Hereditary and Acquired Bleeding Disorders: von Willebrand Disorders

Pathophysiology and Classification

- von Willebrand factor (VWF) deficiencies may be inherited or acquired.
- VWF is a multimeric protein involved in platelet adhesion and blood coagulation by transporting factor VIII (FVIII) and preserving it from clearance.
- von Willebrand disease (VWD) is caused by the congenital deficiency of VWF.
  - Type 1: partial deficiency of VWF (75% of cases)
  - Type 2: impairment of VWF interactions with platelets or FVIII (second most common variant)
    - Further subdivided into 2A, 2B, 2M, 2N based on details of the phenotype
  - Type 3: severe deficiency of VWF (extremely rare, ~ 1 in 1 million)
- Acquired von Willebrand Syndrome (AVWS) is an acquired rare bleeding disorder associated with several underlying diseases and different pathogenic mechanisms.
  - Decreased synthesis of VWF: Hypothyroidism
  - Normal synthesis but increased clearance of VWF: Antibodies in autoimmune diseases, monoclonal gammopathies, myeloproliferative and lymphoproliferative malignancies
  - Proteolysis of VWF: Acute pancreatitis, liver cirrhosis, leukemia or high shear stress in the heart (aortic stenosis) or a device that unfolds VWF (LVAD), increasing susceptibility of VWF to proteolysis by ADAMTS-13
  - There is a high frequency of blood type O in the United States, and it is associated with “low” VWF.

LVAD = left ventricular assist device

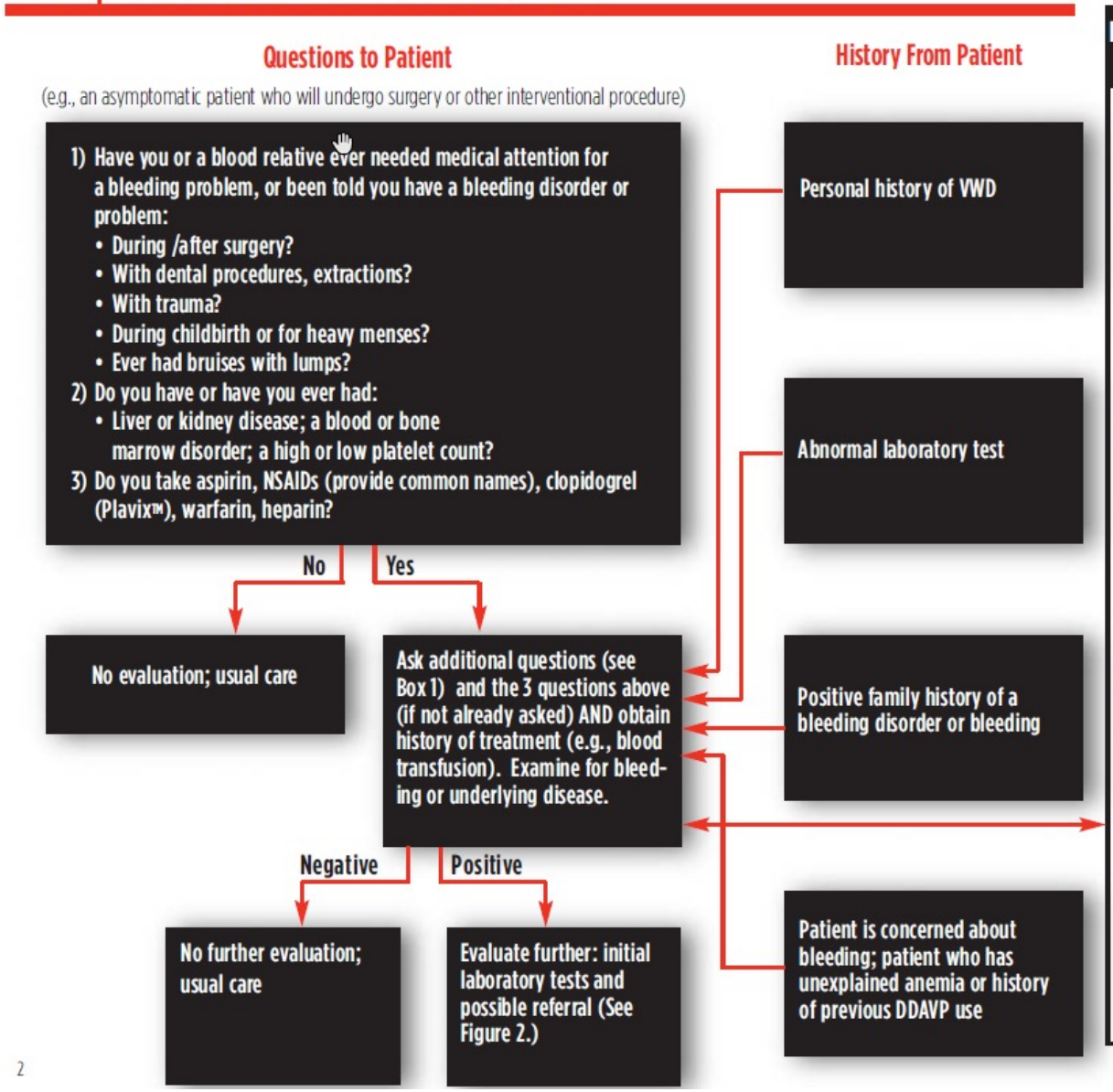
Mehta R, et al. *J Thromb Thrombolysis.* 2019;48(1):14-26.

von Willebrand Disease: Presenting Signs and Symptoms

- Bleeding and bruising are the most common presenting symptoms.
  - Mucosal bleeding symptoms such as easy bruising, epistaxis, gingival bleeding
  - Surgical bleeding
  - Heavy menstrual bleeding
  - Gastrointestinal bleeding (more common in type 2 AVWS)
  - Joint bleeds (more common in type 2N VWD and type 3 due to low factor VIII)
- Patients may be referred for surgical clearance or due to a recent bleeding episode or recurring bleeding episodes.
- Obtaining a detailed history to discern bleeding risk and any history of bleeding will be key to further work-up and possible treatment.

Sharma R, et al. *Blood*. 2017;130(22):2386-2391.

Figure 1: Initial Evaluation for VWD or other Bleeding Disorders



Box 1: Additional Questions To Screen for a Bleeding Disorder

1. Do you have a blood relative who has a bleeding disorder, such as von Willebrand disease or hemophilia?
2. Have you ever had prolonged bleeding from trivial wounds, lasting more than 15 minutes or recurring spontaneously during the 7 days after the wound?
3. Have you ever had heavy, prolonged, or recurrent bleeding after surgical procedures, such as tonsillectomy?
4. Have you ever had bruising, with minimal or no apparent trauma, especially if you could feel a lump under the bruise?
5. Have you ever had a spontaneous nose-bleed that required more than 10 minutes to stop or needed medical attention?
6. Have you ever had heavy, prolonged, or recurrent bleeding after dental extractions that required medical attention?
7. Have you ever had blood in your stool, unexplained by a specific anatomic lesion (such as an ulcer in the stomach, or a polyp in the colon), that required medical attention?
8. Have you ever had anemia requiring treatment or received a blood transfusion?
9. For women, have you ever had heavy menses, characterized by the presence of clots greater than an inch in diameter and/or changing a pad or tampon more than hourly, or resulting in anemia or low iron level?

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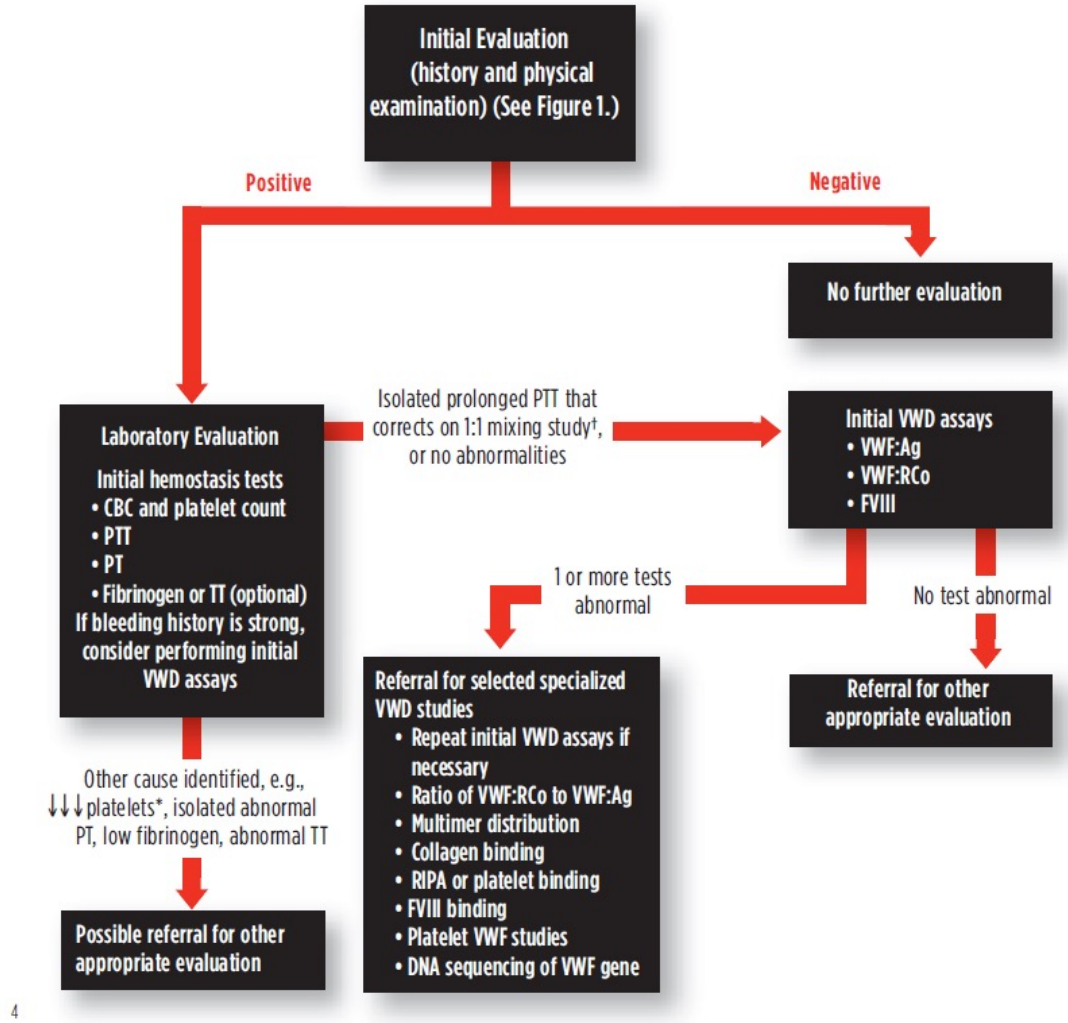
Figure 2. | Laboratory Assessment for VWD or other Bleeding Disorders



* Isolated decreased platelets may occur in VWD type 2B.

\+ Correction in the PTT mixing study immediately and after 2-hour incubation removes a factor VIII (FVIII) inhibitor from consideration. Investigation of other intrinsic factors and lupus anticoagulant also may be indicated.

CBC = complete blood count; PT=prothrombin time; PTT = partial thromboplastin time; RIPA = Ristocetin-induced platelet aggregation; TT = thrombin time; WVF:Ag = VWF antigen; VWF:RCo = VWF Ristocetin cofactor activity. Referral to a hemostasis specialist is appropriate for help in interpretation, repeat testing, and specialized tests.

See full guidelines for levels of evidence for each recommendation www.nhlbi.nih.gov/guidelines/vwd

NIH Publication No. 08-5833 February 2008 http://www.nhlbi.nih.gov

Laboratory Values for von Willebrand Disease

Condition	Description	VWF:Rco (IU/dL)	VWF:Ag (IU/dL)	FVIII	VWF:Rco/ VWF:Ag
Type 1	Partial quantitative VWF deficiency (75% of symptomatic VWD patients)	< 30*	< 30*	↓ or Normal	> 0.5–0.7
Type 2A	↓ VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	< 30*	< 30–200*#	↓ or Normal	< 0.5–0.7
Type 2B	Increased affinity for platelet GPIb	< 30*	< 30–200*#	↓ or Normal	< 0.5–0.7
Type 2M	↓ VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers	< 30*	< 30–200*#	↓ or Normal	< 0.5–0.7
Type 2N	Markedly decreased binding affinity for FVIII	30–200	30–200	↓↓	> 0.5–0.7
Type 3	Virtually complete deficiency of VWF (severe, rare)	< 3	< 3	↓↓↓↓ (< 10 IU/dL)	N/A
"Low VWF"**		30–50	30–50	Normal	> 0.5–0.7
Normal		50–200	50–200	Normal	> 0.5–0.7

*< 30 IU/dL is designated as the level for a definitive diagnosis of VWD; some patients with type 1 or type 2 VWD have levels of VWF:RCo and/or VWF:Ag of 30–50 IU/dL.
The VWF:Ag in the majority of individuals with type 2A, 2B, or 2M VWD is < 50 IU/dL.
** This does not preclude the diagnosis of VWD in patients with VWF:RCo of 30–50 IU/dL.

Ag = antigen; FVIII = factor VIII; GPIb = glycoprotein Ib; Rco = ristocetin cofactor; VWD = von Willebrand disease; VWF = von Willebrand factor

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von Willebrand Disease: Clinical Management

- Treatment is aimed at cessation of bleeding or prophylaxis for surgical procedures
- Strategies include
  - Increasing plasma concentration of VWF by releasing endogenous VWF stores through stimulation of endothelial cells with desmopressin (DDAVP)
  - Replacing VWF by using human plasma-derived, viral-inactivated concentrates
  - Using agents that promote hemostasis and wound healing but do not substantially alter the plasma concentration of VWF

Treatment to Reduce or Prevent Bleeding in VWD

Desmopressin (DDAVP)

- Hormone that causes release of FVIII and VWF from storage sites within endothelial cells
- Can be given intranasally, subcutaneously, or intravenously
- Dosing varies by procedure/ bleeding risk
- Most common side effects
  - Vasomotor effects: facial flushing, headache, hypotension
  - Fluid retention: requires fluid restriction for first 24 hours after each dose to avoid hyponatremia and rare seizures

Antifibrinolytics

- Aminocaproic acid and tranexamic acid
- Help prevent clot degradation by inhibiting action of plasminogen
- Oral or intravenous
- Dosing varies by procedure/bleeding risk
- Most common adverse events: nausea, diarrhea (dose dependent)

VWF Replacement

- Generally reserved for patients with type 3 VWD, or patients refractory to other treatments
- May also be considered for procedures with a very high risk of bleeding, long duration, | high-risk location

FVIII = factor VIII; VWD = von Willebrand disease; VWF = von Willebrand factor

O'Brien SH, et al. *Hematol Oncol Clin North Am*. 2019;33(3):425-438.

von Willebrand Disease: Clinical Resources

- General resources from the Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/ncbddd/vwd/index.html
- von Willebrand disease treatment guidelines from the CDC: https://www.cdc.gov/ncbddd/vwd/guidelines.html
- In January 2021, the American Society of Hematology (ASH) published updated international guidelines on VWD diagnosis (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7805340/) and management (https://pubmed.ncbi.nlm.nih.gov/33570647/)