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

• AHCD0 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:FVIIIIB 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**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>-</td>
<td>No or trivial (&lt;5 per year)</td>
<td>&gt;5 per year OR &gt;10 minutes duration</td>
<td>Consultation only</td>
<td>Packing, cautery or antifibrinolytics</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>-</td>
<td>No or trivial (&lt;1cm)</td>
<td>&gt;1cm AND no trauma</td>
<td>Consultation only</td>
<td>-</td>
</tr>
<tr>
<td>Minor wounds</td>
<td>-</td>
<td>No or trivial (&lt;5 per year)</td>
<td>&gt;5 per year OR &gt;5 minutes duration</td>
<td>Consultation only or Steri-Strips</td>
<td>Surgical hemostasis or antifibrinolytics</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>-</td>
<td>No</td>
<td>Reported at least once</td>
<td>Consultation only</td>
<td>Surgical hemostasis or antifibrinolytics</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>-</td>
<td>No</td>
<td>Identified cause</td>
<td>Consultation or spontaneous</td>
<td>Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin</td>
</tr>
<tr>
<td>Tooth extraction</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, repacking or antifibrinolytics</td>
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<tr>
<td>Surgery</td>
<td>No bleeding in at least 2 surgeries</td>
<td>None done or no bleeding in 1</td>
<td>Reported, no consultation</td>
<td>Consultation only</td>
<td>Surgical hemostasis or antifibrinolytics</td>
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<tr>
<td>Menorrhagia</td>
<td>-</td>
<td>No</td>
<td>Reported or consultation only</td>
<td>Antifibrinolytics or contraceptive pill use</td>
<td>D&amp;C or iron therapy</td>
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<tr>
<td>Post-partum</td>
<td>No bleeding in at least 2 deliveries</td>
<td>No deliveries or no bleeding in 1 delivery</td>
<td>Reported or consultation only</td>
<td>D&amp;C, iron therapy or antifibrinolytics</td>
<td>Blood transfusion, replacement therapy or desmopressin</td>
</tr>
<tr>
<td>Muscle hematoma</td>
<td>Never</td>
<td>Post-trauma, no therapy</td>
<td>Spontaneous, no therapy</td>
<td>Spontaneous or traumatic, requiring replacement therapy or desmopressin</td>
<td>Spontaneous or traumatic, requiring surgical intervention or blood transfusion</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>Never</td>
<td>Post-trauma, no therapy</td>
<td>Spontaneous, no therapy</td>
<td>Spontaneous or traumatic, requiring replacement therapy or desmopressin</td>
<td>Spontaneous or traumatic, requiring surgical intervention or blood transfusion</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Never</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Subdural, any intervention</td>
</tr>
</tbody>
</table>

**Other**

- Post-circumcision
- Umbilical stump
- Cephalohematoma
- Macroscopic hematuria
- Post-venepuncture
- Conjunctival hemorrhage

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<td>No</td>
<td>Reported</td>
<td>Consultation only</td>
<td>Surgical hemostasis, antifibrinolytics or iron therapy</td>
<td>Blood transfusion, replacement therapy or desmopressin</td>
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</table>
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

<table>
<thead>
<tr>
<th></th>
<th><strong>Biostate®</strong> (CSL Bioplasma)</th>
<th><strong>Wilate®</strong> (Octapharma)</th>
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</thead>
<tbody>
<tr>
<td><strong>Plasma Source</strong></td>
<td>ARCBS donors</td>
<td>US donors</td>
</tr>
<tr>
<td><strong>Viral inactivation</strong></td>
<td>SD and dry heat</td>
<td>SD and dry heat</td>
</tr>
<tr>
<td><strong>FVIII:c to VWF:RCo</strong></td>
<td>1:2</td>
<td>Approx 1:1</td>
</tr>
<tr>
<td><strong>Vial size 5mL</strong></td>
<td>250 IU FVIII:C 500 IU VWF:RCo</td>
<td>450 IU FVIII:C 400 IU VWF:RCo</td>
</tr>
<tr>
<td><strong>Vial size 10mL</strong></td>
<td>500 IU FVIII:C 1000 IU VWF:RCo</td>
<td>900 IU FVIII:C 800 IU VWF:RCo</td>
</tr>
<tr>
<td><strong>VWF HMWMultimers</strong></td>
<td>Preserved</td>
<td>Preserved</td>
</tr>
<tr>
<td><strong>VWF:RCo t1/2 (h) in VWD</strong></td>
<td>11.6</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>FVIII:C t1/2 (h) in haemophilia A</strong></td>
<td>12.4</td>
<td>14.8</td>
</tr>
</tbody>
</table>
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 100 IU/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
<table>
<thead>
<tr>
<th></th>
<th>MINOR SURGERY</th>
<th>MAJOR SURGERY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (FVIII) and interval</strong></td>
<td>30 IU/Kg every 24hrs</td>
<td>50 IU/kg every 12-24hrs</td>
</tr>
<tr>
<td><strong>Pre-op target</strong></td>
<td>FVIII:C and VWF:RCo &gt;50 IU/dL</td>
<td>FVIII:C and VWF:RCo near 100 IU/dL</td>
</tr>
<tr>
<td><strong>Maintenance target</strong></td>
<td>FVIII:C and VWF:RCo &gt;30 IU/dL</td>
<td>FVIII:C and VWF:RCo &gt;50 IU/dL</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>1-5 days until bleeding risk has passed</td>
<td>5-10 days until bleeding risk has passed</td>
</tr>
<tr>
<td><strong>Borderline</strong></td>
<td>FVIII, VWF:Ag and RCo &gt;30-50IU/dL. No therapy</td>
<td>DDAVP if response VWF concentrate</td>
</tr>
<tr>
<td><strong>Mild-mod type 1</strong></td>
<td>FVIII, VWF:Ag and VWF:RCo &gt;15 IU/dL</td>
<td>DDAVP if response VWF concentrate</td>
</tr>
<tr>
<td><strong>Severe type 1</strong></td>
<td>FVIII&gt;10 IU/dL and VWF:Ag&lt;15 IU/dL</td>
<td>VWF concentrate</td>
</tr>
<tr>
<td><strong>2A or M</strong></td>
<td>VWF:RCo to VWF:Ag &lt;0.6-0.7</td>
<td>DDAVP if response VWF concentrate</td>
</tr>
<tr>
<td><strong>2B</strong></td>
<td>VWF:RCo to VWF:Ag &lt;0.6-0.7 and enhanced low dose RIPA</td>
<td>VWF concentrate</td>
</tr>
<tr>
<td><strong>2N</strong></td>
<td>FVIII &lt;40 IU/dL and FVIII:C to VWF:Ag &lt;0.5. Low VWF:FVIIIIB</td>
<td>DDAVP if responsive (t 1/2) VWF concentrate</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>FVIII &lt;10 IU/dL and/or VWF:Ag &lt;5 IU/dL</td>
<td>VWF concentrate (consider continuous infusion)</td>
</tr>
</tbody>
</table>

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