Myths and Facts:
von Willebrand Disease

With increased knowledge and understanding about VWD, the disease can be more quickly diagnosed and treated, helping patients to lead normal and healthy lives.

By Ronale Tucker Rhodes, MS

In 1926, Erik Adolf von Willebrand, a physician who spent his professional career studying the properties of blood and its coagulation, was the first to describe a blood coagulation disorder that was later named after him: von Willebrand disease (VWD). His discovery occurred while treating a 5-year-old girl with an extensive history of bleeding in her family. After mapping the girl’s 66 family members, he found that 23 of them were also affected.1 Von Willebrand described patients with the syndrome as having mucocutaneous bleeding, normal clotting time, autosomal inheritance and prolonged bleeding times by the Duke method (ear lobe bleeding time).2

VWD is a bleeding disorder that affects the blood’s ability to clot due to low to no levels of a certain protein that acts like glue to help platelets stick together to plug the hole in the blood vessel and stop the bleeding.3 Today, it is estimated that one in 100 people (or 1 percent of the population) suffers from VWD, yet most are unaware they have it. In fact, research has shown that nine out of 10 people suffering from VWD have yet to be diagnosed. And, of those who have been diagnosed, a Centers for Disease Control and Prevention (CDC) study reports an average of 16 years between the onset of bleeding symptoms and diagnosis.4 Quicker diagnosis of VWD so that it can be properly treated can occur only if more is known and understood about VWD, a less severe bleeding disorder that is similar to hemophilia and that, in most cases, causes little or no disruption to the lives of those affected except when there is a serious injury or need for surgery.5

Separating Myth from Fact
MYTH: Like other forms of hemophilia, VWD is a male disease.
FACT: While VWD is a bleeding disorder similar to hemophilia, its cause differs and, therefore, it equally affects both males and females. Hemophilia types A and B are typically

caused by low to no levels of two types of proteins known as clotting factor VIII (FVIII) and IX. They are typically inherited diseases passed on to children from a gene located on the X chromosome. Females have two X chromosomes and males have an X and Y chromosome. A female carrier of hemophilia has the hemophilia gene on one of her X chromosomes, so there is a 50/50 chance of passing that gene on to her children. If passed on to a son, he will have the disease. If passed on to a daughter, she will be a carrier. If a father has hemophilia but the mother doesn’t carry the hemophilia gene, then none of the sons will acquire hemophilia, but all of the daughters will be carriers.

With VWD, on the other hand, the missing protein is called von Willebrand factor (VWF), which is not located on the X chromosome. Instead, it is on a chromosome that is not gender determined, which is why the disease affects both males and females equally. VWD is autosomal dominant, meaning a parent with the gene has a 50/50 chance of passing it on. If passed on, the child will likely develop symptoms.

**Myth:** VWD is not a common bleeding disorder.

**Fact:** While most people have heard of hemophilia, that’s not true of VWD. However, VWD is more common than either of the most common types of hemophilia, occurring in approximately one in 100 people vs. one in 5,000 for hemophilia A and one in 25,000 for hemophilia B.

**Myth:** VWD is an inherited disease.

**Fact:** Most people with VWD inherited it from a parent. Yet, it is possible for “spontaneous mutation” to occur due to a change in a person’s gene. Normally, though, this mutation occurs prior to birth, and children are born with the affected gene. Only rarely does a person who is not born with VWD acquire it or have it first occur later in life. VWD is acquired when a person’s immune system destroys his or her VWF caused by the use of a medication or as a result of another disease. Acquired VWD cannot be passed along to children.

**Myth:** There is only one type of VWD.

**Fact:** Like hemophilia, there are several types of VWD. Type 1, which is the most common and mildest form, occurs when a person has lower than normal levels of VWF. Those with type 1 may also have low levels of FVIII. With type 2, a person’s body makes normal levels of VWF, but the protein doesn’t work properly. There are four subtypes of type 2 — 2a, 2b, 2m and 2n — depending on the specific problem with the VWF protein, which is important to know because treatment is different for each. The most severe form of VWD is type 3 in which there is very little or no VWF and low levels of FVIII.

**Myth:** Symptoms of VWD are the same for men and women.

**Fact:** While the symptoms of VWD are similar for men and women, the severity of symptoms differs for all VWD patients, and women experience additional symptoms. Bleeding usually involves the mucous membranes of the body. Symptoms can present as frequent, large bruises from minor bumps and injuries, frequent or hard-to-stop nosebleeds, prolonged bleeding from the gums after a dental procedure, bleeding in the stools from bleeding in the intestines or stomach, blood in the urine from bleeding in the kidneys or bladder, and heavy bleeding after a cut or other accident. Women also suffer from menorrhagia (heavy menstrual bleeding) and bleeding problems during delivery and heavy bleeding for an extended time after childbirth.
Myth: VWD is easy to diagnose.
Fact: Because VWD types 1 and 2, the more common types, don’t present with major bleeding problems, they are sometimes hard to diagnose. In some instances, these types may not be diagnosed unless the person has heavy bleeding after surgery or some other trauma. VWD type 3, on the other hand, is almost always diagnosed during the first year of life because it can cause major bleeding problems during infancy and childhood.

To diagnose VWD, a physician will conduct a medical history and physical exam, checking for bruises or other signs of recent bleeding, and will ask about past bleeding episodes and whether parents or siblings have had bleeding problems. Blood tests will also be conducted. Specific blood tests include a VWF antigen that measures the VWF protein to determine the level of VWF in the blood; a ristocetin cofactor activity to analyze how well the VWF works in the clotting process; a FVIII clotting activity test to show whether there are abnormally low levels and activity of FVIII; a von Willebrand factor multimers test to evaluate the specific structure of VWF in the blood, its protein complexes (multimers) and how its molecules break down to help identify the type of VWD that is present; and a platelet function test (PFA-100) to measure how efficiently platelets are functioning in the blood.

Unfortunately, VWD is on the rise.

Myth: All people with VWD need treatment.
Fact: Most people have very mild VWD, so they don’t need treatment unless they have a surgical or dental procedure. For those with more severe VWD, the two main treatment options are desmopressin (DDAVP) and transfusion therapy with blood products. DDAVP, a synthetic analogue of vasopressin, is the treatment of choice for type 1 VWD. It is a naturally occurring hormone in the body that works by stimulating release of both VWF and FVIII found in storage sites lining the blood vessels to correct the prolonged bleeding time. It also is used prior to procedures involving mucous membranes such as dental work, for home treatment of minor injuries and for minor or moderate surgeries. DDAVP comes in a nasal spray, but it can also be injected intravenously or subcutaneously.

Because DDAVP is not effective in the majority of type 2 and 3 VWD patients, transfusion with plasma concentrates containing VWF and FVIII is prescribed. When major surgery or treatment for serious bleeding episodes is required, VWF-containing FVIII concentrates are the treatment of choice. Factor concentrates with VWF to treat people with types 2a, 2b and 3 include Alphanate (Grifols), Humate P (CSL Behring), Koate DVI (Kedrion) and Wilate (Octapharma). In April, Baxter announced results of its Phase III clinical trial evaluating the safety, efficacy and pharmacokinetics of BAX III, a recombinant VWF. Baxter intends to file for approval of BAX III before the end of 2014. Although the bleeding time defect is not always corrected by plasma concentrates, they are effective and safe. When there is poor correction of bleeding time associated with continued bleeding, platelet concentrates or DDAVP can be used as adjunctive treatments.

Other treatments include birth control pills to control heavy menstrual periods in women with type 1 VWD and antifibrinolytic agents (Amicar [aminocaproic acid] and Cyklokapron [tranexamic acid]) to treat nosebleeds and to prevent bleeding in the mouth during dental surgery. Antifibrinolytic agents help prevent blood clots from breaking down in the mucous membranes of the mouth, nose, stomach, intestines and urinary tract, and they are sometimes used in combination with DDAVP and plasma replacement therapy. If antibodies to VWF develop, recombinant FVIIIa is prescribed.

Myth: Symptoms of VWD can’t be prevented.
Fact: There are steps that can be taken to prevent bleeding and stay healthy. For instance, over-the-counter medicines that can affect blood clotting such as aspirin, ibuprofen and other nonsteroidal anti-inflammatory drugs should be avoided. Before dental work, patients should ask their doctor, dentist or pharmacist whether any medicine is needed to reduce bleeding. For those with serious forms of VWD, a medical ID bracelet or necklace can be worn to let healthcare providers know of the disease in case of a serious accident or injury. And, patients may also want to let other people such as an employee health nurse, gym trainer or sport coach know about their condition in case of an injury.

Myth: Individuals with VWD should avoid sports.
Fact: VWD patients are encouraged to be physically active. According to Ann Kirschman, WHNP, BSN, women’s health nurse practitioner at the Mountain States Regional Hemophilia and Thrombosis Center at the University of Colorado, Aurora, “the health benefits of being in shape outweigh, in most cases, the risks of playing sports. Muscles that are not in good shape cannot hold the joints in proper alignment and protect them.” Kirschman adds, however, that she doesn’t encourage high-contact sports because of the risk of abdominal or intracranial bleeding, but she does promote weight control and muscle training and fitness as a protection against bleeding. Some safe physical activities include swimming, biking and walking.

Myth: Pregnancy is too risky for women with VWD.
Fact: Pregnancy can be a challenge for women with VWD,
ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is indicated for:

• Control and prevention of bleeding in patients with hemophilia A

• Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP®) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

**Important Safety Information**

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with ALPHANATE should be discontinued, and emergency treatment should be sought.

Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 von Willebrand disease (VWD) patients has been occasionally reported in the literature.

Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The most frequent adverse events reported with ALPHANATE in >5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain, and fatigue.

Please see brief summary of ALPHANATE full Prescribing Information on adjacent page.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
**ALPHANATE®**
Antihemophilic Factor/von Willebrand Factor Complex (Human)

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use Alphanate safely and effectively. See full prescribing information for Alphanate.

**ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])**
Sterile, lyophilized powder for injection.
Initial U.S. Approval: 1978

**INDICATIONS AND USAGE**
Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:
- Control and prevention of bleeding in patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

**DOSAGE AND ADMINISTRATION**

For Intravenous use only.

Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial.

**Hemophilia A: Control and prevention of bleeding episodes**
- **Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).**
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician.

**von Willebrand Disease: Surgical and/or invasive procedure in adult and pediatric patients except Type 3 undergoing major surgery**
- **Adults:** Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.
- **Pediatric:** Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.

**WARNINGS AND PRECAUTIONS**
- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients has been occasionally reported in the literature.
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).
- Rapid administration of a FVIII concentrate may result in vasomotor reactions.
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

**ADVERSE REACTIONS**
The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**
- **Pregnancy:** No human or animal data. Use only if clearly needed.
- **Pediatric Use:** Hemophilia A - Clinical trials for safety and effectiveness have not been conducted. VWD - Age had no effect on PK.
but most women can have successful pregnancies. Monitoring during and after pregnancy is required. Limited evidence suggests that DDAVP use is relatively safe during pregnancy. But, with DDAVP, women should limit their fluid intake to reduce the risk of hyponatremia, especially after repeated doses. Women unresponsive to DDAVP or with other contraindications should receive a VWF-FVIII concentrate for prophylaxis or treatment of bleeding.

Women with type 3 VWD require VWF replacement at the time of delivery and postpartum. Prophylaxis is also recommended for those with persistently low FVIII and VWF levels at term.

Although rare, spontaneous miscarriage can occur before childbirth. And, because of the rapid fall in FVIII and VWF levels after birth, women are at substantial risk for postpartum hemorrhage (PPH), although the risk is higher for those with VWD types 2 and 3, and that risk persists for several weeks after delivery. PPH is the leading cause of death among women during childbirth, and women with VWD are more likely to experience PPH and are 10 times more likely to die from childbirth complications than women without VWD.\(^{20}\)

### Dispelling the Myths Now

While there is no cure for VWD, it can be treated, and individuals can live a normal life. Unfortunately, VWD is on the rise. CDC reports that the number of women seeking treatment at hemophilia treatment centers for bleeding disorders such as VWD has increased by 50 percent during the past 10 years to more than 10,000 in 2009.\(^{4}\) Therefore, much more needs to be known about the disease to better diagnose and treat it.

The National Heart, Lung and Blood Institute has identified a number of areas that would benefit from further research, including a better understanding about the pathophysiology and classification of VWD since the level of functional VWF and many other factors are poorly understood, as is the disease’s heterogeneity. Increasing awareness and understanding how to diagnose and evaluate VWD is needed, as well as how to manage it since many of the standard treatments for the disease have limited experimental support. Further, it’s possible that severe type 3 VWD can be treated with gene therapy, but its prevalence and clinical symptoms have not yet warranted gene therapy trials. It’s clear more needs to be understood about VWD issues related to women.\(^{21}\) CDC is conducting research that aims to improve the health outcomes of women with bleeding disorders, including determining what percentage of women who had PPH have a bleeding disorder; identifying symptoms, risk factors and other complications; and assessing the adverse pregnancy outcomes.\(^{20}\)

In addition to research needs, there is a shortage of skilled clinicians and laborators with expertise in VWD and other bleeding disorders. The National Heart, Lung and Blood Institute provides grants for clinical opportunities in non-malignant hematology (grants.him.gov/grants/guide/rfa-files/RFA-HL-06-006.html), and the National Hemophilia Foundation has established a clinical fellowship program funded by Baxter Healthcare Corp. for the study of hemophilia (www.hemophilia.org/Researchers-Healthcare-Providers/Research-Grant-Programs/NHF-Baxter-Clinical-Fellowship-Program).\(^{21}\)

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### References