GUIDELINES

for the diagnosis and management of von Willebrand disease (VWD)

Canadian Hemophilia Society
Help Stop the Bleeding

CODErouge
WHEN WOMEN BLEED TOO MUCH

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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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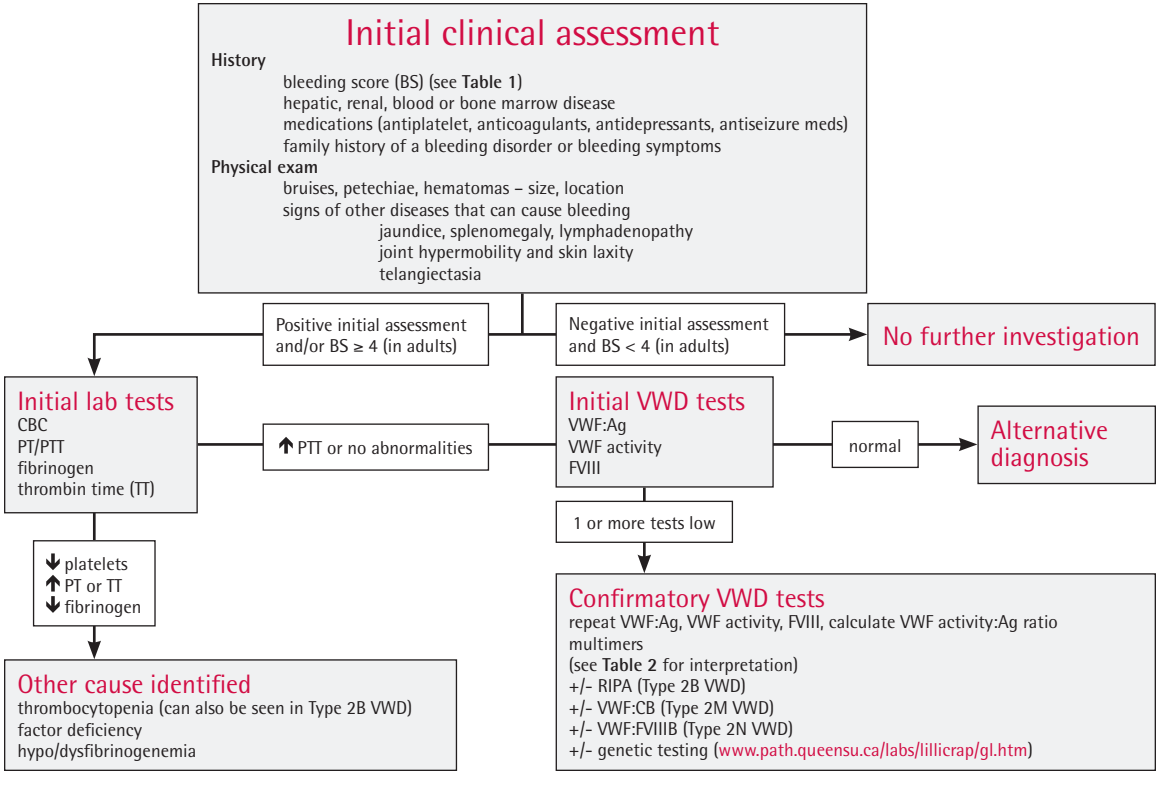
Initial clinical assessment
History
bleeding score (BS) (see Table 1)
hepatic, renal, blood or bone marrow disease
medications (antiplatelet, anticoagulants, antidepressants, antiseizure meds)
family history of a bleeding disorder or bleeding symptoms
Physical exam
bruises, petechiae, hematomas – size, location
signs of other diseases that can cause bleeding
jaundice, splenomegaly, lymphadenopathy
joint hypermobility and skin laxity
telangiectasia
Positive initial assessment and/or BS ≥ 4 (in adults)
Negative initial assessment and BS < 4 (in adults)
No further investigation
Initial lab tests
CBC
PT/PTT
fibrinogen
thrombin time (TT)
↑ PTT or no abnormalities
Initial VWD tests
VWF:Ag
VWF activity
FVIII
normal
Alternative diagnosis
↓ platelets
↑ PT or TT
↓ fibrinogen
1 or more tests low
Other cause identified
thrombocytopenia (can also be seen in Type 2B VWD)
factor deficiency
hypo/dysfibrinogenemia
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)

Table 1: Condensed MCMDM-1VWD Bleeding Questionnaire

	-1	0	1	2	3	4
Epistaxis	–	No or trivial (≤ 5 per year)	> 5 per year or more than 10'	Consultation only	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy or desmopressin
Bruising	–	No or trivial (≤ 1 cm)	> 1 cm and no trauma	Consultation only	–	–
Bleeding from minor wounds	–	No or trivial (≤ 5 per year)	> 5 per year or more than 5'	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
Gastrointestinal bleeding	–	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytic	–
Tooth extraction	No bleeding in at least 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

	-1	0	1	2	3	4
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1 surgery	Reported, no consultation	Consultation only	Surgical hemostasis or 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 at least 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 hematomas	–	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
Central nervous system bleeding	–	Never	–	–	Subdural, any intervention	Intracerebral, any intervention

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.

Bowman M et al. Generation and Validation of the Condensed MCMDM-1VWD Bleeding Questionnaire. J Thromb Haemost 2008; 6: 2062-6.

For VWD, a bleeding score ≥ 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 including the Pediatric Bleeding Questionnaire (PBQ).

Table 2: Common laboratory results in VWD

	VWF:Ag	VWF activity	FVIII	VWF activity: Ag ratio	Multimers
Type 1	↓ or ↓↓	↓ or ↓↓	normal or ↓	> 0.6	normal
Type 2A	↓ or ↓↓	↓↓ or ↓↓	normal or ↓	< 0.6	↓ HMW (+/- ↓ IMW)
Type 2B	↓ or ↓↓	↓↓	normal or ↓	< 0.6	↓ HMW
Type 2M	↓ or ↓↓	↓↓	normal or ↓	< 0.6	normal
Type 2N	normal or ↓	normal or ↓	0.01-0.50 IU/mL FVIII < VWF	< 0.6	normal
Type 3	absent	absent	< 0.10 IU/mL	n/a	absent

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 a patient 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 website 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

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

Table 4: VWF concentrates

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

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

* 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.

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