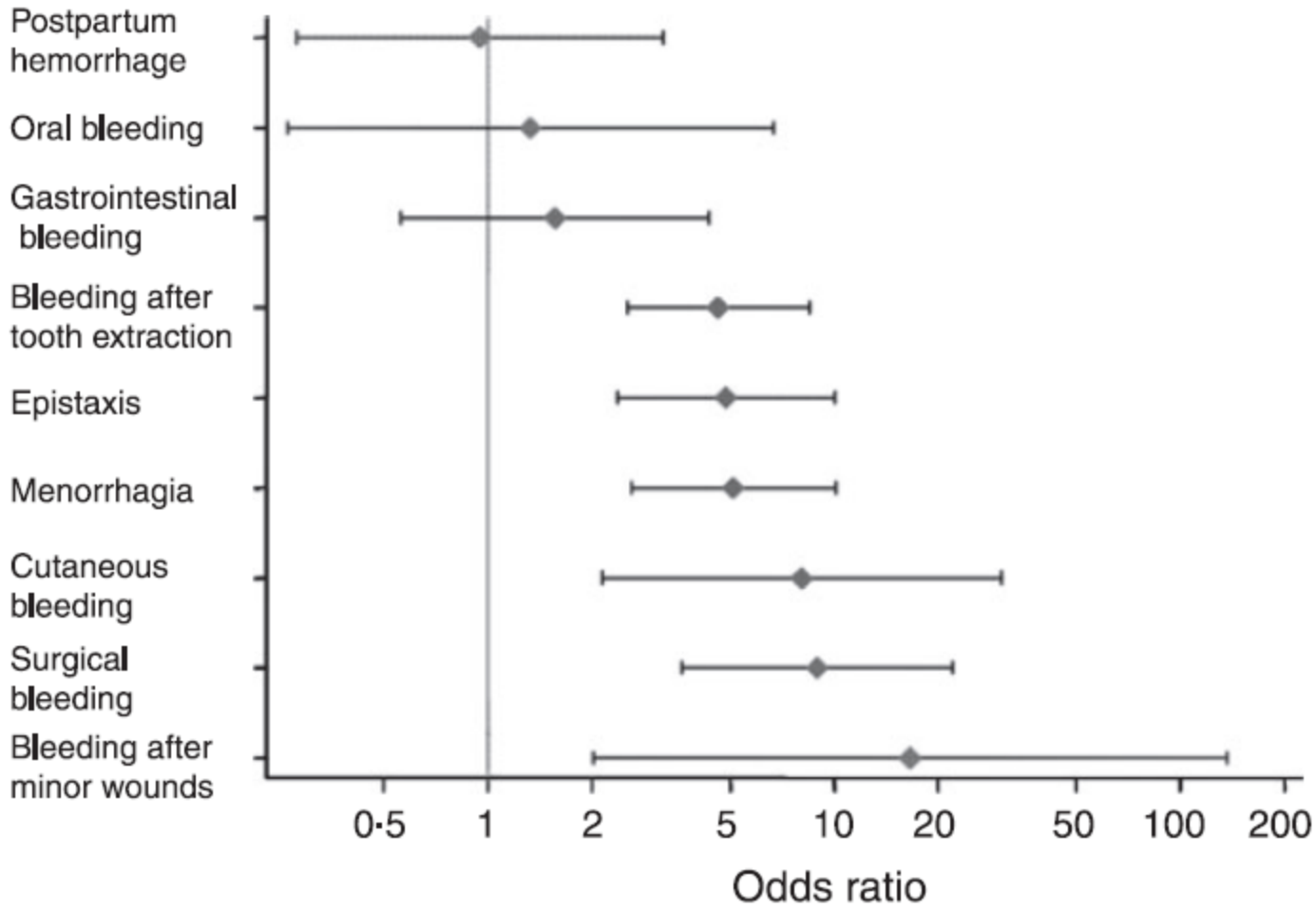
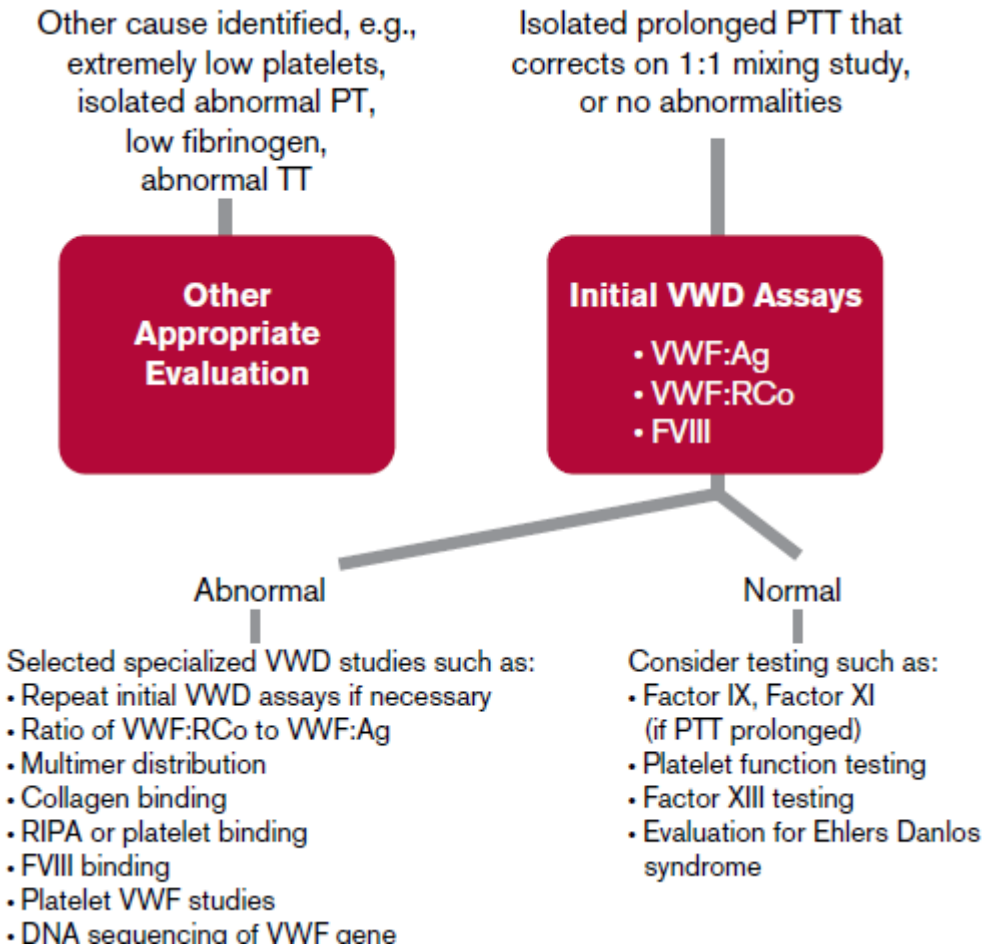


Fig 1. Predictive value of bleeding symptoms in diagnosis of type 1 VWD. Reproduced with permission, from Tosetto *et al* (2006).


Other cause identified, e.g., extremely low platelets, isolated abnormal PT, low fibrinogen, abnormal TT
Isolated prolonged PTT that corrects on 1:1 mixing study, or no abnormalities
Other Appropriate Evaluation
Initial VWD Assays
• VWF:Ag
• VWF:RCo
• FVIII
Abnormal
Normal
Selected specialized VWD studies such as:
• Repeat initial VWD assays if necessary
• Ratio of VWF:RCo to VWF:Ag
• Multimer distribution
• Collagen binding
• RIPA or platelet binding
• FVIII binding
• Platelet VWF studies
• DNA sequencing of VWF gene
Consider testing such as:
• Factor IX, Factor XI (if PTT prolonged)
• Platelet function testing
• Factor XIII testing
• Evaluation for Ehlers Danlos syndrome

Blood group!

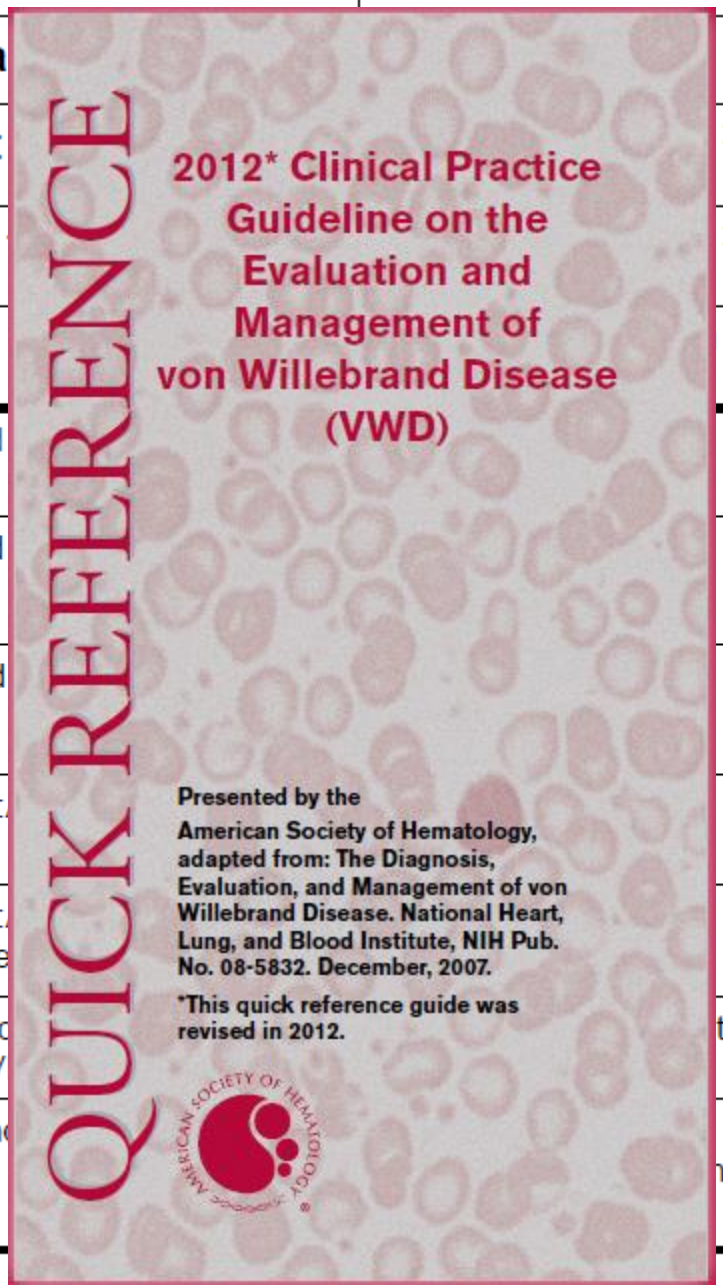
Factors that increase VWF levels

- neonatal period
- stress (i.e.: excessive crying during phlebotomy, fainting, active bleeding, surgery)
- acute illness (i.e.: infection)
- exercise
- oral contraceptive pill
- pregnancy
- hormone replacement therapy
- hyperthyroidism
- cushing syndrome
- older age

Factors that decrease VWF levels

- hypothyroidism
- anti-VWF antibodies

		MINOR SURGERY	MAJOR SURGERY
	Dose (FVIII) a		50 IU/kg every 12-24hr
	Pre-op target	>50 IU/dL	FVIII:C and VWF:RCo near 100 IU/dL
	Maintenance	>30 IU/dL	FVIII:C and VWF:RCo >50 IU/dL
	Duration	risk has	5-10 days until bleeding ris has passed
Borderline	FVIII, VWF:Ag and		DDAVP if response VWF concentrate
Mild-mod type 1	FVIII, VWF:Ag and		DDAVP if response VWF concentrate
Severe type 1	FVIII>10 IU/dL and		VWF concentrate
2A or M	VWF:RCo to VWF:		DDAVP if response VWF concentrate
2B	VWF:RCo to VWF: enhanced low dose		VWF concentrate
2N	FVIII <40 IU/dL and <0.5. Low VWF:FV	t 1/2)	VWF concentrate
3	FVIII <10 IU/DL an	nfusion)	VWF concentrate (consider continuous infusi



The addition of Tranexamic acid should be considered in all situations

Summary

- Nature & severity of defect
- Congenital / acquired
- Antecedent exposures (and their risks)
- Other med problems
- Local factors
- Medications
- Treatments reduce bleeding? For other reason?

References

Ballas, M., & Kraut, E. H. (2008). Bleeding and bruising: a diagnostic work-up. *American family physician*, *77*(8), 1117-1124.

Castaman, G., Goodeve, A., & Eikenboom, J. (2013). Principles of care for the diagnosis and treatment of von Willebrand disease. *Haematologica*, *98*(5), 667-674.

Hayward, C. P., Moffat, K. A., Plumhoff, E., & Van Cott, E. M. (2012). Approaches to investigating common bleeding disorders: an evaluation of North American coagulation laboratory practices. *American journal of hematology*, *87*(S1), S45-S50.

Hayward, C. P., & Moffat, K. A. (2013). Laboratory testing for bleeding disorders: strategic uses of high and low-yield tests. *International journal of laboratory hematology*, *35*(3), 322-333.

Laffan, M. A., Lester, W., O'Donnell, J. S., Will, A., Tait, R. C., Goodeve, A., ... & Keeling, D. M. (2014). The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *British journal of haematology*, *167*(4), 453-465.

Tripodi, A., & Mannucci, P. M. (2011). The coagulopathy of chronic liver disease. *New England Journal of Medicine*, *365*(2), 147-156.

Table 2. Differential diagnosis of abnormalities in coagulation tests

	PT/INR	APTT	TT	fibrinogen
Cause and pattern of abnormalities				
Fibrinogen deficiency (hypofibrinogenemia) or dysfunction (dysfibrinogenemia)	N – ↑	N – ↑	↑	↓
Afibrinogenemia	NC	NC	NC	ND
FVII deficiency	↑	N	N	N
FVIII, FIX, and/or FXI deficiency	N	↑	N	N
Acquired or congenital hemophilia, with an inhibitor	N	↑ †	N	N
FII, FV, and/or FX deficiency	↑	↑	N	N
Factor deficiencies not associated with bleeding (FXII, high molecular weight kininogen or prekallikrein deficiency)	N	↑	N	N
Lupus anticoagulant	N – ↑	N – ↑ ‡	N	N
Lupus anticoagulant with FII deficiency	↑	↑	N – ↑	N
Unfractionated heparin - therapy or sample contamination	N – ↑	↑	↑↑*	N
Low molecular weight heparin therapy	N	N – ↑	N – ↑	N
Direct thrombin inhibitors	N – ↑	N – ↑	↑↑	N
Direct inhibitors of FXa	N – ↑	N – ↑	N	N
Liver disease† (if early, often affects FVII, FXI and/or FXII; if late or end stage, fibrinogen is usually low; spares FVIII but can affect all other factors)	N – ↑	N – ↑	N – ↑	↓ - N – ↑
Vitamin K deficiency (or treatment with a vitamin K antagonist) which reduce levels of FVII and also FII, FIX and FX†	↑	N – ↑	N	N
Fibrinolytic therapy	↑	↑	↑	↓
Consumptive coagulopathy†	N – ↑	↑	N – ↑	N – ↓
Dilutional coagulopathy†	N – ↑	N – ↑	N – ↑	↓ - N
VWD	N	N – ↑	N	N
Preanalytical error – collected in potassium EDTA§	↑	↑	N – ↑	N
Preanalytical error – serum instead of plasma	NC	NC	NC	ND