von Willebrand disease (VWD): Treatment of major bleeding and major surgery

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INTRODUCTION

von Willebrand disease (VWD) is the most common inherited bleeding disorder. Management can vary widely depending on the type of VWD, severity and location of bleeding, and need for invasive procedures.

This topic reviews the emergency treatment of bleeding and the management of major surgery in individuals with VWD.

Separate topic reviews discuss the non-emergency management including treatment of less serious bleeding, DDAVP trial, management during pregnancy, clinical presentation and diagnosis, and pathophysiology of VWD, as well as the diagnosis and management of acquired von Willebrand syndrome (AVWS):

- Non-emergency management of VWD including DDAVP trial – (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care".)
- Obstetric and gynecologic management – (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations".)
- Clinical presentation and diagnosis of VWD – (See "Clinical presentation and diagnosis of von Willebrand disease".)
- Pathophysiology of VWD – (See "Pathophysiology of von Willebrand disease".)

- Evaluation and management of AVWS – (See "Acquired von Willebrand syndrome".)

OVERVIEW OF APPROACH

Treatment for bleeding or surgery in VWD is achieved by increasing the level of von Willebrand factor (VWF) in the circulation and stabilizing the clot that is formed at the site of injury.

There are two main approaches for increasing the level of VWF, which are used in different situations (table 1):

- **VWF concentrates** – Administering VWF in a concentrate form is appropriate for individuals who have a VWF activity level <50 international units (IU)/dL in the setting of major or life-threatening bleeding, major surgery. Most major bleeding in patients with VWD is treated with VWF concentrates. Examples include:

  - Bleeding that causes a decrease in hemoglobin concentration of 2 or more g/dL
  - Bleeding that leads to transfusion of 2 or more units of whole blood or red blood cells
  - Bleeding into a closed space or compartment such as intracranial, spinal, or joint bleeding
  - Major surgical procedures for which serious bleeding could be life-threatening
  - Uncontrolled surgical or traumatic bleeding
  - Pregnant women with baseline VWF activity <50 IU/dL during and shortly after delivery and/or invasive procedures (amniocentesis, neuraxial anesthesia/analgesia)
  - Any bleeding requiring treatment in a person with type 3 VWD (absent VWF) or severe types 1 or 2 VWD (table 2)

  Many of these situations are considered a medical emergency, and VWF should be administered without delay. Dosing and monitoring are discussed below. (See 'VWF concentrates for major bleeding' below.)

  When the individual with major bleeding is stabilized, they should be transferred as appropriate to a location where there is expertise in managing VWD and laboratory monitoring of VWF levels is available.

- **DDAVP** – Administering DDAVP (desmopressin) leads to the release of endogenous VWF from storage sites in endothelial cells. Although the response is predictable in patients who have demonstrated a response to DDAVP in the past, the rise in VWF level may not be sufficient or last for a long enough period in situations of serious bleeding. DDAVP is generally more appropriate for minor bleeding and minor surgery. It can be given only for

approximately three days, after which tachyphylaxis occurs. If more prolonged therapy is needed, VWF concentrates are used.

- **Antifibrinolytic therapy** – An antifibrinolytic agent such as tranexamic acid is often helpful in stabilizing clots, especially in areas with high fibrinolytic activity such as the uterus (for heavy menstrual bleeding and postpartum bleeding). This should be done as an adjunct to raising VWF levels but is not sufficient to treat most serious bleeding by itself.

Appropriate treatment is generally based on the type of VWD and the patient's baseline VWF activity level. There are three main types of inherited VWD (type 1, quantitatively reduced VWF; type 2, various forms of dysfunctional VWF; type 3, absent VWF), as outlined in the table (table 2); as well as acquired von Willebrand syndrome (AVWS). (See "Acquired von Willebrand syndrome".)

There are special treatment considerations for different types of VWD patients. Additional considerations for monitoring and therapy in patients with VWD types 2B, 2N, and 3, and for AVWS are discussed below. (See 'Caveats for uncommon VWD types (2B, 2N, 3)' below.)

While the type of VWD informs treatment, therapy should **not** be withheld while obtaining this information if there is serious or life-threatening bleeding and obtaining this information would create a significant delay that could adversely affect outcomes. In such settings, blood samples for VWF measurements should be obtained, and VWF concentrate should be administered as quickly as possible. Analysis of the blood samples obtained prior to VWF infusion should be performed concurrently, as well as a review of the patient's prior history, which may be helpful in guiding subsequent testing and treatment.

Treatment with VWF concentrates (or DDAVP) may be accompanied by additional, less specific treatments, including antifibrinolytic agents and topical therapy in some circumstances (table 1). Antifibrinolytic agents stabilize the clot by preventing clot breakdown and are especially useful in areas of high fibrinolytic activity such as the uterus, nose, or oropharynx. Attention should also be paid to other conditions that might contribute to bleeding, such as an anatomic/surgical defect, concomitant factor VIII deficiency (factor VIII activity <30 IU/dL) or thrombocytopenia, which would necessitate additional interventions, as discussed below. (See 'Other therapies' below.)

For severe, persistent, or refractory bleeding, other therapies such as recombinant activated factor VII (rFVIIa) may be added. (See 'Refractory bleeding' below.)

Cryoprecipitate is not used as a source of VWF because it has not undergone pathogen inactivation procedures that are used for the plasma-derived VWF concentrates. Cryoprecipitate can provide VWF in the rare setting of serious bleeding when no VWF concentrate is available. (See "Cryoprecipitate and fibrinogen concentrate".)

Our approach is consistent with the 2021 guidelines from the American Society of Hematology, the International Society on Thrombosis and Haemostasis, the National Hemophilia Foundation, and the World Federation of Hemophilia on the management of VWD, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health, the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO), the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation, and other agencies [1-4]. (See 'Society guideline links' below.)

VWF CONCENTRATES FOR MAJOR BLEEDING

Overview of administration and dosing (VWF concentrates) — von Willebrand factor (VWF) concentrates increase the VWF activity level (measured in international units [IU]/dL; equivalent to percent activity) by providing a source of VWF intravenously. Raising the VWF level into the normal range is the primary treatment for severe or life-threatening bleeding or major surgery in most individuals with VWD; even patients with a VWF inhibitor may receive a VWF concentrate initially to assess any effect on clinical bleeding, particularly if a bypassing agent is not immediately available. Exceptions may include those with a VWF inhibitor who require a bypassing agent or those for whom VWF concentrates are not available. (See 'Overview of approach' above.)

Available concentrates are listed below (see 'Available VWF concentrates' below). Regardless of which type of concentrate is used, we generally administer it as follows:

- With rare exception, we give VWF concentrate by intravenous bolus at a rate of approximately 2 to 4 mL/minute. This is generally administered 30 to 60 minutes prior to the surgery (or as soon as possible for major bleeding).
- We target a VWF activity of approximately 100 IU/dL (table 1); generally the level is checked in the recovery room so as not to delay the procedure, unless there is reason to believe there may be rapid clearance or other issues with normal recovery of VWF levels, in which case it can be checked prior to surgery.
- We provide repeated infusions, usually at 8 to 12 hours, as needed to maintain the VWF level above 50 IU/dL.

- The length of therapy should be individualized and may range from three to seven or more days.

In some cases (eg, if the individual has developed a VWF inhibitor and does not have a response to bolus injections), concentrates are given by continuous infusion. (See 'Continuous infusion of plasma-derived VWF concentrates' below.)

Available VWF concentrates — The decision of whether to use a plasma-derived or recombinant VWF concentrate is generally based on availability and cost. The plasma-derived and recombinant products have not been directly compared in a head-to-head trial, but efficacy and adverse effects are similar in separate studies. A concern with plasma-derived products is the accumulation of factor VIII, which carries an increased risk of thrombosis. Neither type of VWF concentrate has had concerns with transmission of bloodborne pathogens. (See 'Evidence for efficacy of VWF concentrates' below and 'Adverse effects (VWF concentrates)' below.)

Plasma-derived VWF concentrates — In the United States, the approved plasma-derived VWF products are Humate-P, Alphanate, and Wilate. Each product is labeled with VWF activity expressed in units of ristocetin cofactor activity (VWF:RCo, one of the assays of VWF activity) (see "Clinical presentation and diagnosis of von Willebrand disease"), and dosing is calculated using the VWF:RCo units (table 1). The plasma-derived products all contain factor VIII in addition to VWF; the ratio of VWF:factor VIII is different for each product [5].

Dosing of plasma-derived VWF for major bleeding and major surgery is as follows:

- **Initial dose** – The goal is to infuse sufficient concentrate to reach a VWF:RCo activity (and factor VIII activity) of 100 IU/dL. Although there are slight variations in dose recommendations with each product, the usual initial dose to reach this activity is in the range of 40 to 60 VWF:RCo units/kg. With some concentrates, when administered to individuals with type 2 or type 3 VWD, the initial dose recommended by the manufacturer ranges as high as 60 to 80 units/kg. The package insert for each product details this information.

- **Subsequent doses** – The goal is to provide additional doses of VWF to maintain the plasma VWF:RCo activity (and factor VIII activity) above 50 IU/dL. This is done by giving approximately one-half the initial dose given every 8 to 24 hours. Doses of each product may be adjusted according to the ongoing clinical picture and the measured VWF:RCo and factor VIII activity levels. (See 'Monitoring and duration of therapy (VWF concentrates: plasma derived and recombinant)' below.)

  There are two potential implications of the factor VIII in the plasma-derived products:

- Individuals treated with these products generally do not require a separate initial source of factor VIII.
- Repeated doses may lead to factor VIII accumulation, which increases the risk of thrombosis.

High plasma levels of factor VIII (>200 percent) lead to concerns about an increased risk of thrombosis; however, this is generally extrapolated from populations with venous thromboembolism (VTE) [6]. The accumulation of factor VIII is greater with the plasma-derived concentrates that have a low ratio of VWF to factor VIII.

Recombinant VWF (rVWF) concentrates — In the United States, the only recombinant VWF (rVWF) product is Vonvendi; it was approved in the United States for adults in 2015. Compared with plasma-derived concentrates, rVWF has the following characteristics [7]:

- Approved for adults only (age ≥18)
- Less clinical experience with the product
- Less exposure to human plasma proteins
- Longer half-life (approximately 22 hours, compared with approximately 12 to 16 hours for plasma-derived VWF)
- Contains the most hemostatically active ultrahigh molecular weight multimers; these are proteolyzed to lower molecular weight multimers within hours
- Does not contain factor VIII; therefore, a dose of factor VIII is given with the first infusion of the recombinant product in emergency settings

Dosing for major bleeding and major surgery is as follows:

- **Initial dose of rVWF** – The goal is to infuse sufficient concentrate to reach a VWF:RCo activity of 100 IU/dL. The usual initial dose to reach this activity is 50 to 80 units/kg. The package insert details this information.

- **Initial dose of factor VIII (for use with rVWF only)** – Since rVWF does not contain factor VIII, patients being treated for acute bleeding are given an infusion of factor VIII with the first dose of rVWF, with the goal of raising the factor VIII activity level to 100 IU/dL. Recombinant factor VIII has been used with rVWF in the early studies of bleeding and surgery. The factor VIII dose is calculated based on patient weight; the dose is 50 units/kg to raise the factor VIII level to 100 IU/dL. After the first dose of rVWF has been given, the individual's endogenous factor VIII will increase, and additional doses of a factor VIII product are generally not required. Dosing is discussed below. (See 'Factor VIII' below.)

For elective major surgery, the initial dose of factor VIII can be omitted in the majority of patients if a dose of rVWF alone is given 12 hours before the surgery; this allows the person's endogenous factor VIII level to rise to hemostatic levels [8]. The next dose of rVWF is given approximately one hour prior to the procedure.

- **Subsequent doses of rVWF** – The goal is to provide additional doses to maintain VWF:RCo levels above 50 IU/dL. This is done by giving doses of 40 to 60 units/kg every 8 to 24 hours, with the frequency of dosing determined by the ongoing clinical picture and the measured VWF:RCo and factor VIII activity levels. This is generally continued for seven days or more, depending on clinical monitoring of the healing. (See 'Monitoring and duration of therapy (VWF concentrates: plasma derived and recombinant)' below.)

Continuous infusion of plasma-derived VWF concentrates — Continuous infusion of a VWF concentrate has been used for individuals who have an inhibitor (alloantibody to infused VWF) or acquired von Willebrand syndrome due to an autoantibody against their own endogenous VWF and have not had a response to bolus injections. Continuous infusion may also be used in individuals without inhibitors; this approach has been shown to decrease the total dose needed for treatment (and cost) by as much as 20 to 50 percent [9]. In one study involving eight individuals with VWD (three mild and five severe) without inhibitors who had 17 episodes of bleeding or surgery, the dose required to maintain the hemostasis (assessed clinically and by measuring VWF:RCo and factor VIII activity) was approximately one-half of what would have been given with bolus infusions [9]. The mechanism is thought possibly to be a reduction of the clearance of the infused product.

The dose for continuous infusion is not well established either for patients with inhibitors or those without inhibitors. Case reports have described continuous infusion rates in the range of 2 to 15 units/kg per hour (equivalent to approximately 50 to 360 units/kg per day) [10].

Common sense indicates that an initial bolus infusion should be given based on a target of at least 100 IU/kg and followed by continuous infusion of a dose calculated based on an anticipated total daily dose, with dose adjustments made by following the clinical status and levels of VWF:RCo and factor VIII. (See 'Monitoring and duration of therapy (VWF concentrates: plasma derived and recombinant)' below.)

Continuous infusion of VWF concentrates may be more challenging to administer than intermittent bolus infusions, and data on the comparative efficacy of the two approaches are very limited.

Monitoring and duration of therapy (VWF concentrates: plasma derived and recombinant)

- **Monitoring** – Although there is no laboratory parameter that adequately predicts the hemostatic effect of VWF concentrates, we follow the clinical status, and, in most individuals, we monitor VWF activity, factor VIII activity, and CBC at least once per day during treatment. An unexpected low VWF response can indicate inhibitor formation, which will require higher doses of concentrate and possibly the addition of other measures. (See "Acquired von Willebrand syndrome", section on 'Management'.)

  - **VWF activity** – A measurement of VWF activity (VWF:RCo or other VWF activity assay) is used to monitor adequate replacement. Typically this is measured once per day except that an initial measurement is evaluated at 6 to 12 hours after the first infusion and at any time that unexpected bleeding occurs. The subsequent daily measurements are most often done at a time just prior to the next injection (a trough level).

    The measures of VWF activity (VWF:RCo, VWF:GPIbR, VWF:GPIbM, and VWF:Ab) are discussed in more detail separately. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM)'.)

  - **Factor VIII activity** – Factor VIII activity should be monitored in individuals treated with VWF concentrates. The goal is to maintain the plasma factor VIII activity above 50 percent (but not more than 200 percent), the former to promote hemostasis and the latter to reduce the risk of VTE. (See 'Adverse effects (VWF concentrates)' below.)

  - **Platelet count** – For individuals with type 2B VWD, monitoring the platelet count is appropriate at the start of treatment and daily thereafter during VWF administration; it can be discontinued when the patient and the platelet counts are stable, usually after three or more days.

  - **CBC and signs of bleeding** – Patients are monitored for signs of bleeding including a clinical examination and daily CBC to note whether the hemoglobin level is stable.

- **Duration of therapy** – The duration of therapy is individualized according to the type of bleeding or surgery, the hemostatic response, and the patient's baseline VWF levels. For serious bleeding or major surgery, we usually continue therapy at the target VWF activity level for 5 to 10 days or more as needed. In some cases, treatment duration may be reduced (eg, a patient who is stable and has accessible sites for which recurrent bleeding can be treated rapidly if needed).

Adverse effects (VWF concentrates) — Adverse effects of VWF concentrates (plasma-derived and recombinant) appear to be minor [7,11]. Since plasma-derived and recombinant VWF

(rVWF) products have not been compared directly, it is not possible to determine whether adverse effects are greater with one or the other, except for the risk of the elevated factor VIII levels when using plasma-derived concentrates (see 'Thrombosis' below). Additional data on adverse effects are awaited.

Thrombosis — Case reports have described VTE in individuals treated with plasma-derived VWF products who had elevated factor VIII levels following prolonged administration (these products contain factor VIII) [12,13]. However, the individuals had additional risk factors for VTE, and it is difficult to determine the role of the VWF concentrates. However, since an association between elevated factor VIII and venous thrombosis has been verified, and the patients receiving VWF concentrate therapy had a high factor VIII level (>200 percent), it seems likely that the elevated factor VIII contributed to the thrombosis. As noted above, it has been recommended that factor VIII levels be followed on a daily basis to avoid levels in excess of 200 percent [14]. (See 'Monitoring and duration of therapy (VWF concentrates: plasma derived and recombinant)' above.)

rVWF does not contain factor VIII, and individuals treated with rVWF generally are not given more than one initial dose of a factor VIII product. Thus, concerns about excessive factor VIII levels are reduced. One patient receiving rVWF was reported to have chest discomfort and tachycardia for 10 minutes following administration, but he did not develop any cardiac events [7].

Allergic reactions — Individuals with VWD may develop a serious allergic reaction to a VWF concentrate, but the likelihood is extremely low.

Inhibitor development — Inhibitors (antibodies against VWF or factor VIII) are uncommon in VWD but have been reported, especially in individuals with type 3 VWD. Some individuals with type 3 VWD due to a gene deletion appear to be at increased risk for inhibitor development [15].

We do not monitor routinely for inhibitors, but we do test for them if there is refractory bleeding and/or the expected response (expected increase in VWF activity) does not occur with infusion of VWF concentrates. (See 'Refractory bleeding' below.)

Once an inhibitor develops, options for therapy become more limited. Bleeding can be treated with a bypassing agent such as recombinant activated factor VII (rFVIIa) [16,17] (see 'Refractory bleeding' below). ITI can be attempted, analogous to ITI in hemophilia, although experience with ITI is extremely limited in VWD. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Immune tolerance induction'.)

Infection — There is always a remote possibility that a plasma derivative could transmit an infection, although VWF concentrates are pasteurized or treated with solvent detergent methods to reduce the risk of transmission of viruses such as hepatitis viruses and HIV and other pathogens.

Evidence for efficacy of VWF concentrates — There are no randomized trials comparing a VWF concentrate with DDAVP (desmopressin) or comparing different VWF concentrates with each other for the management of VWD-associated bleeding or surgery. Available evidence for efficacy comes mainly from single-arm studies or retrospective cohort analyses, typically involving a mixture of VWD subtypes and bleeding severities. rVWF has been studied only in adults.

- **Plasma-derived concentrates**
  - **Children** – Observational studies have demonstrated good to excellent efficacy in infants and children with bleeding or surgery, with most major surgery requiring approximately seven days of therapy [18-20].
  - **Adults** – Observational studies have demonstrated good to excellent efficacy in adults with bleeding or surgery [18,20-23].
- Recombinant VWF **(rVWF)**
  - **Bleeding** – A prospective study demonstrated excellent or good results in 100 percent of 37 bleeding episodes in patients with VWD [7]. In most cases, an initial dose of recombinant factor VIII was administered with the rVWF, and the latter was then given every 8 to 12 hours for three days and up to seven days as needed.
  - **Surgery** – A prospective study showed excellent or good results in 15 of 15 patients with severe VWD who were treated with the product prior to elective surgery [8]. The initial dose of rVWF was given 12 hours before the procedure, allowing endogenous factor VIII to rise to hemostatic levels before surgery in the majority of patients. The remaining dose schedule was similar to that used in the study for patients with bleeding.
  - **Delivery** – A small, retrospective study compared outcomes in six women who were treated with a VWF concentrate during delivery (vaginal or cesarean) [24]. The response was equivalent regardless of whether they received rVWF or plasma-derived VWF.

OTHER THERAPIES

Factor VIII — Individuals with VWD have normal production of factor VIII. von Willebrand factor (VWF) is essential in maintaining a normal factor VIII level in the circulation, since it stabilizes the factor VIII and prevents its degradation. Consequently, individuals who have a severe deficiency of VWF (type 3 VWD) or impaired binding to factor VIII (type 2N VWD) have concomitant factor VIII deficiency that is usually severe enough to contribute to bleeding.

Once a VWF concentrate is administered to a patient with type 3 VWD, the patient's endogenous factor VIII becomes stabilized and the factor VIII levels reach the normal range. However, the synthesis of endogenous factor VIII can take several hours. Thus:

- For major bleeding, a source of factor VIII is often administered either as a component of plasma-derived VWF concentrate or as a separate infusion in individuals treated with recombinant VWF (rVWF).
- For elective major surgery, providing the first dose of rVWF 12 hours before the procedure provides sufficient time to allow the individual's endogenous factor VIII to accumulate.

The dose of factor VIII is similar to that given for a bleeding episode in a patient with hemophilia A (primary factor VIII deficiency). A typical dose is 50 international units/kg by intravenous infusion. No separate infusion of factor VIII is needed when using plasma-derived concentrates, and only a single dose is needed with an rVWF concentrate for type 3 VWD.

For type 2N VWD, the VWF is unable to bind and protect factor VIII; the platelet-related VWF functions are normal. Treatment of type 2N VWD requires administration of VWF concentrates (which bind factor VIII normally), restoring the normal plasma level and half-life of factor VIII. The endogenous production of factor VIII is normal in these patients. (See 'Caveats for uncommon VWD types (2B, 2N, 3)' below.)

Platelet transfusions — Platelet transfusions may be appropriate for individuals who have thrombocytopenia. Thrombocytopenia may occur in individuals with type 2B VWD or from other causes unrelated to VWF. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Summary of VWD types'.)

Platelet transfusions are generally appropriate in an individual with bleeding and a platelet count <50,000/microL (higher for central nervous system bleeding). Details are presented separately. (See "Platelet transfusion: Indications, ordering, and associated risks", section on 'Indications for platelet transfusion'.)

Antifibrinolytic agents and topical products — Antifibrinolytic agents may be used as an adjunct to VWF concentrates. They are especially useful for bleeding involving mucosal sites

(nose, oropharynx, urogenital tract). Available agents include epsilon aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron, Lysteda). Dosing is summarized in the table (table 1) and discussed separately. (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'Antifibrinolytic agents'.)

Topical agents may also be used in combination with other therapies. Examples include Gelfoam or Surgicel soaked in topical thrombin and applied to local areas of bleeding; micronized collagen (Avitene), which is available in strips for packing; and fibrin sealant (using human thrombin). (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'Topical therapies'.)

Additional therapies for acquired VWS — Acquired von Willebrand syndrome (AVWS) refers to reduced VWF activity due to a medical condition that interferes with production or stability of VWF or that leads to production of autoantibodies to endogenous VWF. Examples include lymphoproliferative and autoimmune disorders, certain medications, hypothyroidism, and cardiovascular conditions that cause high sheer stress in the vasculature. (See "Acquired von Willebrand syndrome".)

The majority of these individuals have a decrease in functional high molecular weight VWF multimers, which are the most hemostatically active form of VWF. In many of these patients, bleeding responds to treatment with VWF concentrates, as described above. (See 'VWF concentrates for major bleeding' above.)

Many of these individuals have a decrease in functional high molecular weight VWF multimers, which are the most hemostatically active form of VWF. In general, bleeding responds to treatment with VWF concentrates, as described above. (See "Acquired von Willebrand syndrome", section on 'Management'.)

- Intravenous immune globulin (IVIG) and/or immunosuppression for individuals with autoantibodies that may occur with connective tissue or lymphoproliferative disorders
- Cytoreductive therapies for myeloproliferative neoplasms with very high platelet counts (>1 million/microL) or lymphoproliferative disorders
- Discontinuation of implicated medications such as valproic acid
- Surgical correction for vascular abnormalities such as aortic stenosis that cause high shear stress

Caveats for uncommon VWD types (2B, 2N, 3) — VWD types 2B, 2N, and 3 are uncommon or rare (generally <5 percent of VWD cases) (table 2). Special considerations in the treatment of bleeding or surgery in these individuals include the following:

- **Type 2B** – Type 2B VWD involves a dysfunctional VWF protein with increased binding to platelets, leading to clearance of high molecular weight multimers of VWF and platelets and ultimately decreased VWF levels as well as thrombocytopenia. The decrease in VWF and platelets is accentuated by the release of the dysfunctional VWF that occurs with DDAVP and pregnancy. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Summary of VWD types'.)

  For individuals with type 2B disease who have bleeding, it is important to monitor platelet counts and to provide platelet transfusions when appropriate (platelet count <50,000/microL). (See 'Platelet transfusions' above.)

- **Type 2N** – Type 2N VWD is characterized by a dysfunctional VWF protein that has a decreased binding capacity for factor VIII, leading to increased clearance of factor VIII and factor VIII deficiency. The levels of VWF and its platelet-related functions can be normal (the only abnormality is decreased binding for factor VIII in some patients).

  These individuals with low factor VIII initially need to receive concentrates of both factor VIII and VWF for bleeding or major surgery. Since they are able to produce endogenous factor VIII normally, subsequent doses of VWF do not need to contain factor VIII, and either plasma-derived VWF concentrates or recombinant VWF concentrates may be used. Factor VIII levels should be followed and maintained at 50 to 100 IU/dL for the duration of therapy.

  There is a case report using recombinant factor VIII for surgery in a 2N patient, but the literature is very sparse [25].

- **Type 3** – Type 3 VWD is characterized by the absence of VWF protein, which leads to the reduction of both VWF and factor VIII activities; the patients usually have severe bleeding manifestations. These individuals are treated with VWF concentrates and factor VIII (factor VIII given either as part of a plasma-derived concentrate or as recombinant factor VIII when recombinant von Willebrand factor [rVWF] is used; if rVWF is given, factor VIII is administered with only the first dose).

  Individuals with type 3 VWD may have chronic joint bleeding and intramuscular bleeding similar to hemophilia, especially those with factor VIII activity <5 percent [26]. For these patients, prophylactic VWF infusions should be given. (See 'Chronic bleeding (epistaxis, GI)' below and 'Joint bleeding' below.)

  Individuals with type 3 VWD are at risk of developing an inhibitor in response to VWF administration (risk of inhibitor development, 5 to 10 percent). Evaluation for an inhibitor

and options for treatment are discussed above. (See 'Inhibitors' below.)

REFRACTORY BLEEDING

Some patients may have ongoing bleeding despite von Willebrand factor (VWF) replacement and other therapies. Management of this type of bleeding can be challenging; an expert in managing VWD should be consulted if not already involved in the patient's care.

Additional therapies for refractory bleeding — The following may be helpful:

- Review the initial therapy and laboratory testing to ensure that the correct dose of an appropriate VWF concentrate is being administered and the expected increase in VWF activity is occurring. In some cases, an inhibitor to VWF may develop that causes the half-life of infused VWF to be short; in these cases, more frequent bolus doses or continuous infusion may be more effective. (See 'Monitoring and duration of therapy (VWF concentrates: plasma derived and recombinant)' above and 'Continuous infusion of plasma-derived VWF concentrates' above.)

- Review the possibility that other deficiencies may develop during treatment that require additional treatments to correct such as vitamin K deficiency, thrombocytopenia, or other factor deficiencies. (See 'Refractory bleeding' above.)

- Consider adding an antifibrinolytic agent if mucosal bleeding or surface is involved. (See 'Antifibrinolytic agents and topical products' above.)

- Consider platelet transfusions for refractory bleeding. Platelets contain a protected store of VWF within alpha granules. (See "Overview of hemostasis", section on 'Platelet secretion' and "Platelet transfusion: Indications, ordering, and associated risks", section on 'Ordering platelets'.)

- Consider factor VIII for prophylactic use during serious bleeding and invasive procedures. Several VWD patients with inhibitors who have experienced severe allergic reactions to VWF concentrates have been treated successfully with recombinant factor VIII for bleeding episodes [27,28]. Even though VWF platelet-dependent activity is absent, the contribution of factor VIII to clot formation may be sufficient in these situations. A shortened half-life of factor VIII can be expected, and frequent doses may be necessary. (See 'Inhibitors' below.)

Inhibitors — Inhibitors (alloantibodies to infused VWF) can rarely develop, especially in individuals with type 3 VWD (absent VWF), for whom the infused VWF may be recognized as a foreign protein (see 'Adverse effects (VWF concentrates)' above). Inhibitors develop much less

frequently in individuals with VWD than in people with hemophilia A (inhibitor prevalence in type 3 VWD, approximately 6 to 10 percent) [2,29].

Inhibitors often present with a reduced response to infusions of VWF concentrates or, uncommonly, with anaphylaxis upon exposure to VWF. We check for an inhibitor if the individual has symptoms of ongoing bleeding despite appropriate VWF therapy or allergic symptoms, including anaphylaxis. We also check the level of VWF activity 6 to 12 hours after infusion to evaluate the rise in VWF activity.

Mixing studies seldom show evidence of an inhibitor, since the majority of inhibitors are non-neutralizing (ie, they increase VWF clearance but do not inhibit VWF function); evaluation is generally done by measuring the recovery of infused VWF over time to see the rise in VWF and its duration in the circulation. One may also measure the VWF propeptide level and compare with the VWF level [30]. (See "Acquired von Willebrand syndrome".)

Management of bleeding in individuals with inhibitors is challenging. Options include higher dose or more frequent bolus injections, continuous infusion of VWF rather than intermittent dosing, and administration of prohemostatic therapies such as rFVIIa. (See 'Continuous infusion of plasma-derived VWF concentrates' above and 'Additional therapies for refractory bleeding' above.)

Recombinant factor VIII has been used successfully during serious bleeding and invasive procedures in several patients with allergic reactions to VWF concentrates [27,28]. Even though VWF platelet-dependent activity is absent, the contribution of factor VIII to clot formation may be sufficient in some situations. A shortened half-life of recombinant factor VIII can be expected, and frequent doses may be necessary.

A case report has described the successful use of emicizumab in a VWD patient with an inhibitor to VWF. Emicizumab is a monoclonal antibody therapy for hemophilia A that is administered as regular prophylaxis and substitutes for the role of factor VIII in hemostasis [31]. (See "Hemophilia A and B: Routine management including prophylaxis", section on 'Emicizumab for hemophilia A'.)

Experience with immune tolerance induction (ITI) in VWD is quite limited compared with this approach in hemophilia A, but ITI has been used successfully to reduce antibody production in VWD [32]. (See "Inhibitors in hemophilia: Mechanisms, prevalence, diagnosis, and eradication", section on 'Immune tolerance induction'.)

OTHER TYPES OF BLEEDING

Gynecologic and obstetric bleeding — These are discussed separately. (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations".)

Chronic bleeding (epistaxis, GI) — For patients with severe and frequent bleeds (eg, joint and muscle bleeds, recurrent gastrointestinal (GI) bleeding, severe epistaxis, heavy menstrual bleeding unresponsive to other therapies) long term prophylaxis with a VWF concentrate should be used [4]. Recurrent GI bleeding may be treated with VWF concentrates as needed (ie, on demand) or with prophylactic VWF concentrate infusions, similar to other types of bleeding.

In addition to VWF concentrates, it is important to give treatment specific to the cause of bleeding, which may include a proton pump inhibitor in peptic ulcer disease. In addition to the usual causes of GI bleeding such as peptic ulcers, individuals with VWD have a high prevalence of angiodysplasia in the GI tract. This is thought to be due to the role of VWF in angiogenesis; the angiodysplastic lesions are hypothesized to develop due to alterations in the gastrointestinal vasculature that arise in the absence of normal VWF levels [33]. (See "Acquired von Willebrand syndrome", section on 'Consequences of reduced VWF'.)

Individuals with VWD who have GI bleeding should be evaluated for GI angiodysplasia if other causes for the bleeding are not found. Angiodysplastic lesions are commonly associated with more severe types of VWD and often cause recurrent bleeding [34]. Patients who have recurrent GI bleeding due to angiodysplasia may benefit from treatment with antiangiogenic agents such as atorvastatin in addition to VWF concentrate prophylaxis [35]. A review discusses the subject in detail [36]. Treatment decisions should be individualized and discussed with an expert in bleeding disorders. (See "Overview of angiogenesis inhibitors", section on 'Immunomodulatory drugs (IMiDs)'.)

Several studies have demonstrated that regular prophylaxis can provide dramatic reductions in chronic bleeding of various types (epistaxis, oral or GI bleeding, joint bleeding, heavy menstrual bleeding) and can reduce hospitalizations [37-41].

The approach using chronic VWF administration is most likely to be appropriate in individuals with one or more of the following:

- Frequent or chronic bleeding that recurs, usually in the same site, despite appropriate on-demand (intermittent) therapy
- Bleeding that interferes with daily activities, school attendance, or work
- Bleeding that adversely affects quality of life

An antifibrinolytic agent may also be given, particularly if the bleeding is in a site of high fibrinolytic activity (eg, epistaxis). (See "von Willebrand disease (VWD): Treatment of minor

bleeding, use of DDAVP, and routine preventive care", section on 'Antifibrinolytic agents'.)

An international group was organized to determine how to administer long-term replacement VWF to severely affected patients (eg, chronic epistaxis, gastrointestinal bleeding, menstrual bleeding, or joint bleeding) using a prophylactic schedule. Their initial study indicated that in 10 patients using an escalating dose frequency that began with a once weekly schedule of 50 international units/kg and escalated to three times per week if necessary, the bleeding rate had decreased significantly (mean annualized bleeding rate decreased from 25 to 6.1) [40].

An open-label randomized trial involving 19 individuals showed that prophylactic treatment was associated with a decrease in bleeding compared with on-demand treatment given at the time of bleeding [42].

A study involving 2790 VWD patients followed over 22 years showed that individuals with VWD had twice as many hospitalizations and outpatient visits as matched controls; in a subgroup of the VWD patients, prophylactic therapy decreased hospitalizations by one-half [41].

Joint bleeding — Individuals with severe VWD, especially type 3, can experience joint or soft tissue bleeding similar to that seen in people with hemophilia. Acute management is similar to that for other serious bleeding in VWD with the addition of orthopedic consultation. Prophylactic infusions of von Willebrand factor (VWF) may be helpful if there is recurrent bleeding into the same joint or soft tissue. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'Musculoskeletal bleeding' and 'Chronic bleeding (epistaxis, GI)' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: von Willebrand disease".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more

sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: von Willebrand disease (The Basics)")
- Beyond the Basics topic (see "Patient education: von Willebrand disease (Beyond the Basics)")

PATIENT PERSPECTIVE TOPIC

Patient perspectives are provided for selected disorders to help clinicians better understand the patient experience and patient concerns. These narratives may offer insights into patient values and preferences not included in other UpToDate topics. (See "Patient perspective: von Willebrand disease".)

SUMMARY AND RECOMMENDATIONS

- **Available therapies** – VWF levels can be raised with VWF concentrates or DDAVP (desmopressin) (table 1). Cryoprecipitate should only be used if no VWF concentrate is available. Tranexamic acid and topical agents may be used as adjunctive treatment. (See 'Overview of approach' above and "Cryoprecipitate and fibrinogen concentrate" and 'Antifibrinolytic agents and topical products' above.)
- **Choice of therapy** – For individuals with major bleeding or major surgery, we recommend a VWF concentrate (plasma-derived or recombinant) rather than DDAVP. (**Grade 1B**). DDAVP is only effective in some individuals, produces a smaller increase in VWF activity, and has a later onset and shorter duration of action. (See 'Evidence for efficacy of VWF concentrates' above.)
- **Dosing**
  - **Plasma-derived concentrate** – The initial dose of plasma-derived VWF concentrate is in the range of 40 to 60 units/kg (measured in VWF activity). This will raise the VWF activity (VWF:RCo or VWF:GPIbM) and factor VIII activity to approximately 100 IU/dL. For

elective major surgery, the plasma-derived VWF concentrate is given 30 to 60 minutes prior to the procedure. Subsequent doses of VWF are given with monitoring to maintain plasma VWF and factor VIII activity levels >50 IU/dL. (See 'Plasma-derived VWF concentrates' above.)

- Recombinant VWF – Recombinant VWF (rVWF) is only approved for adults and does not contain factor VIII. It carries less exposure to plasma proteins and has a longer half-life. If rVWF is used for bleeding or emergency surgery, a dose of factor VIII is given, or in the case of elective surgery, the product may be given 12 hours in advance to allow endogenous factor VIII to increase. Individuals with type 2N VWD require factor VIII with the first rVWF dose. (See 'Recombinant VWF (rVWF) concentrates' above and 'Factor VIII' above.)

- **Platelet transfusions (type 2B) and inhibitors (type 3)** – People with type 2B VWD may require platelet transfusions in addition to VWF concentrate. Individuals with type 3 VWD may develop inhibitors to infused VWF. (See 'Platelet transfusions' above and 'Caveats for uncommon VWD types (2B, 2N, 3)' above.)

- **Monitoring and duration of therapy** – VWF activity, factor VIII activity, and a complete blood count (CBC) should be monitored approximately once per day during treatment. The duration of therapy is individualized. We typically continue the VWF concentrate for five or more days for major bleeding or surgery. (See 'Monitoring and duration of therapy (VWF concentrates: plasma derived and recombinant)' above and 'Caveats for uncommon VWD types (2B, 2N, 3)' above.)

- **Other bleeding scenarios**

  - **AVWS** – Other therapies may be appropriate such as intravenous immune globulin (IVIG). (See 'Additional therapies for acquired VWS' above and "Acquired von Willebrand syndrome", section on 'Management'.)

  - **Refractory bleeding** – Refractory bleeding may require additional hemostatic therapies such as factor VIII concentrates, platelet transfusions, or recombinant activated factor VII (rFVIIa). Individuals who do not have an increase or have an unexpectedly low response in plasma VWF activity after administration of VWF concentrates, especially those with type 3 VWD, may require testing for an inhibitor (an alloantibody against infused VWF or factor VIII) and may be treated with continuous infusion of VWF as well as the additional measures above. (See 'Refractory bleeding' above and 'Continuous infusion of plasma-derived VWF concentrates' above.)

- **Chronic bleeding or joint bleeding** – For patients with frequent or serious recurrent bleeding, prophylactic administration of VWF concentrates should be used. (See 'Chronic bleeding (epistaxis, GI)' above and 'Joint bleeding' above.)

- **Heavy menstrual and postpartum bleeding** – (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations".)

- **Minor bleeding** – Minor bleeding and minor surgery can often be controlled with DDAVP, provided a response has been demonstrated. (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care".)

- **Diagnosis and pathophysiology** – (See "Clinical presentation and diagnosis of von Willebrand disease" and "Pathophysiology of von Willebrand disease".)

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Topic 1372 Version 42.0

GRAPHICS

Therapies that can be used to treat VWD and AVWS

Medication	Dose	Comments
DDAVP	▪ **Intravenous:** 0.3 mcg/kg (maximum dose, 20 mcg) in 50 mL saline over 20 minutes **or** ▪ **Nasal spray:** Weight >50 kg: 300 mcg (1 spray in each nostril); weight <50 kg: 150 mcg (1 spray in 1 nostril)	▪ Adequate response to a test dose is ideally established before use, but a patient with AVWS and acute bleedin may receive the first dose as a therapeutic trial ▪ Use caution when an antifibrinolytic agent is given concurrently due to risk of thrombosis ▪ Dose may be repeated after 12 hours and 24 hours ▪ Tachyphylaxis and hyponatremia may occur; monitor hemostasis and serum sodium ▪ Thrombocytopenia may worsen in some type 2B patients
VWF concentrates (these contain all VWF multimers)	▪ **Major bleeding or surgery:** Initial dose 40 to 60 ristocetin cofactor units/kg followed by 20 to 40 ristocetin cofactor units/kg every 12 to 24 hours to keep VWF level 50 to 100 international units/dL for 7 to 14 days, or as indicated clinically ▪ **Minor bleeding or surgery:** Initial dose 30 to 60 ristocetin cofactor units/kg followed by 20 to 40 ristocetin cofactor units/kg every 12 to 48 hours to keep VWF level >30 international units/dL for 3 to 5 days, or less as indicated clinically	▪ Dose and duration based on clinical experience ▪ Case reports have described the use of continuous infusion (2 to 15 international units/kg per hour) in cases of serious bleeding that does not respond to intermittent dosing ▪ Increased doses or more frequent administration may be necessary in AVWS
Recombinant VWF	▪ **Major bleeding or surgery:** Initial dose 50 to 80 international units/kg, followed by 40 to 60 international units/kg every 8 to 24 hours to keep the VWF level 50 to 100 international units/kg for 2 to 3 days or longer, as needed clinically	▪ In patients with less than 40% factor VIII activity, 1 dose of recombinant factor VIII is given (dose ratio of 1 to 1.3 for rFVIII to rVWF) within 10 minutes of the first dose of rVWF ▪ Published studies using rVWF are limited, and more data are needed to assess responses in patients of

	▪ **Minor bleeding or surgery:** Initial dose 40 to 50 international units/kg, followed by 40 to 50 international units/kg every 8 to 24 hours as needed clinically	differing ages and severities of VWD and in specific clinical settings
Antifibrinolytic agents	▪ Aminocaproic acid, 25 to 50 mg/kg per dose orally (maximum 5 g dose) 4 times per day **or** ▪ Tranexamic acid, 25 mg/kg per dose orally every 6 to 8 hours or 10 mg/kg intravenously 3 times per day	▪ Can be used alone or in conjunction with other therapies; use caution when combined with DDAVP ▪ Especially useful for mucosal bleeding (often used for dental procedures) ▪ Dose reduction may be required in patients with impaired kidney function
IVIG (only applies to AVWS)	▪ 1 g/kg intravenously once daily for 2 days*	▪ May be particularly helpful in monoclonal gammopathies ▪ May be used in conjunction with VWF concentrates and/or DDAVP, particularly when treating AVWS associated with autoimmune disease

Refer to UpToDate topics on the management of VWD and AVWS for additional information.

VWD: von Willebrand disease; AVWS: acquired von Willebrand syndrome; DDAVP: desmopressin; VWF: von Willebrand factor; rFVIII: recombinant factor VIII; rVWF: recombinant VWF; IVIG: intravenous immune globulin.

* Divided doses may be required; refer to UpToDate topics on IVIG for details.

Adapted from: Rick ME. Diagnosis and management of von Willebrand's syndrome. Med Clin North Am 1994; 78:609. Copyright 1994 WB Saunders.

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Classification of inherited von Willebrand disease (VWD)

Type	Clinical features	Laboratory findings	Comments on treatment
Type 1 (partial quantitative deficiency)	▪ Accounts for approximately 75% of individuals with VWD ▪ Variable bleeding severity from mild to severe ▪ AD inheritance	▪ VWF activity and antigen decreased concordantly ▪ Factor VIII activity normal or reduced ▪ RIPA decreased (may be normal in mild disease) ▪ Multimer electrophoresis: All multimers present and uniformly decreased ▪ In type 1C (increased clearance), the VWF level at 4 hours post DDAVP trial shows rapid reduction in VWF	▪ DDAVP* in most patients ▪ VWF concentrates in moderate, severe, and type 1C patients
Type 2 (qualitative variant)			
Type 2A (selective deficiency of HMW multimers, reduced binding to platelet GPIb)	▪ Accounts for approximately 10 to 20% of individuals with VWD ▪ Moderate to severe bleeding ▪ Mostly AD; occasional AR inheritance	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or reduced ▪ RIPA decreased ▪ Multimer electrophoresis: Large multimers decreased	▪ DDAVP* ▪ VWF concentrates in moderate and severe patients ▪ Follow VWF levels
Type 2B (enhanced binding of HMW VWF multimers to platelet GPIb; may have decrease in	▪ Accounts for approximately 5% of individuals with VWD ▪ Moderate to severe bleeding ▪ Thrombocytopenia	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or reduced	▪ DDAVP* should be used with caution; it may be used to treat minor bleeding if a trial of DDAVP performed when the

circulating HMW multimers)	▪ AD inheritance	▪ Thrombocytopenia ▪ RIPA increased ▪ Multimer electrophoresis: Usually decreased large multimers	patient is not bleeding has demonstrated that the platelet count drop is temporary. Many experts will avoid DDAVP even for a temporary platelet count drop. ▪ VWF concentrates in moderate and severe patients
Type 2M (reduced binding of VWF to platelet GPIb)	▪ Uncommon ▪ Moderate to severe bleeding ▪ AD or AR inheritance	▪ VWF activity decreased out of proportion to VWF antigen ▪ Factor VIII activity normal or decreased ▪ RIPA decreased ▪ Multimer electrophoresis: All multimers present and uniformly decreased	▪ DDAVP* ▪ VWF concentrates in moderate and severe patients
Type 2N (reduced binding of VWF to factor VIII)	▪ Uncommon ▪ Clinically similar to hemophilia A with joint, soft tissue, and urinary bleeding ▪ AR inheritance	▪ VWF activity and antigen normal ▪ Factor VIII levels low (5 to 15%) ▪ RIPA normal ▪ Multimer electrophoresis: Normal	▪ DDAVP* ▪ VWF concentrates ▪ Monitor VWF and factor VIII levels
Type 3 (severe quantitative deficiency/absent VWF)	▪ Rare ▪ Clinically similar to hemophilia A with joint and soft tissue bleeding in addition to mucocutaneous bleeding ▪ AR inheritance	▪ VWF activity and antigen absent or markedly decreased ▪ Factor VIII levels low (1 to 10%) ▪ RIPA absent or very low ▪ Multimer electrophoresis: Undetectable or too faint to visualize	▪ VWF concentrates ▪ Factor VIII replacement ▪ Do **not** use DDAVP to treat bleeding (will not be effective)

This table summarizes types of inherited VWD. Acquired von Willebrand syndrome (AVWS) is an acquired condition (not genetically transmitted) that mimics inherited VWD; AVWS has various underlying causes. Refer to UpToDate for additional details of the presentation, diagnosis, and management of VWD and AVWS.

AD: autosomal dominant; AR: autosomal recessive; AVWS: acquired von Willebrand syndrome; DDAVP: desmopressin; GPIb: platelet glycoprotein Ib; HMW: high molecular weight; RIPA: ristocetin-induced platelet aggregation; VWD: von Willebrand disease; VWF: von Willebrand factor.

* DDAVP should only be used after a therapeutic trial (when not bleeding) shows efficacy in raising VWF levels (or factor VIII levels in type 2N disease) to >50%.

Adapted from:

1. *Sadler JE, Budde U, Eikenboom JCJ, et al. Update on the pathophysiology and classification of von Willebrand disease: A report of the Subcommittee on von Willebrand factor. J Thromb Haemost 2006; 4:2103.*
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