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.**



I. Evaluation

A. History

Ask the following broad questions:

- Have you or a blood relative ever needed medical attention for a bleeding problem or been told you had a bleeding problem?
- Have you ever had a blood disorder, or liver or kidney disease?
- Are you currently taking or have you recently taken anticoagulation or antiplatelet medications?

If answers to questions above are positive, ask the following questions:

- Do you have a blood relative with a bleeding disorder?
- Have you ever had any of the following symptoms?
  - Bleeding from trivial wounds lasting >15 minutes or recurring spontaneously during the 7 days after the injury
  - Heavy, prolonged, or recurrent bleeding after surgical procedures
  - Bruising with minimal or no apparent trauma, especially if you could feel a lump under the bruise
  - Spontaneous nosebleed lasting >10 minutes or that required medical attention
  - Heavy, prolonged, or recurrent bleeding after dental extractions that required medical attention
  - Blood in your stool that required medical attention and was unexplained by an anatomic lesion (stomach ulcer, colon polyp)
  - Anemia that required a blood transfusion or other type of treatment
  - Heavy menses characterized by clots >1 inch diameter, changing a pad or tampon more than hourly, or resulting in anemia or low iron
- Refer to the bleeding score table (panel 2) to help determine the likelihood of a bleeding disorder including possible VWD.

B. Physical Examination

Perform a physical examination to include evaluation for:

- Evidence of bleeding or anemia, including size, location, and distribution of ecchymoses, hematomas, and petechiae.
- Evidence of risks of increased bleeding such as jaundice or spider angiomata, splenomegaly, arthropathy, joint and skin laxity, and telangiectasia.

C. Special Considerations for the Laboratory Diagnosis of VWD

- Patients should be at optimal baseline at the time of testing. Undue stress (illness, struggling or crying in children, anxiety in adults) may transiently elevate VWF and FVIII levels.
- Very recent exercise, acute inflammation due to surgeries or infection, chronic inflammation such as from autoimmune diseases or diabetes, pregnancy, and estrogen containing contraceptives, may also elevate VWF levels.
- Atraumatic blood draws limit the exposure of tissue factor from the site and clotting factor activation, thus minimizing falsely high or low levels.
- Careful handling and processing of samples is critical. Samples must be promptly and thoroughly centrifuged. Samples that will be transported to a reference laboratory must be frozen and delivered promptly and remain frozen until assayed.

D. Bleeding Score[1]

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. For VWD, a bleeding score ≥ 4 has a sensitivity = 100%, specificity = 87%, positive predictive value = 0.20, negative predictive value = 1.00. The higher the bleeding score, the greater is the likelihood of a bleeding disorder including possible VWD. For more information, please visit *www.path.queensu.ca/labs/james/bq.htm*.

	-1	0	1	2	3	4
Epistaxis	-	No or trivial (< 5/year)	> 5/year or > 10 mins	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/year)	> 5/year or > 5 mins	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
Gastro-intestinal bleeding	-	No	Assoc. with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	-
Tooth extraction	No bleeding in ≥ 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 ≥ 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation	Consultation only	Surgical hemostasis and 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 ≥ 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 hemotomas	-	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
CNS bleeding	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention

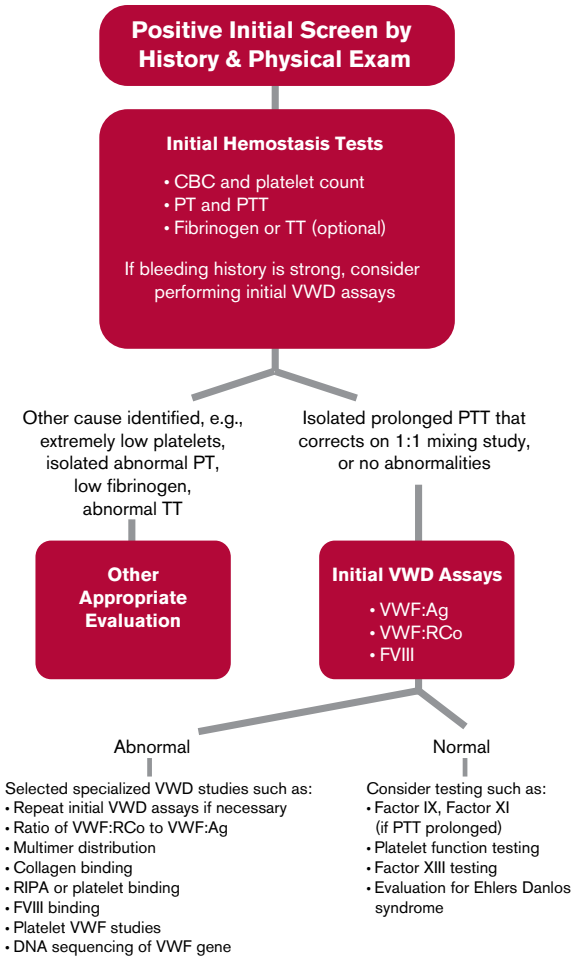
At the time of this report, there are several bleeding assessment tools in various stages of investigation and validation.[2] This quick reference includes the Condensed MCMDM-1 VWD Bleeding Questionnaire, as this tool has been well validated as a research tool, is undergoing investigation as a clinical tool, and can be rapidly administered.[1]

[1]Bowman M, Mundell G, Grabell J, Hopman W, Rapson D, Lillicrap D, James P. Generation and Validation of the Condensed MCMDM1-VWD Bleeding Questionnaire. J Thromb Haemost 2008; 6: 2062-6, from *www.ncbi.nlm.nih.gov/pubmed/18983516*.

[2]Rydz N and James PD. The Evolution and Value of Bleeding Assessment Tools. J Thromb Haemost 2012 Sept 13 [Epub ahead of print] PMID: 22974079, from *www.ncbi.nlm.nih.gov/pubmed/22974079*.

II. Assessment Algorithm

Assessment for VWD or Other Bleeding Disorders



CBC=complete blood count, FVIII=factor VIII activity, PT=prothrombin time, PTT=partial thromboplastin time, TT=thrombin time, VWF:Ag=VWF antigen, VWF:RCo=VWF ristocetin cofactor activity

III. Laboratory Diagnosis

Laboratory Values for VWD*

Condition	Description	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	VWF:RCo/ VWF:Ag Ratio
Type 1	Partial quantitative VWF deficiency	<30**	<30**	Low or Normal	>0.5-0.7
Type 2A	Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers	<30**	<30-200**	Low or Normal	<0.5-0.7
Type 2B	Increased affinity for platelet GPIb; decreased platelets	<30**	<30-200**	Low or Normal	Usually <0.5-0.7
Type 2M	Decreased VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers	<30**	<30-200**	Low or Normal	<0.5-0.7
Type 2N	Markedly decreased binding affinity for FVIII	30-200	30-200	Very Low	>0.5-0.7
Type 3	Virtually complete deficiency of VWF	<3	<3	Extremely Low (<10 IU/dL)	Not applicable
"Low VWF"**		30-50	30-50	Normal	>0.5-0.7
Normal		50-200	50-200	Normal	>0.5-0.7

*These values represent prototypical cases. Exceptions occur, and repeat testing may be necessary.

**<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.

NOTE: 30 IU/dL is recommended as the "cut-off" for the definite diagnosis of VWD for the following reasons: 1) high frequency of blood type O in the United States, which is associated with "low" VWF levels; 2) bleeding symptoms are reported by a significant proportion of normal individuals; 3) no abnormality in the VWF gene has been identified in many individuals who have mildly to moderately low VWF:RCo levels. This does not preclude the use of agents to increase VWF levels in those who have VWF:RCo of 30-50 IU/dL and who may be at risk for bleeding.

IV. Selected Recommendations for the Management of VWD

A. Therapies to Elevate VWF: Desmopressin (DDAVP)

- Administration of DDAVP may be IV (0.3 mcg/kg) or intranasal (Stimate®/Octostim® 150 mcg or 1 spray for persons <50 kg and 300 mcg or 2 sprays for persons weighing ≥50 kg).
- A therapeutic trial of DDAVP is recommended prior to use. VWF:RCo and FVIII activities should be measured at baseline and within 1 hour. Additional testing 2-4 hours after DDAVP should be considered to evaluate for shortened survival.
- Most type 1 VWD patients will respond to DDAVP, although patients with VWF:RCo <10 IU/dL and FVIII activity <20 IU/dL are less likely to have a clinically significant response.
- In type 2 VWD, DDAVP will increase the VWF concentration, but the VWF dysfunction will still be present. In type 2B VWD, DDAVP may result in transient thrombocytopenia. Therefore, DDAVP should be used with caution in type 2 VWD.
- Side effects include facial flushing, transient hyper- or hypotension, headache, abdominal upset, and water retention. Patients should limit fluid intake to maintenance levels for 24 hours following DDAVP. Serum electrolytes should be monitored after surgery or multiple doses of DDAVP.
- Consider alternative therapies to DDAVP in young children and patients at increased risk of hyponatremia and seizures.
- To avoid tachyphylaxis, DDAVP therapy is typically discontinued after 2 or 3 daily doses.

B. Therapies to Elevate VWF: Factor Products

Von Willebrand Factor Replacement Products (available in United States)

Product	VWF:RCo activity (IU/ml) 1	FVIII activity (IU/ml) 1	Ratio of VWF:RCo to FVIII activity
Humate-P®2	120	50	2.4:1
Wilate®2	90	90	1:1
Koate DVI®	50	50	1:1
Alphanate SD/HT®2	16-72	40-180	1:2

[1]Potency may vary. Refer to each individual carton or vial prior to reconstitution.

[2]FDA-approved for the treatment of von Willebrand disease

C. General Management of VWD Patients

- Long-term prophylaxis is rarely required, but should be considered for recurrent joint bleeding or excessive mucocutaneous bleeding not adequately controlled by other treatments.
- Avoid aspirin, other NSAIDs, and other platelet-inhibiting drugs.

D. Notes on Treatment of Minor Bleeding and Prophylaxis for Minor Surgery

- Minor bleeding should be treated with intravenous or nasal DDAVP, if supported by results of a DDAVP trial.
- If response to DDAVP is inadequate, VWF concentrate should be used, with dosing primarily based on VWF:RCo units and secondarily on FVIII units.
- For minor surgery, prophylaxis should achieve VWF:RCo and FVIII activity levels ≥30 IU/dL, and preferably >50 IU/dL, for 1-5 days.
- Management of minor bleeding with DDAVP and proper fluid restriction can be performed without electrolyte monitoring unless DDAVP is used >3 times in 72 hours.
- For mild to moderate VWD, antifibrinolytics combined with DDAVP are generally effective for oral surgery.

E. Notes on Treatment of Major Bleeding and Prophylaxis for Major Surgery

- All treatment plans should be based on objective laboratory determinations of response of VWF:RCo and FVIII activity levels to DDAVP or VWF concentrate.
- For severe bleeding (e.g. intracranial, retroperitoneal) or prophylaxis of major surgery, initial target VWF:RCo and Factor VIII activity levels should be >100 IU/dL, and levels >50 IU/dL should be maintained for at least 7-10 days.
- In all patients receiving VWF concentrate, clinicians should perform proper thrombotic-risk assessment and institute appropriate strategies to prevent thrombosis.
- To decrease risk of perioperative thrombosis, VWF:RCo levels should not exceed 200 IU/dL, and FVIII activity should not exceed 250 IU/dL.

F. Women's Health and von Willebrand Disease

- Hormonal contraceptives are the first-line therapy for menorrhagia in the adolescent or adult woman who does not desire pregnancy.
- During childbirth, women should achieve VWF:RCo and FVIII levels of at least 50 IU/dL before delivery, and those levels should be maintained for 3-5 days, with subsequent surveillance for delayed post-partum bleeding.

G. Acquired von Willebrand Syndrome (AVWS)

- Defects in VWF concentration, structure, or function that are not inherited directly but are consequences of other medical disorders.
- Associated with monoclonal gammopathy, aortic stenosis, thrombocytosis, myelo- or lymphoproliferative disorders, hypothyroidism, congenital heart disease, and solid tumors.
- AVWS patients undergoing surgery may merit pharmacokinetic trial of DDAVP and/or VWF concentrate to evaluate possible accelerated clearance of VWF.

About this Clinical Quick Reference Guide

This quick reference guide originally summarized selected recommendations from Nichols W L, Hultin M B, James A H, Manco-Johnson M J, Montgomery R R, Ortel T L, Rick M E, Sadler J E, Weinstein M, and Yawn B P, *The Diagnosis, Evaluation, and Management of von Willebrand Disease*. National Heart, Lung, and Blood Institute, NIH Pub. No. 08-5832. December, 2007. However, to bring this guide up-to-date, an ASH working group led by Sarah O'Brien, MD, modified several areas in cooperation with the NHLBI expert panel. Members of the ASH working group included Cuker A, James P, DiPaola J, Flood V, Kuo K, and Kentsis A.

Guidelines provide the practitioner with clear principles and strategies for quality patient care and do not establish a fixed set of rules that preempt physician judgment.

For further information, please see the complete guidelines on the NHLBI website at *www.nhlbi.nih.gov/guidelines/vwd* or refer to the Practice Guidelines section of the ASH website at *www.hematology.org/policy/resources/guidelines*. You may also contact the ASH Department of Government Relations, Practice, and Scientific Affairs at 202-776-0544.

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