# S-20200021
# Evaluation and Management of von Willebrand Disease
# TXCH Best Current Practice Standard

## Scope:
To provide guidelines for the diagnosis, comprehensive evaluation, and treatment of children with von Willebrand disease (VWD).

## Definitions:

| | | | |
|---|---|---|---|
| aVWS: | acquired von Willebrand syndrome | LFT: | liver function tests |
| DDAVP: | 1-desamino-8-D-arginine vasopressin | PE: | physical examination |
| FVIII: | factor VIII | PT VWD: | platelet-type von Willebrand disease |
| FFP: | fresh frozen plasma | RCoF: | ristocetin cofactor activity |
| GP: | glycoprotein | rVWF | recombinant von Willebrand factor |
| HAT: | hemostasis and thrombosis | VWD: | von Willebrand disease |
| HMB: | heavy menstrual bleeding | VWF: | von Willebrand factor |
| HTC: | hemophilia treatment center | VWF:Act: | VWF activity |
| IVIG: | intravenous immunoglobulin | VWF:Ag: | VWF antigen |
| LD RIPA: | low-dose ristocetin-induced platelet aggregation | VWF CB: | VWF collagen binding activity |
| | | VWFpp: | VWF propeptide |

## Background
**Definition**: VWD is an inherited bleeding disorder caused by deficiency and/or dysfunction of the plasma protein VWF. Abnormalities in VWF can be quantitative (VWD types 1 and 3) or qualitative (VWD type 2) (see Tables 1 and 2 for VWD Classification and Disorders). The normal range of plasma VWF is 50 – 200 IU/dL, with a half-life of approximately 12 hours. VWF is essential for platelet adhesion and aggregation in the formation of the primary platelet plug and carries/stabilizes FVIII in plasma, thereby prolonging its half-life.

**Factors affecting VWF levels:**
Increased levels: Pregnancy, aging, acute stress, exercise, inflammation, African-American ethnicity, estrogen use, hyperthyroidism, diabetes mellitus.
Decreased levels: Hypothyroidism, blood type O (25% lower levels), and menstruation.

## Diagnosis & Types:
**Table 1: Classification of VWD***

| TYPE | DESCRIPTION | INHERITANCE^ | PREVALENCE | BLEEDING RISK |
|---|---|---|---|---|
| **1** | Partial quantitative deficiency of VWF | AD | ~ 1%* | Mild - moderate |
| **2** | Qualitative deficiencies in VWF | | | |
| **2A** | Decreased VWF-dependent platelet adhesion with selective deficiency of high-molecular-weight (HMW) multimers | AD | Uncommon | Usually moderate |
| **2B** | Increased affinity for platelet GPIb | AD | Uncommon | Usually moderate |
| **2M** | Decreased VWF-dependent platelet or collagen adhesion without selective deficiency of HMW multimers | AD | Uncommon | Usually moderate |
| **2N** | Markedly decreased binding affinity for FVIII | AR | Uncommon | Usually moderate |
| **3** | Complete deficiency of VWF | AR | Rare (1:250,000-1:1,000,000) | Severe |

^AD = autosomal dominant, AR = autosomal recessive
*The prevalence of clinically symptomatic VWD is much lower, estimated to be at least 1:10,000.






| Approved by PSC on | 12/2/20 | Next Review Date | 12/2/22 |
|---|---|---|---|

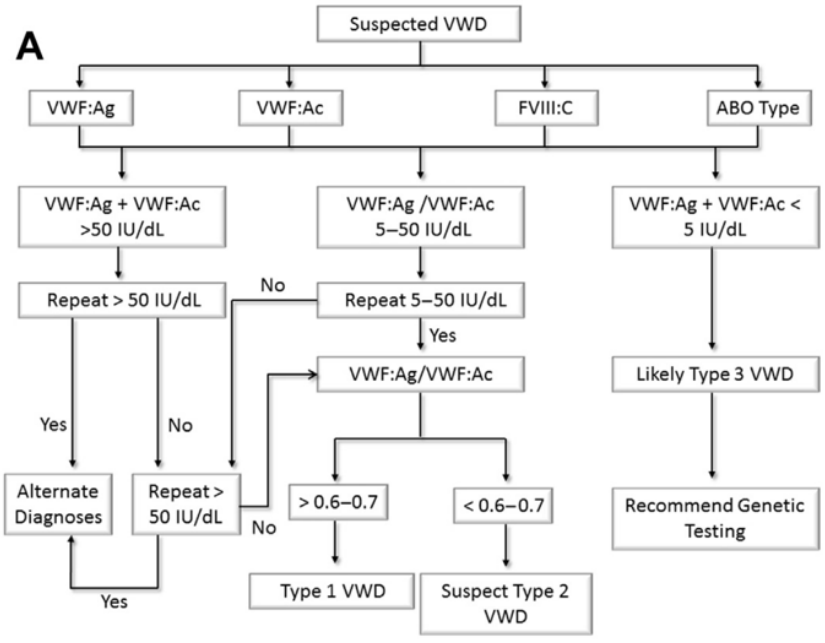
**Table 2: Additional VWD Disorders**

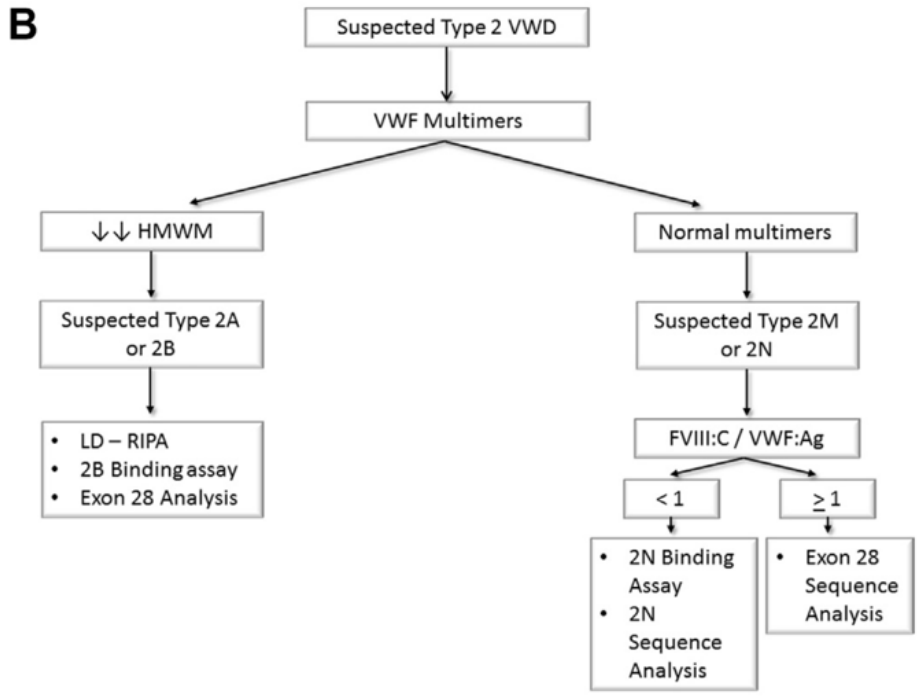
| Type | Diagnostic characteristics | General Treatment Principles |
|---|---|---|
| **Low VWF** | VWF levels of 30-50% | Increased risk of bleeding, treat similar to type 1 VWD |
| **aVWS** | Abnormal VWD panel in certain clinical scenarios, including cardiac conditions with elevated shear stress, malignancies, use of mechanical circulatory devices, and antibody-mediated processes | - Identify and treat underlying disorder<br>- See aVWS in ***Management of Special Circumstances*** section below |
| **PT VWD** | Gain in function mutation in GP-Ib receptors, enhancing binding of normal VWF to abnormal platelets | - Similar phenotype to VWD Type 2B<br>- Treat with platelet transfusions<br>- DDAVP is contraindicated |
| **VWD Type 1C (Vicenza Type)** | Reduced VWF half-life due to increased VWF clearance | - DDAVP challenge may show good response after 1 hour that is not sustained at 4 hours<br>- Increased VWFpp/VWF:Ag ratio<br>- VWF/FVIII replacement for serious bleeding/surg. procedures |

## Diagnostic Studies:

- VWD Panel: VWF:Act (as measured by Glycoprotein (GP) 1bM assay at TCH), VWF:Ag, VWF:Act/VWF:Ag ratio, FVIII activity, and VWF multimers.
  - "Pathologist Review" should be selected on initial diagnosis so that multimer analysis (send out to Versiti) can be obtained by the coagulation physician if necessary
  - VWF:Act & VWF:Ag may need to be repeated two or three times to verify VWD diagnosis, due to elevated levels seen in settings of physiological stress.
- Obtain blood samples using the least traumatic method and process within 2 hours of phlebotomy.
- Blood samples should be obtained when the patient is healthy and off all medications, including estrogens, and off non-steroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen) for > 2 weeks.
  - Process samples within 2 hrs of phlebotomy or immediately freeze and store at –40°C.

## Diagnostic Algorithm for the laboratory evaluation of suspected VWD (A) and Type 2 VWD (B)*






*Adapted from SH O'Brien and S Saini *Hematol Oncol Clin N Am* 33 (2019) 425-428. Of note, Low VWF is considered if VWF:Act or VWF:Ag levels are between 30-50, while VWD is diagnosed when levels are <30. HMWM, high-molecular weight multimers; LD-RIPA, low-dose ristocetin-induced platelet aggregation.

## Overall Management Plan:

The management plan should include the following information:

- Name of HAT team nurse coordinator assigned to patient
- Routine anticipatory guidance:
  - Avoid high impact contact activities (football, rugby, boxing, karate, etc.).
  - Avoid non-steroidal anti-inflammatory drugs (affect platelet function).
  - Avoid intramuscular injections. Injections should be given subcutaneously with local pressure applied for 10 - 15 minutes.
  - Education regarding appropriate local measures for controlling epistaxis.
- Treatment plan for bleeding events or surgical/dental procedures.
  - Including the use of DDAVP (see DDAVP guidelines), if appropriate, vs VWF/FVIII replacement
- If diagnosis is confirmed, consider evaluating family members under 21 years of age. May also suggest adult hematology evaluation for adults in the family; with an emphasis in testing immediate family members who are symptomatic relatives of VWD Type 1 patients, relatives of VWD Type 2 & 3 patients, and relatives who are anticipating major surgery. If necessary, a genetic counselor may be consulted to determine risk and to assist with family counseling.

## Treatment Options:

**Table 3: Summary of treatment options**

| Therapy | Indications | Important Notes |
|---|---|---|
| **DDAVP**<br>• Intravenous formulation (nasal formulations not currently available) | - Minor bleeding events or surgical/ dental procedures in classic type 1 VWD, some type 2 VWD | - Restrict fluid intake following use to avoid hyponatremia (see Appendix 1)<br>- Efficacy should be demonstrated in a DDAVP challenge test prior to use<br>- Not to be used more than 3 consecutive days (tachyphylaxis)<br>- Avoid in children <2 years and in patients with cardiovascular or neurologic conditions |
| **Replacement therapy**<br>• Plasma-derived concentrates<br>• Recombinant VWF | - Major bleeding events or surgical procedures for type 1, 2, and 3 VWD<br>- Non-major bleeding events in DDAVP non-responders<br>- Prolonged treatment required (>3 days) | - Perform outpatient clearance study prior to surgical procedure to determine dose/ frequency<br>- Must monitor VWF and FVIII levels during treatment period to avoid supratherapeutic levels (thrombosis risk) |
| **Antifibrinolytic agents**<br>• Aminocaproic acid<br>• Tranexamic acid | - Mild mucocutaneous bleeding<br>- Adjuncts to DDAVP and VWF replacement for bleeding from oral and gastrointestinal tracts | - Avoid in the setting of hematuria to avoid ureteral clots and hydronephrosis |

**Non-replacement Therapy: Desmopressin (DDAVP)**

**Indications for use:**

- Classic VWD Type 1 and mild hemophilia A (FVIII > 5%)
- Minority of VWD Type 2A and Type 2M
- For minor bleeding symptoms in VWD Type 2N. FVIII in these patients has a very short half-life of 2 - 3 hours after DDAVP administration, hence DDAVP cannot be used for major bleeding.
- DDAVP may be cautiously considered in patients with VWD Type 2B, due to concerns for potential platelet aggregation. Thrombocytopenia may occur after DDAVP administration, but is usually transient and often not associated with bleeding or thrombosis. Checking a platelet count together with VWF activity is recommended during a DDAVP challenge.

**Specific situations (IV formulation is to be given 30 min prior to procedure):**

- Minor surgeries (including tonsillectomy and adenoidectomy)
- Invasive dental procedures
- Mucosal bleeding (menorrhagia, epistaxis, oral bleeding)
- Bleeding or excessive bruising with minor trauma
- Laparoscopic surgeries

**Formulations (currently available)**:

- Intravenous (IV): DDAVP 0.3 mcg/kg given IV over 30 minutes. Maximum dose: 20 mcg/dose

**Contraindications:** Children under 2 years of age have lower response rates and are more susceptible to hyponatremia. Underlying cardiovascular disease, diagnosis of PT VWD, epilepsy.

**Adverse reactions:** Headache, flushing, transient hypertension or hypotension, gastrointestinal upset, fluid retention, and rarely hyponatremia.

**Monitoring:**

- Restrict fluid intake and monitor serum sodium with repeated dosing (i.e. after surgery).
- Tachyphylaxis may occur with repeated doses given more frequently than every 24 hours. Avoid prolonged use (more than 3 consecutive days).

**DDAVP Challenge test:** Prior to using DDAVP for surgical procedure, an adequate response to a challenge test should be documented.

1. Administer DDAVP as directed above.
2. Obtain VWF:Act, VWF:Ag, and FVIII at baseline, and again at 1 and 4 hours after DDAVP administration.
3. Adequate response is defined as a 2- to 3-fold increase in VWF:Act and VWF:Act> 50 IU/dL after 1 hour, with results sustained after 4 hours.

**Replacement Therapy: Plasma-derived Concentrates Containing VWF**

**Indications for use:**

- VWD Type 1:
  - If DDAVP is contraindicated or fails to produce adequate sustained response
  - If protracted therapy required
  - Hemostasis for major surgical procedure
- VWD Type 2
- VWD Type 3

**Plasma-derived concentrates containing VWF:**

- Humate-P® (most commonly used, treatment of choice): plasma-derived, licensed in the US for VWD.
- Alphanate SD/HT® (also plasma-derived, consult HAT team if considering)

**Dosing calculations:** It is important to note that plasma-derived VWF concentrates may be dosed either by VWF:RCoF units or by FVIII units (infused FVIII half-life is approximately twice that of VWF).

- 1 IU VWF:RCoF per kg body weight raises VWF by ~1.5%.
- 1 IU FVIII:C per kg raises FVIII plasma level by ~2%.
- For bolus infusions, dose is calculated by: body weight (kg) x (desired VWF:Act rise [%][IU/dL])/1.5.

**Adverse reactions:** Allergic, anaphylactic reactions, and rare reports of venous thromboembolism, risk of viral infection transmission, development of inhibitory antibodies

**Clearance study:** Recommended prior to major surgery.

- Administer Humate-P (40 - 60 VWF:RCoF units/kg/dose IV).
- Obtain VWF: Act, VWF: Ag, and FVIII at baseline, and again at 1, 4, and 8 hours post Humate-P administration. If possible (or if inpatient) obtain follow up levels at 12 and 24 hours post Humate-P administration as well.
- Final dose and interval calculations should be based on response.

**Table 4: VWF Dosing Guidelines for Procedures and Surgeries**

| Type of bleeding/ surgery | VWFconcentrate | | Monitoring | Therapeutic goal | Safety parameter | Duration |
|---|---|---|---|---|---|---|
| | Loading dose | Maintenance dose | | | | |
| Simple dental extractions, endoscopy, liver biopsy, cardiac catheterization, lacerations | 40-60 RCoF units/kg | | | | | Single dose; additional doses as necessary |
| Minor surgery/ bleeding | 30-60 RCoF units/kg | 20-40 RCoF units/kg q12-48 hrs | VWF:Act & FVIII peak & trough (at least once) | VWF:Act/FVIII trough: > 50 IU/dL for 3-5 days | Peak VWF:Act: < 200 IU/dL; FVIII: < 250 IU/dL | 1 - 5 days |
| Major surgery/ bleeding | 40-60 RCoF units/kg | 20-40 RCoF units/kg q8-24 hrs | VWF:Act & FVIII peak & trough (at least daily) | VWF:Act/FVIII trough: > 50 IU/dl for 7-14 days | Peak VWF:Act GP 1bM: < 200 IU/dL; FVIII: < 250 IU/dL | 7 - 14 days |

**Note:** Since VWF:Act results may not be readily available, VWF:Act may be calculated from the VWF:Ag level based on patient's baseline ratio of VWF:Act /VWF:Ag. Higher VWF:Act of 80-100 IU/dl for 1-3 days may be maintained for major surgeries (CNS/GI) and major trauma. Initial loading dose is to be given 30 min-1 hour prior to surgery.

**Replacement Therapy: Recombinant von Willebrand Factor (rVWF/Vonvendi*)**

**Target population**: rVWF is currently FDA approved for patients 18 years and older.

**rVWF half-life**: 19 - 22 hours (see **Appendix 2** for further administration guidelines)

**Monitoring**: Check VWF:Act and FVIII:C plasma levels starting 12 to 24 hours after surgery and at least every 24 hours in the perioperative period; abide by previously stated VWF bleeding/surgical level recommendations to achieve adequate hemostasis.

**Serious adverse reactions**: Thromboembolic events, hypersensitivity reactions, and development of neutralizing antibodies. Common adverse reactions are generalized pruritis, nausea, vomiting, dizziness.
*Use of rVWF/Vonvendi requires notification of pharmacy 1-2 days prior (drug is by order only)

**Antifibrinolytics: Aminocaproic acid and Tranexamic acid**

**Mechanism of action:** Antifibrinolytics stabilize the clot by blocking the conversion of plasminogen to plasmin, thereby inhibiting fibrinolysis.

**Indications for antifibrinolytic use:** Used as adjuncts to replacement therapy for prevention or treatment of bleeding in mucosal tracts and for menstrual bleeding. Antifibrinolytics may also be used in association with replacement therapy during surgery involving mucosal surfaces, spine and cranial surgery.

**Options and Formulations:**
**Aminocaproic acid** (Amicar®)**:** Available orally (PO) as pills or suspension and intravenously (IV).

- IV: 50 mg/kg/dose (100 mg/kg/dose may be used for severe bleeding) IV every 6 hours for 3-7 days. Maximum daily dose: 24 g/day.
- PO: 50 mg/kg/dose (100 mg/kg/dose may be used for severe bleeding) PO every 6 hours for 3-7 days. Maximum dose: 5 g/dose.

***Monitoring:*** Prolonged use (i.e. greater than 14 days) of aminocaproic acid warrants LFT evaluation.

**Tranexamic acid**:

- IV: 10 mg/kg/dose IV immediately before surgery, then 10 mg/kg/dose IV every 6 – 8 hours for 2 - 8 days. Maximum dose of 1 g every 6 hours.
- PO (Lysteda®): FDA approved for heavy menstrual bleeding in adult women ≥ 18 years of age and used off-label in adolescents and children <18 years of age: 1,300 mg three times daily for up to 5 days during monthly menstruation; 650 mg three times daily recommended in patients <12 years of age. Tablets cannot be scored or crushed.
- Inhalation by nebulization *(for pulmonary hemorrhage or hemoptysis)*: injection solution for inhalation use. Children < 25 kg: 250 mg/dose every 6-12 hours; children ≥ 25 kg: 500 mg/dose every 6-12 hours for a maximum of 3 days.
- Oral rinse (*for dental procedures*): Use 5% solution prepared extemporaneously by pharmacy and swish 5-10 mL in mouth for 2 minutes then rinse.

Note: Dose reductions may be required for renal impairment.

***Monitoring***: Prolonged use (i.e. > 14 days) of tranexamic acid warrants ophthalmic examination.

***Contraindications:***

- Disseminated intravascular coagulation and hematuria (due to the potential for the development of ureteral clots and hydronephrosis).
- Tranexamic acid can cause visual abnormalities with prolonged use, and is contraindicated in patients with acquired color vision defects.

**Table 5: Management of Routine Complications**

| Complication | Treatment considerations |
|---|---|
| Epistaxis | • Consider oral aminocaproic acid or tranexamic acid (dosing above) for 1 - 3 days. Topical amicar may also be an option, especially if PO amicar is not effective<br>• ENT referral for nasal cauterization if recurrent and prolonged |
| Heavy menstrual bleeding (HMB) | • Obtain a complete gynecologic evaluation<br>• Perform VWD testing during menstruation and off estrogen containing contraceptives<br>• Treatment options:<br>  ○ Estrogen containing combination hormonal contraceptives (gynecology consultation)<br>  ○ Oral aminocaproic acid or tranexamic acid for 3 - 5 days<br>  ○ VWF concentrate may be used in VWD Type 2 or Type 3 patients who refuse contraceptives. |
| Dental Procedures, Tonsillectomy/ Adenoidectomy, or Minor Surgery (for patients with good sustained response to DDAVP challenge): | • 24 hours prior to procedure, begin aminocaproic acid 50 -100 mg/kg/dose orally every 6 hours and continue for a maximum of 14 days post-operatively.<br>• Administer 1 dose of DDAVP/Stimate® 30 minutes prior to procedure.<br>• Check VWF:Ag and FVIII trough levels. (Also check VWF:Act ,if feasible) 12 hrs post-procedure, then daily until discharge or 3 days post-procedure.<br>• Administer IV VWF (Humate P at 40-60 RCo units/kg or Vonvendi 50 IU/kg for patients ≥18 years of age) if VWF:Act level is < 50 IU/dL at 12 hours post-procedure.<br>• Repeat DDAVP dose at 24, 48, and 72 hours post-procedure if the VWF:Act and/or FVIII trough is less than 50 IU/dL.<br>• Monitor overnight in the inpatient setting. Restrict fluids following DDAVP administration until patient urinates. Patients should receive isotonic IV fluids only to avoid hyponatremia. Monitor serum sodium at 12 and 24 hours. Do not administer additional doses of DDAVP if serum sodium < 135. Can be replaced by IV VWF (Humate P or Vonvendi based on patient's age).<br>• For tonsillectomy and adenoidectomy, repeat DDAVP/Stimate® dose on Day 7, 9, and 11 days postoperatively (when surgical eschar separates, patients are at risk for bleeding). |

**Prophylaxis for severe VWD:**

- The rationale for implementing long-term prophylaxis in VWD is to limit bleeding events that may jeopardize an individual's quality of life or possibly be life threatening. Avoidance of arthropathy is another consideration in severe VWD, particularly in type 3 VWD.
- Criteria for initiating VWF prophylaxis may include recurrent joint bleeding, gastrointestinal bleeding, excessive bleeding during menstruation, or severe epistaxis in patients not responsive to DDAVP.
- A suggested prophylactic dosing schedule is to start VWF replacement at 50 IU VWF:RCo/kg once per week, increasing the dosing frequency up to 3x/week as indicated by bleeding symptoms.

**Acquired von Willebrand syndrome (aVWS):**

- Key to treating aVWS is identification and treatment of the underlying aVWS-associated disorder.
- Considerations for treatment of bleeding symptoms in aVWS:
  - Clearance study can help to determine the treatment dose and dosing frequency due to increased VWF clearance in aVWS.
  - There may be poor correlation between VWF levels and clinical bleeding; the clinical features of each patient will help develop a bleeding/peri-operative plan.
  - If adequate VWF levels cannot be achieved with intermittent infusions, continuous infusion of VWF is effective, reported starting doses between 2 and 15 RCoF units/kg/hr.
  - Recombinant FVIIa may be considered if unable to achieve hemostasis with standard therapy.
  - Antifibrinolytic agents may be used as supplementary agents (e.g. mucocutaneous bleeding).
  - Intravenous immunoglobulin (IVIG) is effective in the setting of aVWS associated with monoclonal gammopathies of uncertain significance at a dose of 1 g/kg/day x 2 days. This strategy may be considered as second line for patients unresponsive to DDAVP or VWF-containing concentrates.
  - For minor bleeding events or surgical procedures, DDAVP may be helpful though may have a low success rate especially in cases of cardiovascular disease.

**Content Owner:** Clay Cohen, Sarah Sartain
**Team Leaders:** Sarah Sartain, Rosa Diaz
**Date of Approval: 12/02/2020**

**Revision History:**

| Date | Revision Number | Revision |
|---|---|---|
| | | |

**References:**

1. GUIDELINES: VWD: evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute Expert Panel report (USA). Nichols WL, Hultin MB, James AH, et al. Haemophilia (2008), 14, 171–232.
2. Leebeek FW, Eikenboom JC. VWD. N Engl J Med. 2016 Nov 24;375(21):2067-2080
3. Lavin M, O'Donnell JS. New treatment approaches to VWD. Hematology Am Soc Hematol Educ Program. 2016; 2016(1):683-689.
4. O'Brien SH, Saini S. VWD in Pediatrics: Evaluation and Management. Hematol Oncol Clin N Am; 33 (2019): 425-438.
5. Heijdra JM, Cnossen MH, Leebeek FWG. Current and Emerging Options for Management of Inherited VWD. Drugs. 2017; 77(14):1531-1547.
6. Leebeek FWG, Atiq F. How I manage severe VWD. Br J Haematol. 2019; 187(4):418-430.
7. Mannucci PM. Treatment of VWD. N Engl J Med. 2004; 351(7):683-94.
8. Franchini M, Montagnana M, Lippi G. Clinical, laboratory and therapeutic aspects of platelet-type VWD. Int J Lab Hematol. 2008; 30(2):91-4.
9. Kubicki R, Stiller B, Kroll J, et al. Acquired von Willebrand syndrome in paediatric patients during mechanical circulatory support. *Eur J Cardiothorac Surg*. 2019; 55(6):1194-1201.
10. Flood VH, Gill JC, Morateck PA, et al. Gain-of-function GPIb ELISA assay for VWF activity in the Zimmerman Program for the Molecular and Clinical Biology of VWD. *Blood*. 2011; 117(6):e67-74.

## Appendix 1: Patient hand out following DDAVP administration

**Desmopressin (DDAVP)/Stimate®**

**What is Desmopressin (DDAVP)**

DDAVP is a medication used to help control bleeding in patients with mild Hemophilia A or von Willebrand disease. DDAVP increases blood clotting by stimulating the release of factor VIII and von Willebrand factor from storage sites in the body.

**How is DDAVP Given**

DDAVP can be given in a vein (through an IV), and this is typically done in a hospital or clinic setting. DDAVP can also be given in the form of a nose spray. When given as a nose spray, the medication is called Stimate®. It is important to only use the brand name Stimate® nose spray, as the other generic forms are not strong enough to treat bleeding.

**DDAVP/Stimate® Challenge**

DDAVP does not work for everyone. For this reason you/your child will be required to come into the Texas Children's Hematology Center for a test dose of the medication before it can be prescribed to you. This type of appointment is referred to as a DDAVP Challenge. During this time, you/your child will receive an IV followed by a test dose of the DDAVP or Stimate®, and blood tests to evaluate your/your child's response to the medication. The DDAVP Challenge can take up to 5 hours, so please plan accordingly.

**When to Use DDAVP**

Your provider will tell you when to use Stimate®. It is generally given to control nose and mouth bleeding, heavy menstrual bleeding, or prior to dental procedures and minor surgeries as directed by your provider. Stimate® should only be given once every 24 hours, and it should not be used more than 3 days in a row as it will lose effect after 3 consecutive days.

**Side Effects**

More Common:
- Temporary facial redness
- Mild headache
- Fluid retention
- Changes in blood pressure

Less Common:
- Sore throat
- Fast heart rate
- Abdominal cramping
- Seizures due to low blood sodium

**When to Contact Your Doctor**
- If bleeding is not controlled after giving DDAVP/Stimate® for 3 days
- If you/your child is not urinating within 12 hours of taking DDAVP/Stimate®
- If you/your child experiences dizziness, confusion, rash or headaches that are not relieved with acetaminophen (Tylenol®)

**Recommendations for Fluid Intake When Using DDAVP/Stimate®**

- DDAVP/Stimate® causes the body to retain water so we recommend fluid restriction for 24 hours after taking a dose of DDAVP/Stimate®. This helps prevent side effects like low blood sodium levels, which can cause rare, but serious side effects, like seizures.
- Examples of fluid intake includes water, soft drinks, milk, Jello®, popsicles, soup, coffee, and other beverages.

Last Updated: May 9, 2019

## Desmopressin (DDAVP)/Stimate®

- Avoid activities that increase thirst or fluid intake for 24 hours after using DDAVP (exercise, sporting activities) as this could lead to dehydration and low blood sodium levels
- Over the next 24 hours after DDAVP/Stimate®, do not take more fluids then the maximum volumes, by weight, listed below:

| Weight (in pounds) | Maximum 24 hr. fluid intake | Number of 8 oz. glasses |
|---|---|---|
| 22 - 34 | 24 oz. | 3 |
| 34 - 45 | 32 oz. | 4 |
| 46 – 67 | 40 oz. | 5 |
| 68 – 110 | 48 oz. | 6 |
| 111 – 160 | 56 oz. | 7 |
| 161 and above | 64 oz. | 8 |

**Stimate® Dosage**

- Give 1 Spray (150 micrograms) if you/your child weighs less than 50 kg (110 pounds)
- Give 2 Sprays (300 micrograms) if you/your child weighs 50 kg (110 pounds) or more

**Storage of DDAVP/Stimate®**

- Stimate® should be stored upright in the refrigerator or at room temperature not to exceed 77 degrees Fahrenheit.
- Stimate® expires 6 months after opening, or once expiration date has been reached, whichever comes first.

**Instructions for Stimate® Administration**

- Prime the Stimate® nozzle with 4 sprays before using for the first time. If not used for one week, prime the pump once or until an even spray is released.
- Spray Stimate® in the nostril and breathe deeply. *If given for nose bleeds, apply Stimate® to nostril that is not bleeding.

**Hematology Contact Phone Numbers**

| | |
|---|---|
| Hematology Clinic | 832-822-4362 |
| Hematology Doctor On-Call | 832-824-2099 |

Texas Children's Hospital
CANCER AND HEMATOLOGY CENTERS

Last Updated: May 9, 2019

## Appendix 2: Additional guidance for recombinant VWF administration

**Further instructions for rVWF/Vonvendi dosing:**

1. **Elective surgical procedures:** Preoperative dose of rVWF may be administered 12 to 24 hours prior to surgery to allow endogenous factor VIII levels to increase to at least 30 IU/dL for minor surgery or 60 IU/mL for major surgery before the loading dose (1 hour preoperative dose) of rVWF, with or without recombinant FVIII, is administered. Check FVIII within 3 hours prior to the surgery, if FVIII is NOT at recommended minimum level, administer the preoperative dose of rVWF followed by recombinant FVIII within 10 minutes.
   a. When possible, assess incremental recovery of rVWF before surgery by measuring baseline plasma VWF:act 1b, infusing dose of 50 IU/kg rVWF, and repeating 30 minutes after infusion
   b. IR = [Plasma VWF:RCo at 30 minutes (IU/dL) – Plasma VWF:RCo at baseline (IU/dL)]/Dose (IU/kg)
   c. To calculate the dose (IU) = (Desired change in VWF:RCo) x (BW [kg])/IR
2. **Emergency surgical procedures:** Administer 40 to 60 IU/kg of rVWF followed by (within 10 minutes) FVIII at a dose of 30 to 45 IU/dL if plasma FVIII levels are (or likely to be) less than 40 to 50 IU/dL for minor surgery and 80 to 100 IU/dL for major surgery.

**Table 6. rVWF/Vonvendi Dosing for Bleeding Events***

| Bleeding Episodes | Initial Dose# | Subsequent Dose |
|---|---|---|
| Minor (epistaxis, mucosal bleeding, menorrhagia) | 40 to 50 IU/kg | 40 to 50 IU/kg every 8-24 hours |
| Major (severe or refractory epistaxis, menorrhagia, GI bleeding, CNS trauma, hemarthrosis, or traumatic hemorrhage | 50 to 80 IU/kg | 40 to 60 IU/kg every 8 to 24 hours for approximately 2 to 3 days |

**Source = Vonvendi package insert* #As rVWF contains only VWF and no FVIII, additional FVIII infusions may be needed in addition to rVWF dosing. For each bleeding episode or in emergent surgical scenarios, administer first dose of rVWF with FVIII replacement if baseline FVIII levels are < 40% or unknown. Dosing based on VWF:Act

**Table 7. rVWF/Vonvendi Dosing recommendation if baseline VWF:Act and FVIII:C levels are known**

| Type of surgery | VWF:Act 1b Target Peak Plasma Level | FVIII:C Target Peak Plasma level | Calculation of rVWF dose (administered within 1 hour of surgery) |
|---|---|---|---|
| Minor | 50 to 60 IU/dL | 40 to 50 IU/dL | Desired change in VWF: Act x BW (kg)/IR* |
| Major | 100 IU/dL | 80 to 100 IU/dL | |

*If the IR is not available, assume an IR of 2.0. Modified from Vonvendi package insert.

**Table 8. rVWF/Vonvendi Dosing recommendation if baseline VWF:Act and FVIII:C levels NOT known**

| Type of surgery | VWF:RCo (IU VWF:RCo/kg BW) | VWF:Act Target Peak Plasma Level | FVIII:C (IU FVIII:C/kg BW) | FVIII:C Target Peak Plasma level |
|---|---|---|---|---|
| Minor | 25 to 30 IU/kg | 50 to 60 IU/dL | 20 to 25 IU/dL | 40 to 50 IU/dL |
| Major | 50 ± 10 IU/kg | 100 IU/dL | 40 to 50 IU/dL | 80 to 100 IU/dL |

*Modified from Vonvendi package insert*