



NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Recommendation #266
(Replaces Document #244)

**MASAC RECOMMENDATIONS REGARDING THE TREATMENT OF
VON WILLEBRAND DISEASE**

The following recommendations were approved by the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) on February 20, 2021, and adopted by the NHF Board of Directors on March 4, 2021.

von Willebrand disease (VWD) is the most common inherited bleeding disorder and affects males and females equally in up to 1% of the general population. (1,2) VWD is associated with mucous membrane bleeding, excessive bruising, and bleeding from cuts. It can result in excessive bleeding with invasive dental work, during surgical procedures, and after accident or injury. In women, heavy menstrual bleeding is often the major symptom. Women with VWD are also at risk of postpartum hemorrhage, particularly delayed postpartum hemorrhage.

The following are current recommendations for treating bleeding in individuals with VWD. They are adapted from the ASH, ISTH, NHF, WFH 2021 VWD guidelines. (3)

Refer to Connell et al for suggested definitions for desmopressin response, prophylaxis, heavy menstrual bleeding (HMB), post-partum hemorrhage. (4)

Desmopressin (DDAVP) [5-9].

1. Persons with type 1, 2A, 2M, and 2N VWD may be treated with the synthetic agent desmopressin (DDAVP Injectable or Stimate Nasal Spray for Bleeding, 1.5 mg/ml) if they have been shown by a DDAVP trial to be responsive. This is particularly important for patients with type 1 VWD and VWF $\leq 30\%$ and types 2A, 2M, and 2N who may not have sufficient response. Response should be assessed one and four hours after DDAVP; the one-hour assessment is particularly important for patients suspected of having type 1C VWD. A desmopressin response requires an increase of at least >2 times the baseline VWF activity level and a sustained increase of both VWF and factor VIII (FVIII):C levels >0.50 IU/mL for at least 4 hours.
2. Desmopressin is a potent antidiuretic agent, and fluid retention is a potential complication of this drug. Both parenterally administered DDAVP (IV and SQ) and Stimate[®] Nasal Spray have been associated with the development of hyponatremia and seizures. To minimize this risk, the following precautions should be observed when this drug is used at home and in the hospital:
 - a. DDAVP and Stimate should be administered no more often than once every 24 hours.

- b. DDAVP and Stimate should be used for no more than three consecutive days unless directed to do so by Hemophilia Treatment Center medical staff.
- c. DDAVP and Stimate should not be used in children under the age of two years.
- d. DDAVP and Stimate should be used with caution in the elderly and in individuals with a history of heart disease, hypertension, or stroke.
- e. If a patient is treated with DDAVP before surgery, the anesthesiologist should be advised to avoid fluid overload and dilutional hyponatremia.
- f. DDAVP should be used with caution in pregnant women in the peripartum and immediate postpartum period, with careful attention to fluid management to avoid hyponatremia.
- g. Oral fluids should be restricted to maintenance for 24 hours following treatment.

3. VWF Replacement

Persons with type 2B and type 3 VWD, and those with type 1, 2A, 2M, and 2N who have been shown to be nonresponsive to DDAVP, should be treated with a factor VIII/VWF concentrate that is known to contain the higher molecular weight multimers of von Willebrand factor and that has been virally attenuated to eliminate transmission of HIV and hepatitis A, B, and C. Human plasma-derived products Alphanate, Humate P, and Wilate have been approved by the FDA for use in VWD. A recombinant VWF concentrate, Vonvendi, has also been approved. Another plasma-derived product, Koate DVI, may also be effective in these patients, but it has not been approved by the FDA for use in VWD. For further information, see MASAC Document #263, "MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders."

Because of the increased risk of HIV and hepatitis A, B, and C transmission, cryoprecipitate should not be used except in an emergency situation when none of the above-mentioned products are available and delay of treatment would be life- or limb-threatening.

4. Antifibrinolytics

Adjunctive treatments for mucous membrane bleeding include the antifibrinolytic agents aminocaproic acid and tranexamic acid. These agents can be given orally or intravenously. (See MASAC Document #263, "MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders.")

5. Management of Heavy Menstrual Bleeding - See MASAC Document #264.

6. Prophylaxis

In patients with VWD with a history of major and frequent bleeds, the ASH ISTH NHF WFH guideline panel suggests using long-term prophylaxis with factor replacement rather than no prophylaxis.(3) Prophylaxis in VWD is defined as a period of at least 3 months of treatment of VWF concentrate at least once weekly, or for women with HMB, use of VWF concentrate at least once per menstrual cycle.

7. Perioperative Management

Prior to surgery in a patient with VWD, consultation should be obtained with a pediatric or adult hematologist who specializes in the management of individuals with inherited bleeding disorders. This consultation should cover risk of bleeding with procedure and duration of risk. Treatment plan should be developed including such issues as the need for a DDAVP trial; type of fluid replacement or fluid restriction; dose and duration if DDAVP is to be used; appropriate dose, timing, and duration of factor replacement therapy; and use of adjunctive medications (antifibrinolytics and topical agents). The ASH ISTH NHF WFH 2021 guidelines on the management of VWD suggest the following:

- Desmopressin should not be used for major surgery.
- Factor replacement the panel suggests targeting both FVIII and VWF activity levels of 0.50 IU/mL for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects).

Remarks:

- When it is possible to keep both trough levels at 0.50 IU/mL for at least 3 days or as long as clinically indicated after the surgery (instead of choosing only 1), this should be the preferred option.
- The specific target levels should be individualized based on the patient, type of procedure, and bleeding history as well as availability of VWF and FVIII testing.
- The duration of the intervention can vary for specific types of surgeries.
- In patients undergoing minor surgery or minor invasive procedures, the panel suggests increasing VWF activity levels to 0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to 0.50 IU/mL with desmopressin or factor concentrate alone.
- The panel suggests giving tranexamic acid alone over increasing VWF activity levels to 0.50 IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of 0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures.

References:

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4. Connell NT, James PD, Brignardello-Petersen R, Abdul-Kadir R, Ameer B, Arapshian A, Couper S, Di Paola J, Eikenboom J, Giraud N, Grow JM, Haberichter S, Jacobs-Pratt V, Konkle BA, Kouides P, Laffan M, Lavin M, Leebeek FWG, McLintock C, McRae S, Montgomery R, O'Brien SH, O'Donnell JS, Ozelo MC, Scappe N, Sidonio R, Tosetto A, Weyand AC, Kalot MA, Husainat N, Mustafa RA, Flood VH. von Willebrand disease: proposing definitions for future research. *Blood Adv*. 2021 Jan 26;5(2):565-569.
5. Mannucci PM. Desmopressin (DDAVP) for treatment of disorders of hemostasis. *Prog Hemost Thromb* 1986; 8: 19-45.

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