3.0: Von Willebrand Disease (VWD)

3.1 General Information

Von Willebrand Disease (VWD) is a bleeding disorder resulting from deficiency or abnormal function of Von Willebrand Factor (VWF). VWF is a multimeric glycoprotein gene which has two main functions:

- To assist in platelet plug formation by binding circulating platelets to the site of vessel damage
- To bind to coagulation factor VIII preventing its clearance from the plasma

Disease Classification

VWD is subdivided into three types determined by the nature of the mutations in the VWF gene. The 3 types are as follows:

- **Type 1 VWD**: Persons who have true Type 1 have levels of VWF antigen and/or activity of <0.3 IU/ml (level is measured by the Ricos or collagen binding (CBA) assays). FVIII may also be low.

- **Type 2 VWD** is further subdivided into types 2A, 2B, 2M, 2N.
  - Type 2 VWD is characterised by abnormal function of the VWF protein and the Ricos or CBA assays are lower than the VWF antigen in types 2A, 2B and 2M.
  - In Type 2N VWD, the functional abnormality involves the binding of VWF to FVIII and the FVIII is low but the VWF levels may not be low.

- **Type 3 VWD**: Persons with Type 3 have very low levels of VWF and FVIII and have the most severe bleeding phenotype which is akin to severe haemophilia.

In addition the following subcategories are recognised

- **Low VWF**: This relates to persons who have low VWF levels between 0.3 and 0.5 IU/ml. The low levels are not caused by mutations in the gene for VWF but are reduced in a number of ways including for example by faster clearance of the VWF protein from the blood as happens in people who are blood group O.
  - Some people with low VWF levels have bleeding symptoms and may need to have preventative treatment if they are having surgery or other invasive procedures.

- **Platelet-type VWD** is a rare condition caused by a mutation in the glycoprotein on the surface of platelets which interacts with VWF.

3.2 Disease Severity

The disease severity relates to the VWF level and activity. The severity and associated presentation are described in Table 3.0 below.
### Table 3

<table>
<thead>
<tr>
<th>VWF antigen and/or activity</th>
<th>Clinical bleeding phenotype</th>
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<tbody>
<tr>
<td><strong>Low VWF</strong></td>
<td>Some patients may bleed with invasive procedures, or have menorrhagia or mucocutaneous bleeding</td>
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<tr>
<td>0.3-0.5 IU/ml</td>
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<tr>
<td><strong>Type 1</strong></td>
<td>Bleeding after invasive dental or surgical procedures, menorrhagia, mucocutaneous bleeding</td>
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<tr>
<td>&lt;0.3 IU/ml</td>
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<tr>
<td><strong>Type 2</strong></td>
<td>Variable bleeding tendency.</td>
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<tr>
<td>&lt;0.3 IU/ml (Ricof or CBA)</td>
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<tr>
<td>Ratio of activity to antigen</td>
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<tr>
<td>&lt;0.5-0.7</td>
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<tr>
<td><strong>Type 3</strong></td>
<td>Mucocutaneous bleeding, menorrhagia, post operative bleeding, May have haemarthrosis, muscle haematomas</td>
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<tr>
<td>Levels are very low or undetectable</td>
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### 3.3 Bleeding Episode Management

In the event a person with VWF or Low VWF presents with a bleed / potential bleed the Clinician should take the following steps:

#### Step 1: Patient Assessment

- Perform initial evaluation and assessment.
- Identify the site of the suspected bleed
- Assess for compression of vital structures e.g. airway, nerves or blood vessels, and manage accordingly.
- Undertake pain assessment and treat accordingly- Refer to (See Appendix 1: Pain Management Guidelines)
- Where possible, obtain details from patient or relative regarding bleeding disorder diagnosis, factor level, inhibitor status and treatment of choice
- Check patient registration card
- Weigh the patient or estimate weight where necessary
- Undertake initial blood testing to include: FBC, Biochemistry, Group and Cross-match, Coagulation and Factor Levels
- Arrange appropriate imaging but **DO NOT DELAY** haemostatic treatment if a bleed is suspected. Treat first, image after.
- If in doubt manage as a bleed, but consider alternative diagnosis and investigate accordingly.

#### Step 2: Communication to CCC

- Contact the patient’s CCC **IMMEDIATELY** following the initial assessment
- Confirm the patient’s bleeding disorder diagnosis, factor level, inhibitor status and treatment of choice
- Agree a management plan and follow up with the CCC
Step 3: Treatment Administration

- Prescribers must ensure that they prescribe the correct clotting factor concentrate e.g. Wilate for VWD
- In doing so the Prescriber must note that not all patients with low VWF require clotting factor concentrate and the use of alternative treatments may be indicated e.g. DDAVP or Tranexamic Acid
- The patient’s treatment of choice must be confirmed with the relevant CCC.

- Minor bleeding involving mucosal surfaces of the nose, mouth or female genital tract can be treated with Tranexamic acid alone.
- Excessive menstrual bleeding can be treated with the addition of hormonal therapy i.e. the combined oral contraceptive pill or consideration can be given to progesterone releasing intra-uterine system (Mirena).
- For more extensive or major bleeding, DDAVP or VWF concentrate should be used. The choice of agent will depend on the age of the patient, the presence of or risk factors for arteriovascular disease and the documented response of the patient to DDAVP. The CCC will advise on the appropriate treatment to use.
- The Clinician should establish the treatment of choice i.e. Wilate, DDAVP®/Desmopressin Injection and/or Tranexamic Acid.
- The selected treatment should be prepared and administered as follows:

Clotting Factor Concentrate – Wilate

- Wilate is the clotting factor concentrate recommended for use in the prevention and treatment of haemorrhage or surgical bleeding in von Willebrand disease (VWD)
- The required dose must be determined by calculating the patient’s weight and the required post treatment factor level which is determined by the severity and location of the bleed and the patient’s clinical condition.
- Wilate comes as a powder and should be reconstituted using the accompanying solvent (i.e. water for injections with 0.1 % Polysorbate 80) which comes in Mix2Vial™
- Wilate should be reconstituted using aseptic technique in accordance with the Wilate Reconstituted Procedure.

Administration

- Factor concentrate should be administered as a slow intravenous push over 5 minutes
- A post treatment factor level should be drawn 20 minutes post administration (two coagulation samples, send to local laboratory for forwarding to the CCC for analysis)
- Liaise with CCC regarding the post treatment level result in case further treatment is required.
Reactions

In the event of a reaction or suspected reaction the Clinician should undertake the following:
- Discontinue the Factor Concentrate
- Assess the patient
- Contact the relevant CCC for advice on alternative treatments.

In the event of **mild to moderate reaction** the Clinician should undertake the following:
- Administer Chlorpheniramine 10-20 mg IM or slow IV (at least over one minute)
- If required, add Hydrocortisone 100 - 200mg slow IV (over three minutes)

In the event of **severe allergic or anaphylactic reaction** local hospital resuscitation / response protocols should be followed. The use of the following medications is recommended:
- Adrenaline (Epinephrine) should be given by the intramuscular (IM) route at a dose of 500 micrograms (0.5mg) for example 0.5ml of 1:1000 adrenaline.
- Chlorpheniramine 10mg IV or IM and Hydrocortisone 200mg IV or IM should also be given.
- Oxygen should be administered as soon as possible (15 litres/min) using a mask with an oxygen reservoir
- Bronchodilators: Consider salbutamol (inhaled), or ipratropium (inhaled).

**DDAVP*/Desmopressin Injection**

- DDAVP® Injection (Desmopressin Acetate) is a synthetic analogue of the natural hormone arginine vasopressin. It is indicated for use in managing bleeds in persons with hemophilia (Factor VIII) and some Von Willebrands by increasing plasma levels.
- DDAVP Injection 4 mcg/mL is provided as a sterile, aqueous solution for injection
- DDAVP use should be avoided in the following circumstances:
  - Persons over 55 years of age
  - Persons with a history of heart failure or other conditions being treated with diuretic agents
  - Persons with known arteriosclerosis or ischaemic heart disease
- DDAVP should be used with caution in the following circumstances:
  - Persons with risk factors for ischaemic heart disease
  - Pregnant persons
  - Children less than two years of age (Refer to Paediatric Guidelines)

- **Dose Calculation**
  - DDAVP is administered intravenously at 0.3 μg/kg
  - The maximum total dose recommended for any patient is 27μg
  - Example: A 60kg patient requiring DDAVP, the dose should be calculated as 60 kg x 0.3 μg = 18μg.
- **Dose Administration**
  - DDAVP comes in 1ml ampoule which contains Desmopressin acetate 4 micrograms per ml
  - DDVAP should be added to 100mls of normal saline using an aseptic technique
  - The 100ml solution should be administered intravenously over 30-60 minutes
  - The patient’s serum Na level should be >135 mmol/L prior to administration
  - Blood pressure must be monitored before, during and after the infusion
  - The patients must be maintained on a fluid restriction of 1.5 L/24 hours following the infusion
  - Post treatment blood levels should be taken and reviewed 30 minutes following the infusion
  - **Example:** A 60kg patient requiring DDAVP - The intravenous preparation has a concentration of 4 μg/ml. Therefore, the intravenous dose for this 60kg patient will be prepared from 4.5mls of DDAVP (at a concentration of 4 μg/ml) diluted in 100mls of normal saline and administered over 30-60 minutes.

- **Reactions to DDAVP**
  - Reactions to DDAVP can be common
  - **Mild reactions** commonly include the following:
    - Vasodilatation
    - Hypotension
    - Facial flushing
    - Mild reactions should be treated by slowing the intravenous infusion so that it is administered over 60 minutes.
  - **Moderate reactions** should be treated as follows:
    - Discontinue DDAVP
    - Assess the patient
    - Administer Chlorpheniramine 10-20 mg IM or slow IV (over one minute)
    - If required, add Hydrocortisone 100 - 200 mg IM or slow IV (over three minutes)
    - If **required**, add Oxygen (10-12 litre/min) +/- inhaled Salbutamol (2.5mg)
    - The DDAVP infusion can be restarted at a slower rate with close monitoring of the patient
    - In the event a reaction recurs, the infusion should be stopped and the clinician should contact the relevant CCC for advice on alternative treatments.
  - **Severe allergic reactions** should be treated in accordance with local resuscitation / response protocols. The use of the following medications is recommended:
    - Adrenaline (Epinephrine) should be given by the intramuscular (IM) route at a dose of 500micrograms (0.5mg) for example 0.5ml of 1:1000 adrenaline.
    - Chlorpheniramine 10mg IV or IM and Hydrocortisone 200mg IV or IM should also be given as above.
- Oxygen should be administered as soon as possible (15 litres/min) using a mask with an oxygen reservoir.
- Bronchodilators: Consider salbutamol (inhaled), or ipratropium (inhaled).
- The clinician should contact the relevant CCC for advice on alternative treatments.

**Tranexamic Acid (Cyclokapron)**

- Tranexamic Acid is an antifibrinolytic agent indicated in patients with haemophilia for short-term use (two to eight days) to reduce or prevent haemorrhage
- Tranexamic acid should not be used in combination with either FEIBA or factor XI concentrate (risk of thrombosis).
- Tranexamic Acid is available in tablet and Intravenous Injection form
- Oral / Tablet form (500 mg Tranexamic Acid)
  - Recommended dose 15-25 mg/kg TDS or QDS (usually 1g TDS or QDS)
- Intravenous Injection (500mg in 5ml ampoule)
  - Recommended dose 10 mg/kg TDS
  - Bolus injection – The required dose can be administered undiluted slowly i.e. at a rate of 100mg/min
  - Intravenous Infusion – The required dose can be diluted in 100mls normal saline and given as an infusion over 30 minutes.

- **Contraindications**
  - Should not be used in the following circumstances
    - Patients with a history of thromboembolic disease
    - Patient with Disseminated Intravascular Coagulation (DIC)
    - Persons with bleeding from the upper urinary tract (risk of ureteric clot colic and obstruction)
- **Adverse effects**
  - Nausea, vomiting, and diarrhoea
  - Rapid intravenous injection may cause dizziness and hypotension (do not administer faster than 100 mg/min).

**Step 4: Documentation**

- In addition to routine prescribing and recording, the dose and batch number of all Factor Concentrates administered must be recorded in the patient’s medical notes and as per local hospital/laboratory policy.
**Step 5: Initiate ‘PRICE’ for all Joint Bleeds**

- **Protection**: Reduce weight bearing or stress on the affected joint or muscle by providing crutches or other supports such as a ‘collar and cuff’ for the arm. Avoid putting weight on the affected side completely for the first 48 hours; and possibly longer if it is a severe bleed.

- **Rest**: The affected arm or leg should be gently placed on a pillow or in a sling or bandage. The individual should not move the bleeding joint.

- **Ice**: Wrap an ice pack in a damp towel and place over bleed. After 5 minutes, remove ice for 10 minutes. Repeat this step for as long as the joint feels hot. This may help decrease pain and bleeding.

- **Compression**: Gentle pressure from a tensor bandage (e.g. Tubigrip, size appropriate for the patient’s limb) can help to limit bleeding and support the joint. Use compression carefully with muscle bleeds if a nerve injury is suspected.

- **Elevation**: Raise the affected area above the heart. This may slow blood loss by lowering pressure in the area of the bleed.

- **Ensure that the patient is referred to a physiotherapist for assessment and treatment.**

**3.4 Surgery Management**

- Patients with bleeding disorders should ideally have surgery in a hospital where there is a Haemophilia Comprehensive Care Centre and haemostatic management should be supervised by the CCC Team

- In rare circumstances surgery may need to be performed in a hospital without a CCC, such as in emergencies or where the person needs to avail of specialist surgical services.

- In these circumstances, haemostatic management must be determined by the patient’s CCC and it is recommended that the local Haematology service provides on-site consultation.

In the event a person with VWD or low VWF is undergoing surgery in a non-specialist CCC the Clinical staff should ensure the following steps are undertaken:

**Pre-Operative**

- Confirm the patient’s known bleeding diagnosis, baseline levels, inhibitor status and treatment of choice with the patient and the relevant CCC.

- Confirm the patient’s virology (i.e. Hepatitis A, B, C and HIV) and TSE at-risk status with the CCC.

- Obtain a written management plan from the CCC
• Liaise with local Blood Transfusion Laboratory to ensure availability of adequate clotting factor concentrate

• Ensure a ‘No NSAIDS, No Aspirin, No Heparin and No IM injections’ note is communicated and recorded clearly in the drug idiosyncrasies section of the patient’s prescription form, the front cover of their medical chart and in all other relevant healthcare records e.g. Nursing Care Plans etc.

• Ensure that the local Anaesthetic Department / Team are informed that epidural and spinal anaesthesia are contra-indicated in patients with bleeding disorders. This must be clearly documented in the patient’s healthcare record.

Post-Operative

• Liaise with the relevant CCC to determine the requirement for ongoing haemostatic treatment and factor levels.

• Ensure that the patient is provided with adequate haemostatic cover for all invasive procedures e.g. placement of central lines or removal of sutures, clips, drains etc. As these procedures are likely to occur some days after the surgery the patient’s CCC should be contacted to advise regarding additional treatment requirements.

3.5 Pregnancy Management

• Women who have VWD or low VWF should have an individual management plan for labour and delivery determined collaboratively by the woman, her CCC and the woman’s Obstetrician. This plan should be made available to the patient, the woman’s Obstetrical Department / Provider, the local Haematologist and the woman’s GP.

• Many women with low VWF or type 1 VWD will have a physiological increase in FVIII and VWF levels during pregnancy. This should be determined by taking a von Willebrand screen in the late second trimester and early third trimester.

• Women whose FVIII and VWF levels have normalised in pregnancy do not need haemostatic cover for labour and delivery and may have epidural analgesia or caesarean delivery if indicated without specific haemostatic treatment.

• Women with type 3 VWD and some women with type 1 or 2 VWD will not normalise their FVIII or VWF levels in pregnancy. These women will need haemostatic treatment peripartum. This may either consist of DDAVP or VWF concentrate and will be determined by the CCC.

• The woman’s Obstetrical Department / Provider should liaise with their local Blood Transfusion Laboratory to ensure availability of adequate clotting factor concentrate, if indicated.

Maternal Labour, Delivery and Postpartum Period Management

• Patients with FVIII and/or VWF levels of <0.5 IU/ml (<50%) will require treatment at the time of delivery to maintain levels >0.50 IU/ml (>50%). The CCC should be contacted to advise on the appropriate treatment, dose and required blood testing.
Epidural Anaesthesia
- The use of Epidural Anaesthesia is contra-indicated in patients with FVIII and/or VWF levels <0.50 IU/ml (<50%) in the third trimester
- Patients with confirmed normal FVIII and/or VWF levels in the third trimester may receive epidural anaesthesia if required.

Analgesia
- The use of Intramuscular injections e.g. Pethidine are contra-indicated in women with low FVIII and/or VWF levels.
- Alternative analgesia such as inhaled nitrous oxide and oxygen or intravenous Remifentanil is acceptable for patients with low FVIII and/or VWF levels
- For women with low FVIII and/or VWF levels, appropriate options for analgesia MUST be discussed with the local Maternity unit Anaesthetic service in advance.

Post partum management
- Normal factor levels should be maintained for 3 days following vaginal delivery and for 5 days after caesarean section.
- In the event the patient has received haemostatic treatment to cover the delivery, it will be necessary to send factor levels daily for 3 days following vaginal delivery and for 5 days following caesarean section.
- Postpartum, factor VIII and/or VWF levels can fall quickly in women who have low baseline levels but who have had a pregnancy-induced rise in levels and therefore have not needed treatment for labour.
- If a patient with VWD or low VWF has excessive bleeding post-partum, factor levels should be sent and advice obtained from the CCC in addition to usual obstetrical management.
- Delayed post-partum haemorrhage is a feature of inherited bleeding disorders and affected women should be provided with emergency contact numbers for their CCC and Obstetric Unit/Provider following discharge.

Management of the infant During Labour and Delivery
- Ultrasound should be performed to determine position.
- There should be a low threshold for caesarean section.
- Foetal scalp sampling and electrodes should be avoided.
- The use of ventouse and /or mid-cavity forceps is contraindicated due to the increased risk of intracranial haemorrhage.
- Lift out forceps can be performed if deemed necessary by a Consultant Obstetrician.
- If delivery is instrumental, then an urgent cranial ultrasound and VWF measurement of cord blood should be obtained.
- VWF levels should be measured from a cord blood sample from all potentially affected infants. The cord blood sample should be sent in a 2.5 mls citrate tube via the local laboratory to the laboratory at...
Our Lady's Hospital, Crumlin. The specific factor deficiency should be clearly documented on the laboratory request form.

- In the event the child was delivered using a ventouse or forceps delivery the factor level analysis should be undertaken as an emergency. The receiving laboratory must be informed that the factor level is required urgently.

- The use of intramuscular injections should be avoided.

- Vitamin K should be administered by the oral and not the intramuscular route.

- The Bacillus Calmette-Guérin (BCG) vaccine can be administered without haemostatic support.

- A Heel-Prick test can be undertaken for Guthrie card analysis without haemostatic support.

- In the event the factor level is found to be reduced, the child should be referred to the Paediatric Haematologist on–call at Our Lady’s Children’s Hospital, Crumlin.