von Willebrand Disease
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History
von Willebrand disease (VWD) first was described in 1926 by a Finnish physician named Dr. Erik von Willebrand. In the original publication [1] he described a severe mucocutaneous bleeding problem in a family living on the Åland archipelago in the Baltic Sea. The index case in this family, a young woman named Hjördis, bled to death during her fourth menstrual period. At least four other family members died from severe bleeding and, although the condition originally was referred to as “pseudohemophilia,” Dr. von Willebrand noted that in contrast to hemophilia, both genders were affected. He also noted that affected individuals exhibited prolonged bleeding times despite normal platelet counts.

In the mid-1950s, it was recognized that the condition usually was accompanied by a reduced level of factor VIII (FVIII) activity and that the bleeding phenotype could be corrected by the infusion of normal plasma. In the early 1970s, the critical immunologic distinction between FVIII and von Willebrand factor (VWF) was made and since that time significant progress has been made in understanding the molecular pathophysiology of this condition.

\begin{itemize}
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\end{itemize}
von Willebrand factor

Cloning and characterization of the \textit{VWF} gene, by four groups simultaneously in 1985 [2–5], has facilitated understanding of the molecular biology of VWD. Located on the short arm of chromosome 12 at p13.3, the \textit{VWF} gene spans 178 kilobases (kb) and comprises 52 exons that range in size from 1.3 kb (exon 28) to 40 base pairs (bp) (exon 50) [6]. The encoded VWF mRNA is 9 kb in length and the translated pre-pro-VWF molecule contains 2813 amino acids (AA), comprising a 22 AA signal peptide, a 741 AA propolypeptide, and a 2050 AA-secreted mature subunit that possesses all the adhesive sites required for VWF’s hemostatic function [7]. There is a partial, unprocessed pseudogene located on chromosome 22, which duplicates the \textit{VWF} gene sequence for exons 23–34 with 97% sequence homology [8]. Also, the \textit{VWF} gene is highly polymorphic, and to date, 140 polymorphisms are reported, including promoter polymorphisms, a highly variable tetranucleotide repeat in intron 40, two insertion/deletion polymorphisms, and 132 distinct single nucleotide polymorphisms involving exon and intron sequences [9].

VWF is synthesized in endothelial cells [10] and megakaryocytes [11] as a protein subunit that undergoes a complex series of post-translational modifications, including dimerization, glycosylation, sulfation, and ultimately multimerization. The fully processed protein then is released into the circulation or stored in specialized organelles: the Weibel-Palade bodies of endothelial cells or the \textit{\alpha}-granules of platelets. VWF is secreted into the plasma, where it circulates as a very large protein that has a molecular weight ranging from 500 to 20,000 kd depending on the extent of subunit multimerization [12]. After secretion, under the influence of shear flow, high-molecular-weight (HMW) VWF, multimers undergo partial proteolysis mediated by the ADAMTS-13 plasma protease (\textit{A Disintegrin And Metalloprotease with Thrombopondin type 1 motif, member 13}), with cleavage occurring between AA residues tyrosine 1605 and methionine 1606 in the A2 domain of the VWF protein [13].

VWF is a multifunctional adhesive protein that plays major hemostatic roles, including:

A critical role in the initial cellular stages of the hemostatic process. VWF binds to the platelet glycoprotein (GP)Ib/IX receptor complex to initiate platelet adhesion to the subendothelium [14]. After adhesion, platelet activation results in the exposure of the GPIIb/IIIa integrin receptor through which VWF and fibrinogen mediate platelet aggregation (Fig. 1) [15].

As a carrier protein for the procoagulant cofactor FVIII. VWF binds to and stabilizes FVIII; therefore, low levels of VWF or defective binding of VWF to FVIII results in correspondingly low levels of FVIII because of its accelerated proteolytic degradation by activated protein C [16].
Clinical features of von Willebrand disease

VWD is stated as the most common inherited bleeding disorder known in humans. This is based on two large epidemiologic studies that reported the prevalence of VWD in healthy school-aged children to be approximately 1% [17,18]. More recent studies, however, suggest that the prevalence of individuals who have VWD who present to primary care physicians with symptomatic bleeding or bruising is closer to 1 in 1000 [19]. The number of individuals referred to a tertiary care center for management of VWD is much lower, at approximately 1 in 10,000 [20].

VWD is characterized by three key features: a personal history of excessive mucocutaneous bleeding, abnormal VWF laboratory studies, and evidence of a family history of the condition. A diagnostic algorithm for possible VWD cases is presented in Fig. 2.

Bleeding histories

The clinical hallmark of VWD is the presence of excessive and prolonged mucocutaneous bleeding. Most often, this involves bruising, epistaxis, bleeding from the gums and trivial wounds, and menorrhagia and postpartum hemorrhage in women. Prolonged and excessive bleeding also occurs
after surgical and dental procedures. Children who have VWD also may experience bruising after routine immunizations and gum bleeding after the loss of primary teeth. Typically, only patients who have type 3 VWD (characterized by an absence of VWF, accompanied by low FVIII levels, less than 0.10 IU/mL [10%]) experience spontaneous musculoskeletal bleeding, such as that seen in patients who have severe hemophilia. An accurate assessment of hemorrhagic symptoms is a key component in diagnosing VWD but often presents a significant challenge, particularly in the pediatric population.

Although bruising and epistaxis are common among children who have VWD, these symptoms also are reported in normal children. An additional consideration is that bleeding symptoms manifest in children in distinctly different ways compared with adults. Some of the classical symptoms of VWD in adults (eg, menorrhagia and postsurgical bleeding) are not prevalent in the pediatric population. Children who have a bleeding disorder may not have had surgery or (in the case of girls) reached the age of menarche; however, they may have symptoms that cause difficulty and merit treatment. To address these issues, there has been significant recent interest in developing new clinical tools for quantifying bleeding, and although much of this work has focused on adult populations, tools have been developed that are specific to pediatrics [21]. The Epistaxis Scoring System is a semiquantitative system, in which children with recurrent epistaxis are either categorized as “mild” or “severe,” and represents one such tool [22].

Fig. 2. A proposed diagnostic algorithm for possible VWD cases.
Abnormal von Willebrand factor laboratory studies

The laboratory evaluation for VWD involves qualitative and quantitative measurements of VWF and FVIII. The results from affected individuals are highly variable, ranging from the near complete absence of VWF in type 3 VWD to modest quantitative reductions in VWF and FVIII levels as seen in type 1 VWD. The type 2 variants are characterized by qualitative abnormalities in VWF and include four subtypes, 2A, 2B, 2M, and 2N (see classification later). It is critical that the laboratory investigations for VWD be interpreted by physicians who have experience in this area, given the heterogeneity of possible results.

Although it is important to perform screening tests in the diagnostic work-up of patients who have possible VWD, it also is important to recognize the limitations of these tests. The complete blood count can be completely normal in individuals who have VWD but may show evidence of an iron deficiency anemia resulting from chronic blood loss; type 2B VWD often is associated with mild thrombocytopenia. If the VWF level is reduced to levels less than approximately 0.35 IU/mL (35%), the commensurate low level of FVIII may result in the prolongation of the activated partial thromboplastin time (aPTT); however a normal aPTT does not rule out VWD, particularly in milder cases. The bleeding time may be prolonged; however, this test lacks sensitivity and specificity and patients who have known VWD may have normal bleeding times. Parenthetically, the bleeding time is poorly reproducible and invasive and no longer should be a routine component of the investigation of children who have possible VWD. Recently, a newer analyzer, known as the PFA-100, has been evaluated in the diagnostic work-up of VWD. Its reported sensitivity for VWD is high (ranging from 71%–97%); however, given that it is a test of global hemostasis, the specificity is lower. As a result, the PFA-100 may have a role as a screening test; however, its precise clinical usefulness remains unresolved.

Laboratory tests specific for VWD include a measurement of the amount of circulating plasma VWF antigen, a measurement of the VWF function (a ristocetin-based platelet aggregation test, known as the VWF ristocetin cofactor assay [VWF:RCo] [26], or the VWF collagen-binding assay) [27] and a measurement of FVIII coagulant activity. One other VWF test also uses ristocetin, the ristocetin-induced platelet agglutination (RIPA) assay. In contrast to the VWF:RCo (which evaluates the interaction between patients’ VWF and formalin-fixed platelets), the RIPA assay evaluates the sensitivity of patients’ platelets to low-dose ristocetin and is useful particularly in identifying individuals who have type 2B VWD. In these cases, the platelet membrane is “overloaded” with high-affinity mutant VWF, resulting in platelet agglutination at low ristocetin concentrations, less than 0.6 mg/mL [27]. The final laboratory test performed to characterize VWD involves the assessment of the molecular-weight profile of circulating plasma VWF [28]. As discussed previously, VWF circulates in the plasma as
a heterogenous mixture of multimers. HMW multimers are the most hemostatically active, as they contain the most active binding sites for platelets, and characteristically are absent in some type 2 forms of VWD. The molecular-weight profile of VWF is evaluated most often using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), which is technically challenging and available only in a few laboratories (Fig. 3). Recent efforts have been made to simplify and enhance the objectivity of this assay by combining nonradioactive, chemiluminescent detection methods with densitometric analysis of the multimer bands.

Normal plasma levels of VWF are approximately 1 U/mL (100%, correlating to approximately 10 μg/mL) with a wide population range of 0.50 to 2.0 U/mL (50%–200%). These variations are influenced by several genetic and environmental factors. ABO blood group is the genetic influence characterized best; VWF and FVIII levels in individuals who have blood group O are approximately 25% lower than individuals who have blood group A, B, or AB [29]. This difference is believed a result of the lack of glycosylation (and therefore stabilization) of VWF in individuals who are in blood group O. Two major environmental factors affecting VWF levels are stress and hormones. The plasma levels of VWF and FVIII increase approximately twofold to fivefold during physiologic stress, such as fainting [30] or exercise [31]. VWF and FVIII levels also fluctuate over the course of a menstrual cycle and under the influence of oral contraceptive pills and pregnancy [32]. Additionally, VWF levels vary with age, with neonatal levels higher than adult levels [33,34], although many laboratories do not report agespecific normal ranges. These factors all must be considered when interpreting VWF laboratory results and, as a result, most clinicians support at least two sets of tests to confirm or refute a diagnosis of VWD.

![Fig. 3. VMF multimer analysis. Multimer analysis in two patients who have type 2 VWD. Lanes 1 and 4 represent normal plasma multimer patterns. Lane 2 shows the plasma VWF multimers for a patient who had type 2A and lane 3 the plasma multimers for a patient who has type 2B VWD. LMW, low molecular weight.](image-url)
Family history

Most cases of VWD are inherited, and often there is evidence of a family history of excessive bleeding. This issue is complicated, however, by some forms of the disease showing incomplete penetrance of bleeding symptoms. As a result, many clinicians do not consider the lack of a positive family history (especially in type 1 VWD) an exclusion criterion. The disease is inherited as a dominant trait in type 1 and in the qualitative variants types 2A, 2B, and 2M. In contrast, the rare type 2N and severe type 3 forms of the disease show a recessive pattern of inheritance.

Classification of von Willebrand disease

The current International Society on Thrombosis and Haemostasis established classification of VWD comprises three types: type 1 VWD, a partial quantitative deficiency of qualitatively normal VWF; type 2 VWD, a qualitative deficiency caused by functionally abnormal VWF; and type 3 VWD, which represents a virtual absence of the VWF protein (Table 1) [35].

Type 1 von Willebrand disease

Type 1 VWD, which represents approximately 80% of VWD cases unfortunately is the most difficult subtype of VWD to diagnose. As discussed previously, circulating VWF levels are influenced by several factors, and there is overlap between normal individuals who have VWF levels at the lower end of the normal range and those who have mild type 1 VWD. Additionally, mucocutaneous bleeding symptoms in individuals who have type 1 VWD can be mild and potentially overlooked by patients and physicians. Convincing family histories may be absent, given the incomplete penetrance of this subtype. Consideration of all of these factors has led to much recent debate about the proper definition of this disorder [36]. The suggestion has been made that a diagnosis of type 1 VWD be reserved for individuals who have significant reductions in VWF to less than 0.15 IU/mL (15%); although this may not have become a widely accepted clinical definition, it highlights the importance

Table 1
Characteristic laboratory findings in von Willebrand disease by subtype

<table>
<thead>
<tr>
<th>von Willebrand disease subtype</th>
<th>VWF:Ag</th>
<th>VWF:RCo</th>
<th>FVIII:C ratio</th>
<th>RCo:Ag ratio</th>
<th>Multimer pattern</th>
<th>RIPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↓</td>
<td>↓</td>
<td>↓ or ↔</td>
<td>&gt;0.60</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>2A</td>
<td>↓</td>
<td>↓↓</td>
<td>↓ or ↔</td>
<td>&lt;0.60</td>
<td>Abnormal</td>
<td>↓</td>
</tr>
<tr>
<td>2B</td>
<td>↓</td>
<td>↓↓</td>
<td>↓ or ↔</td>
<td>&lt;0.60</td>
<td>Abnormal</td>
<td>↑</td>
</tr>
<tr>
<td>2M</td>
<td>↓</td>
<td>↓↓</td>
<td>↓ or ↔</td>
<td>&lt;0.60</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>2N</td>
<td>↓ or ↔</td>
<td>↓ or ↔</td>
<td>0.10–0.40</td>
<td>&gt;0.60</td>
<td>Normal</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
<td>&lt;0.10</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: FVIII:C, Factor VIII coagulant activity; RCo:Ag Ratio, VWF, ristocetin cofactor/VWF antigen ratio.
of considering a diagnosis carefully. Assigning an incorrect diagnostic label of VWD to patients can be difficult to revise subsequently and may lead to confusion and inappropriate management. In addition, the wider implications of this diagnosis, including the potential social stigma and health insurance implications, should be considered carefully before making a diagnosis. In contrast, underdiagnosis of type 1 VWD can be a concern in young children who may not have been subjected to a sufficient hemostatic challenge to manifest a bleeding tendency that would lead to consideration of a diagnosis of VWD. Taking all of these factors into consideration, a suggested definition of type 1 VWD in children could include both definite (for children with excessive mucocutaneous bleeding and low VWF levels) and possible (for children with low VWF levels but no history of excessive mucocutaneous bleeding potentially because of the lack of opportunity).

The genetic basis of type 1 VWD has been the focus of much recent investigation, and two large multicenter trials have reported consistent results [37,38]. Mutations throughout the VWF gene were identified in approximately 65% of index cases and the majority of these were missense mutations. Mutations were identified more frequently in cases of lower VWF levels and more highly penetrant in those cases. The genetic variation reported most frequently identified in both studies was a missense mutation resulting in an AA substitution of tyrosine to cysteine at codon 1584 (Y1584C), identified in 10% to 20% of patients who had type 1 VWD [39]. In both studies, however, some patients who had type 1 VWD had no obvious VWF mutation identified, and in these (often milder) cases, the genetic determinants likely are more complex and could involve other genetic loci. At this time, genetic testing for type 1 VWD generally is neither available nor required for establishing the diagnosis.

Type 2 von Willebrand disease

Type 2 VWD is characterized by a qualitative deficiency of VWF activity and is classified further into the qualitative variants that affect VWF-platelet interactions (2A, 2B, and 2M) and the rare type 2N characterized by defective VWF binding to FVIII. The clinical presentation of type 2 VWD is similar to type 1 VWD in that patients present with excessive mucocutaneous bleeding; however, in contrast to the variably positive family histories in type 1 VWD, patients who have type 2 VWD usually present with a clearly positive family history.

Type 2A

Type 2A VWD accounts for approximately 10% of all VWD cases and is characterized by the loss of HMW and intermediate-molecular-weight multimers. This is the result of a defect in the synthesis of the higher-molecular-weight multimers (group 1 mutations) or the synthesis of multimers that are more susceptible to cleavage by ADAMTS-13 (group 2 mutations) [40]. Type 2A can be suspected because of disproportionately low functional
activity compared with von Willebrand factor antigen level (VWF:Ag) (ie, VWF:RCo to VWF:Ag ratio of <0.60). The FVIII level may be low or normal. RIPA is reduced and the multimer profile shows a loss of HMW and sometimes intermediate-molecular-weight multimers. The molecular genetic basis of type 2A VWD is well characterized, with missense mutations in the VWF A2 domain predominating. Other type 2A cases are caused by mutations that disrupt dimerization or multimerization; these mutations are located outside of the A2 domain (Fig. 4).

**Type 2B**

Type 2B VWD is the result of gain-of-function mutations within the GpIb-binding site on VWF. This leads to an increase in VWF-platelet interactions that result in the selective depletion of HMW multimers [27,41]. The increased binding of mutant VWF to platelets also results in the formation of circulating platelet aggregates and subsequent thrombocytopenia. As in type 2A VWD, the laboratory profile shows a decrease in VWF:RCo to VWF:Ag ratio; however, in contrast to 2A, there is increased sensitivity to low doses of ristocetin in the RIPA. HMW multimers are absent in the plasma. Type 2B mutations are well characterized and represent a variety of different missense mutations in the region of the VWF gene encoding the GpIb-binding site in the A1 protein domain. A disorder known as platelet-type VWD (PT-VWD) exhibits identical clinical and laboratory features to those of type 2B VWD [42]. This condition is caused by mutations within the platelet GPIB gene that affect the region of the GPIb/IX receptor that binds to VWF [43]. It can be distinguished from type 2B VWD using platelet aggregation tests that identify enhanced ristocetin-induced binding of VWF, by mixing combinations of patient and normal plasma with patient and normal washed platelets. In rare cases, genetic analysis of the A1 domain of the VWF gene and the GPIB gene can be performed. It is assumed that PT-VWD is less prevalent than type 2B VWD although the level of misdiagnosis is not known. The distinction is important, however, because the treatment is plasma based in type 2B VWD and platelet based in PT-VWD.

**Fig. 4.** Type 2 VWD mutations. Repeating multidomain structure of the VWF protein. The regions of the protein comprising the prepropolyptide and mature VWF subunits are indicated at the bottom of the diagram. Regions of the protein in which the causative mutations for types 2A, 2B, 2M, and 2N VWD are shown above the protein diagram.
Type 2M

Type 2M VWD (the “M” refers to multimer) is characterized by decreased VWF-platelet interactions. The laboratory work-up shows a reduced ratio of VWF:RCo to VWF:Ag but a normal multimer pattern. RIPA also is reduced. Causative mutations are localized to the platelet GPIB-binding site in the A1 domain of VWF [44].

Type 2N

Type 2N VWD (the “N” refers to Normandy, where the first cases were reported) is described as an autosomal form of hemophilia A [45] and is an important differential in the investigation of all individuals (male and female) presenting with a low FVIII level. The characteristic laboratory feature is a significant reduction in FVIII level when compared with VWF level (which may be low or normal). The VWF multimer pattern in 2N is normal. The definitive diagnosis requires the demonstration of reduced FVIII binding in a microtiter plate-based assay or the identification of causative mutations in the FVIII-binding region of the VWF gene [46].

Type 3 von Willebrand disease

 Patients who have type 3 VWD typically manifest a severe bleeding phenotype from early childhood, although clinical heterogeneity exists. In addition to more significant presentations of the cardinal mucocutaneous bleeding symptoms seen in the other subtypes, individuals who have type 3 VWD experience joint and soft tissue bleeds frequently, similar to patients who have hemophilia A, because of the commensurate reduction in plasma FVIII levels. In the laboratory, this condition is characterized by prolongation of the aPTT and bleeding time, undetectable levels of VWF:Ag, and VWF:Rco, and FVIII levels less than 0.10 IU/mL (10%). The inheritance of type 3 VWD is autosomal recessive and although parents of affected individuals often are unaffected, there is a growing realization that some obligate carriers of type 3 VWD mutations manifest an increase in mucocutaneous bleeding symptoms compared with normal individuals [47]. Molecular genetic studies of individuals who have type 3 VWD reveal that the phenotype is the result of a variety of genetic defects, including large gene deletions and frameshift and nonsense mutations within the VWF gene, all of which result in a premature stop codon [48]. As a result of the lack of circulating VWF, these mutations in some cases are associated with the development of alloantibodies to VWF, which represent a serious complication of treatment [49,50].

Clinical management of von Willebrand disease

In general, the management of VWD can be divided into three main categories: (1) localized measures to stop or minimize bleeding; (2)
pharmacologic agents that provide indirect hemostatic benefit; and (3) treatments that increase plasma VWF and FVIII levels directly.

Localized measures

The importance of localized measures to control bleeding in VWD, such as the application of direct pressure to a site of bleeding or injury, should not be understated. Biting down on a piece of gauze may halt bleeding from a tooth socket, and application of a compression bandage and cold pack to an injured limb may reduce subsequent hematoma formation. Management of nosebleeds can be problematic particularly for some affected children, however, and patients may benefit from a stepwise action plan that escalates from initial direct pressure to packing after a certain time period and that includes guidelines regarding how long to wait before seeking medical attention. In selected cases, nasal cautery may be required for prolonged or excessive epistaxis.

Adjunctive therapies

Several adjunctive therapies can be used with significant benefit in VWD, particularly at the time of minor surgical and dental procedures and to treat menorrhagia. These interventions include the use of antifibrinolytic agents, such as tranexamic acid and epsilon aminocaproic acid, and the application of topical hemostatic preparations, such as fibrin glue, to exposed sites of bleeding. In women who have menorrhagia, the administration of estrogens (that work, at least in part, by elevating plasma VWF and FVIII levels) often results in significant clinical benefit. Topical estrogen creams applied to the nasal mucosa also are used in children to reduce epistaxis with variable efficacy.

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin) is a synthetic analog of the antidiuretic hormone vasopressin [51]. Its administration increases plasma VWF and FVIII levels by approximately twofold to eightfold within 1 to 2 hours of administration [52]. The effect is presumed to be the result of the release of stored VWF from endothelial cell Weibel-Palade bodies, with the secondary stabilization of additional FVIII. Desmopressin can be administered by the intravenous, subcutaneous, or intranasal route [53]. Its peak effect is achieved within 30 and 90 minutes with the intravenous and intranasal routes, respectively. The usual parenteral dose is 0.3 µg/kg (maximum dose 20 µg) infused in approximately 50 mL of normal saline over approximately 30 minutes. The dose of the highly concentrated intranasal preparation is 150 µg for children under 50 kg and 300 µg for larger children. Highly concentrated products (eg, Stimate) deliver 150 µg per spray, a much higher concentration than found in the nasal sprays used to treat enuresis.
Desmopressin is safe and generally well tolerated; however, its use in pediatric patients must be undertaken cautiously. Common mild side effects include facial flushing and headache. Tachycardia and mild reductions in blood pressure can occur and, given that patients sometimes feel lightheaded during the infusion, it is best to administer it with patients lying down. The most serious side effects that can develop are severe hyponatremia and seizures [54,55] because of the antidiuretic effect of the medication. Reduction of fluid intake for 24 hours after administration to maintenance levels is an important precaution to prevent water intoxication. Children under 3 years of age are especially prone to this complication and extra attention must be paid in these cases. With repeated desmopressin administrations, serial monitoring of serum sodium levels should be performed.

An important limitation in the use of desmopressin is the development of tachyphylaxis with repeated administration. The magnitude of the VWF and FVIII increments often falls to approximately 70% of that documented with the initial dose when given at repeated intervals of less than 24 hours [56]. Presumably, a greater period of time is required for the Weibel-Palade body VWF stores to be replenished. For practical purposes, a single dose of desmopressin before dental procedures or at the onset of menses usually is sufficient. Doses can be repeated at 12 or 24 hours; however, the potential decrease in efficacy (described previously) must be considered. Additionally, in situations where repeat dosing is considered, the duration of fluid restriction must be increased. Generally, more than three doses of desmopressin (preprocedure, at 12 hours, and at 24 hours) are not recommended.

Most patients who have type 1 VWD respond to desmopressin; however, patients who have severe type 1 and many who have type 2 VWD do not respond adequately [57]. Therefore, it is critical to perform a therapeutic trial of the agent before any clinical use. VWF and FVIII levels should be checked before desmopressin administration and at several time points after (eg, at 1, 2, and 4 hours). Although the repeated phlebotomies can present a significant challenge, particularly for young patients, documentation of an adequate response is recommended strongly. An increment of VWF and FVIII to threefold over baseline and to at least 0.30 IU/mL (30%) usually is considered adequate for situations, such as dental procedures, minor surgery, or the treatment of epistaxis or menorrhagia; however, major surgery and significant bleeding episodes should be treated with factor replacement therapy. Desmopressin responsiveness may be sub-optimal in young children (<3 years), and repeat assessment at an older age may be warranted. In addition, certain VWF mutants that show increased clearance are described, limiting the clinical usefulness of desmopressin in this setting [58].

Most patients who have type 1 VWD respond adequately to desmopressin and, for these patients, the concomitant use of desmopressin and an antifibrinolytic agent is sufficient for most clinical situations. Patients who have type 3 VWD typically do not respond to desmopressin, however, given
the lack of stored VWF in this condition. Patients who have type 2 VWD respond variably to desmopressin. Patients who have type 2A often exhibit adequate responses and, therefore, may benefit from a therapeutic trial. Patients who have type 2M typically do not respond well to desmopressin. Desmopressin long has been considered contraindicated in type 2B VWD because of the transient thrombocytopenia that follows the release of the mutant VWF; however, its hemostatic efficacy is documented, allowing its use on an individualized basis [59,60]. Finally, desmopressin has been used in patients who have type 2N, with a twofold to ninefold increase in the VWF and FVIII levels [61]; however, the duration of the FVIII increment usually is only approximately 3 hours. This suggests that for patients who have type 2N, desmopressin should be considered only in clinical situations where a brief, transient rise in FVIII is required.

**Blood component therapy**

Situations, such as major surgery, trauma, and life-threatening bleeding, require intravenous treatment with plasma-derived concentrates of VWF and FVIII. Cryoprecipitate was used commonly in these settings in the 1970s and 1980s, but it no longer is the treatment of choice because of the lack of an effective viral inactivation process for this product. The blood components currently used are plasma-derived, intermediate purity concentrates that have undergone several viral inactivation steps to prevent viral transmission [62–64] (eg, Humate-P and Alphanate). Dosing recommendations currently are made in VWF:RCo units and are weight based; repeat infusions can be given every 12 to 24 hours depending on the clinical situation. It is recommended to measure VWF:RCo and FVIII levels in patients receiving repeat infusions not only to ensure adequate hemostasis but also to monitor for supraphysiologic levels of FVIII. High FVIII levels associated with treatment with these concentrates can contribute to venous thrombosis [65]. In the rare event that infusion of an intermediate purity concentrate is ineffective at stopping bleeding, transfusion of a platelet concentrate is beneficial [66], presumably because it facilitates the delivery of a small amount of VWF (contained in normal platelets) to the site of vascular injury. The role of prophylactic factor infusions in patients who are affected severely currently is the subject of an international randomized trial.

**Summary**

VWD is a common inherited bleeding disorder and many cases are diagnosed in childhood. VWD has a negative impact on the quality of life of affected individuals; therefore, it is important that the condition be recognized and diagnosed. This article reviews the pathophysiology of the condition, the current classification scheme, and the available treatments, highlighting issues specific to the pediatric population.
References


