Notes on Treatment of Major Bleeding and Prophylaxis for Major Surgery

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Women’s Health and von Willebrand Disease

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- 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.

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, or other diseases.
- AVWS patients undergoing surgery may merit pharmacokinetic trial of DDAVP and/or VWF concentrate to evaluate possible accelerated clearance of VWF.


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 Web site at www.nhlbi.nih.gov/guidelines/vwd or refer to the Practice Guidelines section of the ASH Web site at www.hematology.org/policy/resources/guidelines. You may also contact the ASH Policy & Practice Department at 202-776-0544.

American Society of Hematology, 1900 M Street, NW, Suite 200, Washington, DC 20036
I. Evaluating Bleeding Symptoms and Bleeding Risk by History and Physical Exam

A. Ask the following broad questions:
1. Have you or a blood relative ever needed medical attention for a bleeding problem or been told you had a bleeding problem? After surgery? After dental work? With trauma? During childbirth or for heavy menses? Have you ever had bruises with lumps?
2. Do you have or have you ever had liver or kidney disease? A blood or bone marrow disorder? A high or low platelet count? If “Yes,” obtain relevant details.
3. Are you currently taking or have you recently taken anticoagulation or antiplatelet medications (warfarin, heparin, aspirin, NSAIDs, clopidogrel)? If “Yes,” obtain relevant details.

B. If answers to questions IA. are positive, ask the following questions:
1. Have you or a blood relative ever needed medical attention for a bleeding problem or been told you had a bleeding problem? After dental work? With trauma? During childbirth or for medical attention? Heavy menses characterized by clots >1 inch in diameter, changing a pad or tampon more than hourly, or resulting in anemia or low iron?
2. Heavy, prolonged, or recurrent bleeding after surgical procedures?
3. Bruising with minimal or no apparent trauma, especially if you could feel a lump under the bruise?
4. Spontaneous nosebleed lasting >10 minutes or that required medical attention?
5. Blood in your stool that required medical attention and was unexplained by an anatomic lesion (stomach ulcer, colon polyp)?
6. Anemia that required a blood transfusion or other type of treatment?
7. Heavy menses characterized by clots >1 inch in diameter, changing a pad or tampon more than hourly, or resulting in anemia or low iron?

C. Perform a physical examination to include evaluation for:
1. Evidence of a bleeding disorder, including size, location, and distribution of ecchymoses, hematomas, petechiae, and other evidence of recent bleeding and/or anemia.
2. Echocardiography or other imaging studies to evaluate for abnormalities of the heart or blood vessels.

II. Assessment for VWD or Other Bleeding Disorders

Positive Initial Screen by History & Physical Exam

Initial Hemostasis Tests
- CBC and platelet count
- PT and PTT
- Fibrinogen or TT (optional)

If bleeding history is strong, consider performing initial VWD assays

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Initial VWD Assays
- VWF:Ag
- VWF:RCo
- FVIII

Other VWD Assays
- VWF:RCo
- VWF:Ag
- FVIII

Other Appropriate Evaluation

Abnormal
- 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

Not abnormal
- Refer for other evaluation

III. Summary of the Laboratory Diagnosis of VWD

Laboratory Values for VWD

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<tr>
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<td>Type 2A</td>
<td>VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers</td>
<td>&lt;30**</td>
<td>&lt;30-200**</td>
<td>Normal</td>
<td>&lt;1.0-1.7</td>
</tr>
<tr>
<td>Type 2B</td>
<td>Increased affinity for platelet GPIb–IX/VWF</td>
<td>&lt;30**</td>
<td>&lt;30-200**</td>
<td>Normally</td>
<td>&lt;1.0-1.7</td>
</tr>
<tr>
<td>Type 2M</td>
<td>VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers</td>
<td>&lt;30**</td>
<td>&lt;30-200**</td>
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</tr>
<tr>
<td>Type 2N</td>
<td>Markedly decreased binding affinity for FVIII</td>
<td>50-200</td>
<td>50-200</td>
<td>Normal</td>
<td>&lt;1.0-1.7</td>
</tr>
<tr>
<td>Type 3</td>
<td>Virtually complete deficiency of VWF</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;1.0 IU/dL</td>
<td>Not applicable</td>
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| Low VWF   | ** <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.

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2. Do you have or have you ever had liver or kidney disease? A blood or bone marrow disorder? Is your blood pressure low or high? A high or low platelet count? If "Yes," obtain relevant details.
3. Are you currently taking or have you recently taken anticoagulation or antiplatelet medications (warfarin, heparin, aspirin, NSAIDs, clopidogrel)? If "Yes," obtain relevant details.

B. If answers to questions IA. are positive, ask the following questions:
1. Do you have a bleeding relative with a bleeding disorder?
2. 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 nosebleeds 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 in diameter, changing a pad or tampon more than hourly, or resulting in anemia or low iron?

C. Perform a physical examination to include evaluation for:
1. Evidence of a bleeding disorder, including size, location, and distribution of ecchymoses, hematomas, petechiae, and other evidence of recent bleeding and/or anemia.
2. Evidence that suggests other causes or risks of increased bleeding, such as jaundice or spider angiomas, splenomegaly, arthropathy, joint and skin laxity, and telangiectasia.

II. Assessment for VWD or Other Bleeding Disorders

A. Initial Hemostasis Tests

- CBC and platelet count
- PT and PTT
- Fibrinogen or TT (optional)

B. Other Appropriate Evaluation

- VWF:Ag
- VWF:RCo
- FVIII

C. Positive Initial Screen by History & Physical Exam

- Normal: 50-200 IU/dL
- Low: <30 IU/dL
- Abnormal: ratio of VWF:RCo to VWF:Ag >0.5-0.7

D. Isolated prolonged PTT that corrects on a 1:1 mixing study, or no abnormalities

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<td>VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight multimers</td>
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<td>Type 2B</td>
<td>Increased affinity for platelet GPIba-IIIa receptors</td>
<td>&lt;30**</td>
<td>&lt;30-200**</td>
<td>Usually</td>
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<tr>
<td>Type 2M</td>
<td>VWF-dependent platelet adhesion without selective deficiency of high-molecular-weight multimers</td>
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<tr>
<td>Type 2N</td>
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<tr>
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<td>Virtually complete deficiency of VWF</td>
<td>&lt;3</td>
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B. If answers to questions IA. are positive, ask the following questions:
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   6. Spontaneous nosebleed lasting >10 minutes or that required medical attention?
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B. Perform a physical examination to include evaluation for:
   1. CBC and platelet count
   2. PT and PTT
   3. Fibrinogen or TT (optional)

   Other cause identified, e.g., platelets, isolated abnormal PT, low fibrinogen, abnormal TT

   Isolated prolonged PTT that corrects on 1:1 mixing study, or no abnormalities

C. If bleeding history is strong, consider performing initial VWD assays

   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

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Abnormal | Not abnormal
---|---
Selected specialized VWD studies such as: Repeat initial VWD assays if necessary | Referral for other appropriate evaluation
- Ratio of VWF:RCO to VWF:Ag
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- Platelet VWF studies
- DNA sequencing of VWF gene

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
IV. Selected Recommendations for the Management of VWD

Testing Prior to Treatment
- Persons without a definite diagnosis of VWD but with VWF:RCo levels of 30-50 IU/dL and a bleeding history may benefit from treatment or prophylaxis of bleeding in certain situations.
- Persons with VWF:RCo >10 IU/dL and FVIII activity >20 IU/dL should undergo a trial of DDAVP while in a nonbleeding state.
- Persons with levels below these thresholds are less likely to respond usefully to DDAVP.

General Management of VWD Patients
- Long-term prophylaxis is rarely required.
- Avoid aspirin, other NSAIDs, and other platelet-inhibiting drugs.
- Consider restricting fluids to maintenance levels in persons receiving DDAVP (especially young children and surgical patients) to avoid hyponatremia and seizures.

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.

Notes on Treatment of Major Bleeding and Prophylaxis for Major Surgery
- All treatment plans should be based on objective laboratory determination of response of VWF:RCo and FVIII activity levels to DDAVP or VWF concentrate.
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- Combined oral contraceptives are the first-line therapy for menorrhagia in the adolescent or adult woman who does not desire pregnancy.
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