Clinical Guidelines for the Management of Von Willebrand Disease

Position Statement on behalf of the Australian Haemophilia Centre Directors' Organisation

Background

- Von Willebrand disease is the most common hereditary bleeding disorder
- VWD includes a range of subtypes of variable severity with differing management requirements
- Individuals with VWD will also be seen by health professionals other than specialist haematologists
- There is an opportunity to provide non-haematologist health professionals with clinical guidelines to assist with recognition and management of VWD

AHCDO guidelines

- AHCDO Symposium October 2008 to initiate the development of consensus guidelines
- Plan to publish on AHCDO website and in local medical journal
- Not intended to replace the development of individual management plans in conjunction with a haemophilia treatment centre

Outline

- Diagnosis
  - General recommendations
    - Family testing
- Management of bleeding episodes and surgery
  - General recommendations
    - DDAVP
    - Anti-fibrinolytics
    - VWF Concentrates available in Australia
    - Dosage
    - Minor surgery
    - Major surgery
    - Monitoring
    - Peri-operative thromboprophylaxis
  - Dental issues
  - Women's issues
  - Prophylaxis

Diagnosis – general recommendations

- The diagnosis of VWD rests on the clinical bleeding history, supportive diagnostic tests and a family history
- The diagnosis of VWD should be made in conjunction with a haematologist experienced in managing individuals with bleeding disorders

Diagnosis – general recommendations

- Laboratory screening for VWD should include FBE, Coag profile, FVIII:C, VWF:Ag, VWF function (VWF:RCo +/- VWF:CBA)
- where appropriate further studies including VWF multimers, RIPA, VWF:FVIIIB and possibly VWF gene testing (in research setting)
- Testing should be repeated on at least one occasion

Pediatric Hemostasis & Thrombosis Update 2008

Workshop: Evaluation of the Child with a Suspected Bleeding Disorder
Development and use of standardized bleeding questionnaires in children - Dr. Paula James

Score / Symptom	-1	0	1	2	3	4
Epistaxis	-	No or trivial (≤5 per year)	>5 per year OR >10 minutes duration	Consultation only	Packing, cauterization or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Cutaneous	-	No or trivial (≤1cm)	>1cm AND no trauma	Consultation only	-	-
Minor wounds	-	No or trivial (≤5 per year)	>5 per year OR >5 minutes duration	Consultation only or Steri-strips	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Oral cavity	-	No	Reported at least once	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Gastrointestinal tract	-	No	Identified cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
Tooth extraction	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Surgery	No bleeding in at least 2 surgeries	None done or no bleeding in 1	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	-	No	Reported or consultation only	Antifibrinolytics or contraceptive pill use	D&C or iron therapy	Blood transfusion, replacement therapy, desmopressin or hysterectomy
Post-partum	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Reported or consultation only	D&C, iron therapy or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	-
Muscle hematoma	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Hemarthrosis	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
Central nervous system	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention
Other Post-circumcision Umbilical stump Cephalohematoma Macroscopic hematuria Post-venepuncture Conjunctival hemorrage	-	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytics or iron therapy	Blood transfusion, replacement therapy or desmopressin

Family screening

- Family members of individuals with von Willebrand disease should be assessed for bleeding history and where appropriate tested for von Willebrand disease

General management recommendations

- Bleeding episodes or surgery in individuals with von Willebrand disease should be managed in collaboration with the nearest haemophilia treatment centre
- The nature of the bleeding episode or potential for bleeding, the VWD subtype and severity, documented response to therapy and potential risks of therapy need to be considered.
- Patients should be registered on the Australian Bleeding Disorder Registry to access von Willebrand factor concentrate

DDAVP

- DDAVP trial is recommended prior to haemostatic challenge where DDAVP will be used therapeutically
- Test dose 0.3µg/kg in 50mL N Saline given IV over 30mins (or as s/c injection)
- FBE, FVIII:C, VWF:Ag, VWF:RCo, should be measured before and at 60 mins (+/- 4hrs for rapid clearance) (or 90mins after s/c)
- Response defined as FVIII and VWF increase into the target range for the intended indication

DDAVP

- May be used in conjunction with antifibrinolytics
- Dose daily for 1-5 days depending on indication
- When used therapeutically for more than a single dose for minor bleeding, monitoring of FVIII and VWF:RCo should be done daily to detect loss of response.
- Fluid restrict and monitor electrolytes if repeated dosing

DDAVP

- adverse effects and tachyphylaxis
  - Response rate falls to 75% after fourth daily dose
- Indication
  - Insufficient in type 3 and some severe type 1
  - May be ineffective in type 2 and relatively contraindicated in 2B
- Home therapy
  - Subcutaneous route (15mcg/mL)

Antifibrinolytics

- Tranexamic acid
  - Oral 15-25mg/kg tds
  - IV 10mg/kg tds
  - 10mL 5% mouthwash qid (=500mg)

VWF concentrate

- Virally inactivated VWF concentrate is the preferred product for VWF replacement
- Cryoprecipitate should not be used for management of VWD except in an emergency situation where VWF concentrate is not available
- In this setting an initial adult dose of 10 units of cryoprecipitate is recommended

VWF concentrates approved in Australia

	Biostate® (CSL Bioplasma)	**Wilate®** (Octapharma)
Plasma Source	ARCBS donors	US donors
Viral inactivation	SD and dry heat	SD and dry heat
FVIII:c to VWF:RCo	1:2	Approx 1:1
Vial size 5mL	250 IU FVIII:C 500 IU VWF:RCo	450 IU FVIII:C 400 IU VWF:RCo
Vial size 10mL	500 IU FVIII:C 1000 IU VWF:RCo	900 IU FVIII:C 800 IU VWF:RCo
VWF HMWMultimers	Preserved	Preserved
VWF:RCo t1/2 (h) in VWD	11.6	17.5
FVIII:C t1/2 (h) in haemophilia A	12.4	14.8

Choice of VWF concentrate

- There is insufficient evidence to guide the clinical decision between the VWF concentrates currently available in Australia

Dosing

- Both Biostate and Wilate state doses according to FVIII:C
- different VWF:RCo to FVIII:C ratio means different VWF:RCo dose
- Clinical trials in each revealed mean doses of 30 IU/kg FVIII:C

Minor surgery

- Target pre-op FVIII and VWF:RCo >50 IU/dL and maintain >30 IU/dl for 1-5 days until bleeding risk passed
- A single dose of DDAVP may be sufficient
- Documented response to DDAVP is recommended before minor surgery where this is the intended therapy
- VWF concentrate may be required

Major surgery

- Target pre-op FVIII and VWF:RCo near 100IU/dL
- Maintain VWF:RCo and FVIII:C > 50 IU/dL for 7 days or until bleeding risk passed
- Documented response to DDAVP is recommended before major surgery where this is the planned therapy
- Avoid FVIII:C levels >200 IU/dL

		MINOR SURGERY	MAJOR SURGERY
	Dose (FVIII) **and interval**	30 IU/Kg every 24hrs	50 IU/kg every 12-24hr
	Pre-op target	FVIII:C and VWF:RCo >50 IU/dL	FVIII:C and VWF:RCo near 100 IU/dL
	Maintenance target	FVIII:C and VWF:RCo >30 IU/dL	FVIII:C and VWF:RCo >50 IU/dL
	Duration	1-5 days until bleeding risk has passed	5-10 days until bleeding risk has passed
Borderline	FVIII, VWF:Ag and RCo >30-50IU/dL.	No therapy DDAVP if response	DDAVP if response VWF concentrate
Mild-mod type 1	FVIII, VWF:Ag and VWF:RCo >15 IU/dL	DDAVP if response VWF concentrate	DDAVP if response VWF concentrate
Severe type 1	FVIII>10 IU/dL and VWF:Ag<15 IU/dL	DDAVP if response VWF concentrate	VWF concentrate
2A or M	VWF:RCo to VWF:Ag <0.6-0.7	DDAVP if response VWF concentrate	DDAVP if response VWF concentrate
2B	VWF:RCo to VWF:Ag <0.6-0.7 and enhanced low dose RIPA	VWF concentrate	VWF concentrate
2N	FVIII <40 IU/dL and FVIII:C to VWF:Ag <0.5. Low VWF:FVIIIB	DDAVP if responsive (t 1/2) VWF concentrate	VWF concentrate
3	FVIII <10 IU/DL and/or VWF:Ag <5 IU/dL	VWF concentrate (consider continuous infusion)	VWF concentrate (consider continuous infusion)

The addition of Tranexamic acid should be considered in all situations

Monitoring

- Where DDAVP is used for >2 consecutive days, monitoring of response and electrolytes is recommended
- Where VWF containing products are used, monitoring with FVIII and VWF:Rco levels is recommended to ensure target levels are achieved and to monitor for FVIII accumulation

Perioperative thromboprophylaxis

- In patients that are receiving perioperative VWF concentrate replacement therapy, consideration should be given to standard thromboprophylaxis

Dental issues

- Bleeding from oral mucosa and epistaxis may be managed with oral or topical tranexamic acid initially.
- For ongoing or severe bleeding DDAVP (in responders) and/or VWF concentrate is recommended.
- Dental extraction
  - Tranexamic acid orally and/or mouthwash started preop and continued for 1-5 days
  - Single dose of DDAVP in responders and/or single dose of VWF concentrate is usually adequate
  - Target VWF:Rco 50 IU/dL

Menorrhagia

- Defined as >80mL, passing clots >2.5cm diameter, changing pad or tampon hourly or developing anaemia
- Menorrhagia should be managed in consultation with the haematologist and gynaecologist
- 73% good response to the combined oral contraceptive pill
- Tranexamic acid orally 1g qid d1-4 of menstruation
- DDAVP may be used s/c daily for a maximum of 3 days
- Intrauterine progesterone contraceptive device
- Iron supplementation should be considered if there is evidence of iron deficiency anaemia

Obstetric issues

- Link/reference the AHCDO “guidelines for management of pregnancy and delivery in women who are either carriers or patients with bleeding disorders”
- Management of pregnancies in individuals with von Willebrand disease should occur in consultation with the nearest haemophilia treatment centre and in an obstetric unit with appropriate facilities
- VWF and FVIII rise during pregnancy and should be repeated in the third trimester between 32-34 weeks.

Obstetric issues

- Levels of FVIII and VWF:Rco >50 IU/dL are considered adequate for delivery
- VWF concentrate should be used to achieve these levels if necessary and to maintain them for 5-7 days post partum
- Mode of delivery should be decided on obstetric grounds

Prophylaxis

- Role in severe von Willebrand disease
- Recurrent bleeding
  - Severe menorrhagia
  - Angiodysplasia with recurrent severe GIT bleeding
- 25-50 IU VWF:RCo 1-3 times/week
- Must be initiated and supervised by the nearest haemophilia treatment centre