GUIDELINES
for the diagnosis and management of von Willebrand disease (VWD)
The Canadian Hemophilia Society (CHS) is committed to improve the health and quality of life of all people with inherited bleeding disorders and ultimately to find a cure.

The CHS consults qualified medical professionals before distributing any medical information. However, the CHS does not practice medicine and in no circumstances recommends particular treatments for specific individuals. In all cases, it is recommended that individuals consult a physician before pursuing any course of treatment.

For further information, please contact:
Canadian Hemophilia Society
1-800-668-2686
www.hemophilia.ca

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**Initial clinical assessment**

**History**
- bleeding score (BS) (see Table 1)
- hepatic, renal, blood or bone marrow disease
- medications (antiplatelet, anticoagulants, antidepressants, aniseizure meds)
- family history of a bleeding disorder or bleeding symptoms

**Physical exam**
- bruises, petechiae, hematomas – size, location
- signs of other diseases that can cause bleeding
  - jaundice, splenomegaly, lymphadenopathy
  - joint hypermobility and skin laxity
  - telangiectasia

**Other cause identified**
- thrombocytopenia (can also be seen in Type 2B VWD)
- factor deficiency
- hypo/dysfibrinogenemia

**Initial lab tests**
- CBC
- PT/PTT
- fibrinogen
- thrombin time (TT)
- platelets
- PT or TT
- fibrinogen

**Initial VWD tests**
- VWF:Ag
- VWF activity
- FVIII
- PTT or no abnormalities
- 1 or more tests low

**Confirmatory VWD tests**
- repeat VWF:Ag, VWF activity, FVIII, calculate VWF activity: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)

**Initial VWD tests**
- normal

**No further investigation**

**Positive initial assessment and/or BS ≥ 4 (in adults)**

**Negative initial assessment and BS < 4 (in adults)**
<table>
<thead>
<tr>
<th></th>
<th>-1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epistaxis</strong></td>
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<tr>
<td></td>
<td></td>
<td>No or trivial (≤ 5 per year)</td>
<td>&gt; 5 per year or more than 10’</td>
<td>Consultation only</td>
<td>Packing or cauterization or antifibrinolytic</td>
<td>Blood transfusion or replacement therapy or desmopressin</td>
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<tr>
<td><strong>Bruising</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>No or trivial (≤ 1 cm)</td>
<td>&gt; 1 cm and no trauma</td>
<td>Consultation only</td>
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<tr>
<td><strong>Bleeding from minor wounds</strong></td>
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<td></td>
<td></td>
<td></td>
<td>Surgical hemostasis</td>
<td>Blood transfusion or replacement therapy or desmopressin</td>
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<tr>
<td><strong>Oral cavity</strong></td>
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<tr>
<td></td>
<td></td>
<td>No</td>
<td>Reported, no consultation</td>
<td>Consultation only</td>
<td>Surgical hemostasis or antifibrinolytic</td>
<td>Blood transfusion or replacement therapy or desmopressin</td>
</tr>
<tr>
<td><strong>Gastrointestinal bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic</td>
<td>–</td>
</tr>
<tr>
<td><strong>Tooth extraction</strong></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>No bleeding in at least 2 extractions</td>
<td>None done or no bleeding in 1 extraction</td>
<td>Reported, no consultation</td>
<td>Consultation only</td>
<td>Resuturing or packing</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
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<tr>
<td><strong>Surgery</strong></td>
<td>No bleeding in at least 2 surgeries</td>
<td>None done or no bleeding in 1 surgery</td>
<td>Reported, no consultation</td>
<td>Consultation only</td>
<td>Surgical hemostasis or antifibrinolytic</td>
<td>Blood transfusion or replacement therapy or desmopressin</td>
</tr>
<tr>
<td><strong>Menorrhagia</strong></td>
<td>–</td>
<td>No</td>
<td>Consultation only</td>
<td>Antifibrinolytics, oral contraceptive pill use</td>
<td>Dilation &amp; curettage, iron therapy, ablation</td>
<td>Blood transfusion or replacement therapy or desmopressin or hysterectomy</td>
</tr>
<tr>
<td><strong>Postpartum hemorrhage</strong></td>
<td>No bleeding in at least 2 deliveries</td>
<td>No deliveries or no bleeding in 1 delivery</td>
<td>Consultation only</td>
<td>Dilation &amp; curettage, iron therapy, antifibrinolytics</td>
<td>Blood transfusion or replacement therapy or desmopressin</td>
<td>Hysterectomy</td>
</tr>
<tr>
<td><strong>Muscle hematomas</strong></td>
<td>–</td>
<td>Never</td>
<td>Post-trauma, no therapy</td>
<td>Spontaneous or traumatic, requiring desmopressin or replacement therapy</td>
<td>Spontaneous or traumatic, requiring surgical intervention or blood transfusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>Never</td>
<td>Post-trauma, no therapy</td>
<td>Spontaneous, no therapy</td>
<td>Spontaneous or traumatic, requiring desmopressin or replacement therapy</td>
<td>Spontaneous or traumatic, requiring surgical intervention or blood transfusion</td>
</tr>
<tr>
<td><strong>Hemarthrosis</strong></td>
<td>–</td>
<td>Never</td>
<td>Post-trauma, no therapy</td>
<td>Spontaneous, no therapy</td>
<td>Spontaneous or traumatic, requiring desmopressin or replacement therapy</td>
<td>Spontaneous or traumatic, requiring surgical intervention or blood transfusion</td>
</tr>
<tr>
<td><strong>Central nervous system bleeding</strong></td>
<td>–</td>
<td>Never</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Subdural, any intervention</td>
</tr>
</tbody>
</table>

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 $\geq 4$ has a sensitivity = 100%, specificity = 87%, positive predictive value = 0.20, negative predictive value = 1.00 in adults. The Condensed MCMDM-1VWD Bleeding Questionnaire has not been validated in children.

More info can be found at [www.path.queensu.ca/labs/james/bq.htm](http://www.path.queensu.ca/labs/james/bq.htm) including the Pediatric Bleeding Questionnaire (PBQ).
<table>
<thead>
<tr>
<th>Type</th>
<th>VWF:Ag</th>
<th>VWF activity</th>
<th>FVIII</th>
<th>VWF activity: Ag ratio</th>
<th>Multimers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>↓ or ↓↓</td>
<td>↓ or ↓↓</td>
<td>normal or ↓</td>
<td>&gt; 0.6</td>
<td>normal</td>
</tr>
<tr>
<td>Type 2A</td>
<td>↓ or ↓↓</td>
<td>↓↓ or ↓↓</td>
<td>normal or ↓</td>
<td>&lt; 0.6</td>
<td>↓ HMW (+/− ↓ IMW)</td>
</tr>
<tr>
<td>Type 2B</td>
<td>↓ or ↓↓</td>
<td>↓↓</td>
<td>normal or ↓</td>
<td>&lt; 0.6</td>
<td>↓ HMW</td>
</tr>
<tr>
<td>Type 2M</td>
<td>↓ or ↓↓</td>
<td>↓↓</td>
<td>normal or ↓</td>
<td>&lt; 0.6</td>
<td>normal</td>
</tr>
<tr>
<td>Type 2N</td>
<td>normal or ↓</td>
<td>normal or ↓</td>
<td>0.01–0.50 IU/mL FVIII &lt; VWF</td>
<td>&lt; 0.6</td>
<td>normal</td>
</tr>
<tr>
<td>Type 3</td>
<td>absent</td>
<td>absent</td>
<td>&lt; 0.10 IU/mL n/a</td>
<td>absent</td>
<td></td>
</tr>
</tbody>
</table>

Generally, two sets of abnormal results are required to diagnose VWD. Normal range for VWF:Ag, VWF activity and FVIII ~ 0.50 – 1.50 IU/mL. HMW = high molecular weight, IMW = intermediate molecular weight.
Other considerations

Patient factors that increase VWF levels
- stress (i.e.: excessive crying during phlebotomy, fainting, active bleeding, surgery)
- acute illness (i.e.: infection)
- exercise or physical trauma
- oral contraceptive pill
- pregnancy
- hormone replacement therapy
- neonatal period
- hyperthyroidism
- cushing syndrome (high cortisol states)
- ageing

Patient factors that decrease VWF levels
- hypothyroidism
- anti-VWF antibodies
- blood group 0

Important considerations for interpreting lab results
- The patient factors listed above should be taken into account.
- Improper sample processing, transport or storage can affect the results, most often causing falsely low (false positive) results.
- VWD testing and interpretation should only be done by experienced laboratories.
- If low VWF levels are identified in an older individual with no personal or family history of bleeding, consider acquired von Willebrand syndrome, which is classified and managed differently than inherited VWD.

For more information about the testing and diagnosis of VWD, or to refer patients, please contact one of the 26 Canadian treatment centres that provide comprehensive care to patients with inherited bleeding disorders. A listing of the bleeding disorder treatment centres can be found on the Canadian Hemophilia Society Web site at www.hemophilia.ca.
General management

- Consult local bleeding disorder treatment centre and/or hematologist for management advice and prior to dental or surgical procedures.
- Avoid aspirin, NSAIDs and other antiplatelet agents.
- Maintain good dental care.

Treatment of minor/moderate bleeds and prophylaxis for minor surgery

- Tranexamic acid +/- desmopressin (if adequate response and not contraindicated).
- Minor/moderate bleeds may include nose, mouth, joint, menorrhagia, abrasions and superficial lacerations.

Treatment of life/limb-threatening bleeds and prophylaxis for major surgery

- VWF concentrate is main treatment, especially for major surgery.
- Desmopressin could be considered (if adequate response and not contraindicated).
- Tranexamic acid as adjuvant therapy.
- Thromboprophylaxis (pharmacologic or mechanical) should be individualized.
- Life/limb-threatening bleeds may include intracranial, neck, chest, abdomen, GI, pelvis, spine, hip, massive vaginal hemorrhage, muscle compartment, fractures or dislocations, and any deep laceration.

Prophylaxis

- Consider for select patients with more symptomatic/severe disease, should be directed by a hematologist.
Specific therapy information

1) Improve clot retention
   Tranexamic acid (Cyklokapron)
   - IV 10 mg/kg Q 6 – 8H
   - PO 25 mg/kg tid (max 1,500 mg per dose)
   - duration varies
   - oral rinse 4.8% swish and spit 4 times daily
   - contraindicated if visible blood in the urine

2) Elevate VWF levels
   Desmopressin (DDAVP, Stimate, Octostim)
   - IV/SC 0.3 mcg/kg (max dose 20 mcg) Q 12 – 24H
   - intranasal 150 mcg per spray, 1 spray if < 50 kg or 2 sprays for ≥ 50 kg
   - response may be variable (see Table 3) and consideration should be given to documenting VWF/FVIII increases with a therapeutic trial, measuring VWF activity and FVIII at baseline and 1 hour, plus additional testing at 2 – 4 hours to identify increased VWF clearance
   - risk of hyponatremia, therefore:
     - avoid in children < 2 – 3 years old and others at risk
     - restrict fluids to maintenance levels for 24 hours following administration
   - tachyphylaxis occurs with repeated doses (> 3 doses)
   - see Table 3 for typical responses by VWD type/subtype
### Table 3

<table>
<thead>
<tr>
<th>VWD Type</th>
<th>Is desmopressin effective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Usually yes, except if increased VWF clearance</td>
</tr>
<tr>
<td>Type 2A</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Type 2B</td>
<td>Relatively contraindicated, can cause worsening thrombocytopenia</td>
</tr>
<tr>
<td>Type 2M</td>
<td>Usually not</td>
</tr>
<tr>
<td>Type 2N</td>
<td>Response typically short-lived (especially FVIII)</td>
</tr>
<tr>
<td>Type 3</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table 4: VWF concentrates

- Monitor levels with repeat dosing, adjust dose based on levels

<table>
<thead>
<tr>
<th>Product</th>
<th>Type of bleed</th>
<th>Dose</th>
<th>VWF:RCo:FVIII ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humate-P</td>
<td>major</td>
<td>60 – 80 IU VWF:RCo/kg IV q 8 – 12H</td>
<td>2.4:1</td>
</tr>
<tr>
<td></td>
<td>minor/moderate</td>
<td>40 – 60 IU VWF:RCo/kg IV q 8 – 12H</td>
<td></td>
</tr>
<tr>
<td>Wilate</td>
<td>major</td>
<td>40 – 60 IU VWF:RCo/kg IV q 12 – 24H</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td>minor/moderate</td>
<td>20 – 40 IU VWF:RCo/kg IV q 12 – 24H</td>
<td></td>
</tr>
<tr>
<td>rVWF*</td>
<td>major</td>
<td>50 – 80 IU IV loading, 40 – 60 IU/kg q 8 – 24H</td>
<td>if patient FVIII &lt; 0.40 IU/mL, rFVIII should also be administered in a 1.3:1 ratio**</td>
</tr>
<tr>
<td></td>
<td>minor/moderate</td>
<td>40 – 50 IU IV q 8 – 24H</td>
<td></td>
</tr>
</tbody>
</table>

*Expected to be available in Canada in the future – **Give 30% more rVWF than rFVIII
Issues specific to women

- Use hormonal agents (oral contraceptives/or IUD) for menorrhagia if pregnancy not desired:
  - tranexamic acid is an alternative for someone trying to conceive.
- Treat iron deficiency.
- In pregnancy, check VWF and FVIII levels at ~ 32 weeks:
  - most women with mild VWD will experience normalization;
  - if VWF and FVIII levels have not normalized, treatment should be directed by a hematologist;
  - regional anesthesia is considered safe if VWF and FVIII normalized;
  - surveillance for a delayed post-partum hemorrhage is important.

Issues specific to pediatrics

- Give vaccinations using the normal route and schedule, apply 10 minutes of direct pressure after.
- Give vitamin K to newborns (IM or SC, 10 minutes of direct pressure afterward).
- Testing children in Type 2 and 3 families should be done, regardless of symptoms.
- Testing children with a family history of Type 1 VWD but no personal history of bleeding usually not recommended but may be considered in families with significant bleeding history and/or VWF < 0.30 IU/mL.