Acquired von Willebrand syndrome

AUTHOR: Paula James, MD, FRCPC
SECTION EDITOR: Lawrence LK Leung, MD
DEPUTY EDITOR: Jennifer S Tirnauer, MD

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INTRODUCTION

Inherited von Willebrand disease (VWD) is the most common inherited bleeding disorder. Acquired von Willebrand syndrome (AVWS; acquired deficiency or dysfunction of von Willebrand factor [VWF]) is much less common. Additionally, the diagnosis is not often suspected in a bleeding patient.

AVWS can be caused by a number of underlying medical conditions, and bleeding symptoms in an individual with any of these diseases should raise suspicion and prompt an evaluation for AVWS. Evaluation and management may be complex, especially in those for whom the underlying disorder requires antithrombotic therapy, such as anticoagulation for a prosthetic heart valve or aspirin for essential thrombocythemia.

This topic reviews the pathophysiology, evaluation, diagnosis, and management of AVWS. Inherited VWD and other causes of bleeding are discussed in separate topic reviews:

- **Inherited VWD**
  - **Diagnosis and classification** – (See "Clinical presentation and diagnosis of von Willebrand disease".)
  - **Major bleeding** – (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery".)

- **Minor bleeding** – (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care".)
- **Gynecology and obstetrics** – (See "von Willebrand disease (VWD): Gynecologic and obstetric considerations".)
- **Pathophysiology** – (See "Pathophysiology of von Willebrand disease".)

- **Evaluation for suspected bleeding disorders**
  - **Children** – (See "Approach to the child with bleeding symptoms".)
  - **Adults** – (See "Approach to the adult with a suspected bleeding disorder" and "Easy bruising".)

PATHOPHYSIOLOGY

Role of VWF in hemostasis — von Willebrand factor (VWF) is an extremely large glycoprotein that is synthesized in megakaryocytes and endothelial cells; it undergoes extensive post-translational processing. Dimeric subunits of VWF undergo multimerization, and the multimers are stored in (and released from) Weibel-Palade bodies in endothelial cells and alpha granules in platelets and megakaryocytes. The high molecular weight multimers are the most active in hemostasis. Several proteases can cleave VWF, including ADAMTS13 (and possibly other metalloproteinases), leukocyte-derived proteases, and plasmin. (See "Pathophysiology of von Willebrand disease", section on 'Initial description'.)

VWF contributes significantly to primary hemostasis by binding to platelet receptors and vascular subendothelial structures at sites of endothelial injury, where it forms an adhesive bridge between platelets and the endothelial surface and also forms adhesions between adjacent platelets, especially in areas of high shear (figure 1) [1,2]. High molecular weight VWF multimers provide multiple binding sites that can interact with platelets and the subendothelium; as a result, they are the most active functional forms of VWF. (See "Overview of hemostasis", section on 'Formation of the platelet plug'.)

VWF also acts as a protective carrier protein for coagulation factor VIII and thus contributes to fibrin clot formation by maintaining factor VIII levels. In individuals with severe VWF deficiency, factor VIII levels can be as low as those in patients with moderate hemophilia A [3]. (See "Pathophysiology of von Willebrand disease", section on 'VWF functions'.)

Mechanisms of reduced VWF — Mechanisms of reduced VWF activity in AVWS include immune and non-immune mechanisms (table 1) [4-11]. Analysis of the multimeric structure of the

patient's VWF often shows a decrease in the high molecular weight multimers in both immune and non-immune types of mechanisms [10,12,13].

- **Antibody-mediated decrease** – Immune-mediated reduction of VWF (eg, by autoantibodies to the VWF protein) may occur in monoclonal gammopathies, lymphoid neoplasms, and autoimmune diseases [10,14,15]. The first case of AVWS was described in a teenager with systemic lupus erythematosus (SLE) [16].

  Many cases of immune-mediated AVWS do not have detectable inhibitory antibodies demonstrated by using mixing studies (assays of platelet-dependent VWF function); however, the absence of detectable autoantibodies does not eliminate the possibility of AVWS due to antibody-mediated enhanced VWF clearance [17]. Some antibodies may have a higher affinity for larger multimers and possibly lead to a more selective clearance of high molecular weight (HMW) forms.

  Autoantibodies that interfere with VWF function often lead to more serious bleeding [15]. In a 1998 series of 25 patients with AVWS of different causes, those with a detectable autoantibody had a greater frequency of bleeding than those without a functionally detectable autoantibody (6 of 8 versus 1 of 16 [75 versus 6 percent]) [10]. (See 'Lymphoproliferative disorders' below and 'SLE and other autoimmune disorders' below.)

- **Shear stress-induced proteolysis** – The multimeric structure of VWF makes the protein sensitive to changes in fluid flow and shear stress, and in the normal circulation, VWF tumbles and undergoes oscillatory force cycles every few milliseconds. In areas of high shear stress, VWF multimers become unfolded and elongated, and are more susceptible to cleavage by ADAMTS13. Patients who have normal ADAMTS13 activity will have proteolysis of VWF in these circumstances.

  High levels of shear stress can occur with vessel stenosis (ventricular septal defect associated with certain congenital malformations, aortic stenosis, paravalvular leak after mitral valve replacement, hypertrophic obstructive cardiomyopathy) [18-20].

  Certain extracorporeal devices (eg, ECMO) and left ventricular assist devices (LVAD) can also produce extremely high shear stress and account for an increasing number of cases of AVWS [21-23]. (See 'Cardiovascular disease' below.)

  The levels of shear stress associated with these conditions (in Pascals [Pa]) have been reported to be as follows [24]:

  - Normal veins – <1 Pa

- Normal arteries and arterioles – 1 to 7 Pa
- Stenotic vessels – 4 to 45 Pa
- Centrifugal flow LVAD – approximately 200 Pa
- Axial flow LVAD – 600 Pa

However, not all patients with the shear stress conditions noted above have clinically significant bleeding, and LVAD and EMCO are also associated with a significant prothrombotic risk, suggesting that additional mechanisms may contribute to the hemostatic balance in these individuals. (See 'Cardiovascular disease' below and 'Left ventricular assist device or extracorporeal membrane oxygenation' below.)

- **Adsorption onto cells or proteins** – VWF can be adsorbed onto cells (removing it from the circulation), and this may lead to increased clearance [25,26]. This is a possible mechanism of AVWS in patients with Wilms tumor, Waldenström macroglobulinemia, and some non-Hodgkin lymphoma (NHL) and multiple myeloma patients [27]. An aberrantly expressed platelet receptor for VWF, glycoprotein Ib (GPIb), has been reported on the cells in some patients with AVWS and a plasma cell dyscrasias [27,28].

  In patients with myeloproliferative neoplasms (MPNs), several reports have noted an inverse relationship between high platelet counts and the decrease of large VWF multimers, suggesting that adsorption of HMW VWF multimers onto platelets may cause reduced VWF levels; however, other mechanisms of VWF loss such as platelet activation, binding, and consequent proteolytic cleavage are also likely [29-31].

- **Other proteases** – Other proteases besides ADAMTS13 may contribute to VWF cleavage and reduction. As an example, states of excessive fibrinolysis such as disseminated intravascular coagulation (DIC), decompensated cirrhosis, and some cases of multiple myeloma have been associated with degradation of VWF, likely due to increased plasmin levels [11,32].

  Some patients with essential thrombocythemia (ET) also show evidence of increased VWF proteolysis, possibly due to released platelet metalloproteinases other than ADAMTS13 (as well as to ADAMTS13) [31,33].

- **Decreased synthesis** – Although uncommon, acquired reduction in VWF synthesis can occur in certain conditions such as hypothyroidism [34,35]. (See 'Hypothyroidism' below.)

In some conditions, several mechanisms may coexist.

Consequences of reduced VWF — The major complication of AVWS is an increased risk of bleeding. However, not all individuals with reduced VWF levels have increased bleeding [21]. Bleeding occurs more often in patients who have VWF levels <20 international units/dL. Those with levels of 20 to 30 international units/dL are at increased risk for bleeding, but there is no firm level that predicts bleeding. Other risk factors such as platelet dysfunction and medications may contribute to excessive bleeding in these patients. Patients with detectable inhibitory antibodies in mixing studies using platelet-dependent VWF activity have been noted to have more severe bleeding than those without inhibitory antibodies [10]. (See 'Mechanisms of reduced VWF' above.)

Mechanisms of increased bleeding risk in AVWS may include:

- **Impaired platelet interactions** – The most obvious and widely cited consequence of reduced VWF is impaired primary hemostasis due to reduced ability of platelets to interact with the subendothelium and other platelets. This may lead to mucosal bleeding and/or serious internal bleeding.

- **Reduced levels of plasma factor VIII** – VWF acts as a carrier protein for factor VIII and increases factor VIII half-life substantially. In severe AVWS, decreased factor VIII may contribute to muscle or joint bleeding.

- **Angiodysplasia** – VWF is thought to suppress angiogenesis; a direct causal association between AVWS and increased angiogenesis remains to be demonstrated [36,37]. The increase in angiogenesis observed in some patients with AVWS may explain the common finding of bleeding from gastrointestinal angiodysplasia seen in some individuals with accompanying aortic stenosis or severe mitral regurgitation (Heyde syndrome) [38]. (See 'Aortic stenosis' below and 'Severe mitral regurgitation' below.)

  Potential mechanisms by which VWF controls angiogenesis may include changes in integrin-mediated adhesion and vascular endothelial growth factor receptor (VEGF) signalling, which in turn may alter several stages of blood vessel development and maturation [37,39]. The likelihood of angiodysplasia in patients with von Willebrand disease has been estimated to be approximately 12 percent, although some reports suggest a lower frequency [40,41].

- **Antithrombotic therapies** – Some individuals with AVWS may also receive antiplatelet agents or anticoagulants, which may further increase bleeding risk. (See 'Patients who require antithrombotic therapy' below.)

EPIDEMIOLOGY

AVWS is less common than inherited von Willebrand disease (VWD). In a 1993 international survey sent to 300 medical centers (4503 patients with VWD) asking for the distribution of VWD cases between inherited and acquired forms, only 1.2 percent were acquired [40]. Other sources have quoted slightly higher ratios (approximately 5 percent in the Mayo Clinic experience) [6,42].

The true prevalence of AVWS is unknown, since many cases may be clinically silent or mild and remain undiagnosed [33]. Over 700 cases have been reported in the literature [43]. Underreporting is likely because testing is not routinely performed for individuals who are not bleeding. An estimated prevalence of up to 0.04 percent (1 in 2500) has been quoted based on a review of the Mayo Clinic database [42].

The prevalence of AVWS may be much higher in certain populations:

- Lymphoproliferative disorders – Unknown. However, these diseases are one of the most common associated diseases reported in series of patients with AVWS. (See 'Lymphoproliferative disorders' below.)
- Myeloproliferative neoplasms – 10 to 20 percent. (See 'Myeloproliferative neoplasms including ET' below.)
- Autoimmune disorders – Unknown. (See 'SLE and other autoimmune disorders' below.)
- Congenital cardiac anomalies or aortic stenosis – 10 to 70 percent. (See 'Congenital heart disease' below and 'Aortic stenosis' below.)
- Left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO) – Up to 100 percent. (See 'Left ventricular assist device or extracorporeal membrane oxygenation' below.)
- Wilms tumor – 4 to 8 percent. (See 'Wilms tumor' below.)

ASSOCIATED DISEASES

Overview of associated diseases — AVWS may be diagnosed in a patient with a previously identified underlying cause (table 1), concurrently with the other diagnosis, or before the underlying cause has been identified.

- **Children** – In children, the most common causes of AVWS include congenital heart disease, Wilms tumor, and autoimmunity [44].

- **Adults** – Common causes of AVWS in adults include autoimmune and lymphoproliferative disorders and cardiac conditions [45]. In an international survey from 1993, all the adults with AVWS had a lymphoproliferative, myeloproliferative, or autoimmune disorder [40]. However, the association between aortic stenosis and AVWS had not been well established at the time and was probably under-reported. The number of cases due to left ventricular assist devices (LVADs) or other devices that alter blood flow and cause high shear stress may be increasing and may comprise a larger number of cases of AVWS as these devices are used more frequently.

Additional rare disorders associated with AVWS include amyloidosis, pesticide ingestion, viral and parasitic infections, glycogen storage disease, graft-versus-host disease (GVHD), systemic mastocytosis, and Ehlers-Danlos syndrome [6,33,46].

Vaccines — One case of AVWS was described after COVID-19 vaccination in a patient with a previously unclear bleeding disorder who also had an acquired factor VIII inhibitor [47].

Hematologic disorders

Lymphoproliferative disorders — Lymphoproliferative disorders and plasma cell dyscrasias associated with AVWS include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), Waldenström macroglobulinemia (WM), chronic lymphocytic leukemia (CLL), hairy cell leukemia, lymphosarcoma, and non-Hodgkin lymphoma (NHL) [11,14,48-50]. In some cases, AVWS has been the presenting finding [43].

A 2000 report from an international VWD registry found lymphoproliferative disorders to be the most common cause of AVWS, representing 89 of 186 cases (48 percent) [5]. In a 2003 report from a single institution that included 22 individuals with AVWS, 12 had a paraproteinemia, including six with MGUS, four with WM, one with MM, and one with NHL [42]. The international registry report also conducted a literature review that found lymphoproliferative disorders accounted for approximately one-third; this lower frequency is likely due to reporting bias [5].

The likelihood of developing AVWS in an individual with a lymphoproliferative disorder is unknown, but given the high prevalence of the lymphoproliferative disorders, AVWS is probably a relatively uncommon complication. (See 'Epidemiology' above.)

Myeloproliferative neoplasms including ET — AVWS has been seen in all of the myeloproliferative neoplasms (MPNs); it is most commonly found in association with essential

thrombocythemia (ET).

- **Essential thrombocythemia (ET)** – In a 2015 series of 170 consecutive patients with ET who had laboratory testing, AVWS was diagnosed in 34 (20 percent) [51]. Features that correlated with AVWS in this study included younger age at the time of ET diagnosis (defined as <56 years); greater frequency of bleeding symptoms; and higher red blood cell (RBC), monocyte, and platelet counts. Three-quarters of individuals with AVWS had platelet counts between 450,000 and 1,000,000/microL; three had platelet counts >1 million/microL, and five had normal platelet counts. Most of the patients were diagnosed with AVWS within a few years of their ET diagnosis.

  The high prevalence of AVWS in patients with ET, even those with modest thrombocytosis, raises important management considerations, as individuals with ET are at increased risk of thrombosis and may be treated with an antiplatelet agent such as aspirin to reduce this risk. Our approach to decision-making in these individuals is discussed below. (See 'Patients who require antithrombotic therapy' below.)

  The mechanism of AVWS in individuals with ET is not fully understood, but evidence shows higher molecular weight multimers of VWF are often missing, suggesting increased proteolysis by platelet proteases may play a significant role. In some patients, the markedly increased numbers of platelets alone may bind a higher quantity of VWF, allowing VWF to unfold and become susceptible to ADAMTS13, the primary enzyme that cleaves VWF in the circulation [31,51]. (See 'Mechanisms of reduced VWF' above.)

- **Polycythemia vera (PV)** – In a 2015 series of 142 consecutive patients with PV who had testing of VWF levels, AVWS was identified in 17 (12 percent) [52]. Features that correlated with AVWS in this group included younger age (age of PV diagnosis, 48 years in those with AVWS versus 60 years in those without); bleeding symptoms; higher RBC, white blood cell, and platelet counts; and lack of remission of PV.

- **Myelofibrosis** – In a 2015 series of 32 consecutive patients with myelofibrosis (primary or secondary to another MPN) who had bleeding symptoms that prompted laboratory testing, AVWS was diagnosed in five (16 percent) [53]. An additional 12 of 27 (44 percent) had bleeding for other reasons, emphasizing the need to evaluate these patients for other bleeding conditions.

These studies did not identify any obvious predictors of which patients would develop AVWS. In the large series of patients with ET, the risk of AVWS was higher with higher platelet counts, but some patients had normal platelet counts, and there was no threshold platelet count that could be used to stratify risk [51].

We recommend testing for AVWS in any patient with MPN and bleeding, and we follow all patients with MPNs closely after the initiation of aspirin or other platelet inhibitory medications. Those receiving antiplatelet agents should have an evaluation for AVWS if they have bleeding or bruising. (See 'Diagnostic evaluation' below.)

The mechanism of AVWS in these disorders may be multifactorial. (See 'Mechanisms of reduced VWF' above.)

SLE and other autoimmune disorders — The prevalence of AVWS in patients with systemic lupus erythematosus (SLE) or other autoimmune disorders has not been systematically evaluated. Case reports have described AVWS as the initial presentation of SLE or that preceded the diagnosis of SLE by one or more years [45,54]. The mechanism is likely to involve autoantibody production. (See 'Mechanisms of reduced VWF' above.)

Cardiovascular disease

Congenital heart disease — Studies in individuals with congenital heart disease have shown AVWS with a number of stenotic cardiovascular lesions; sometimes AVWS is not diagnosed until adulthood.

- A 2016 study that evaluated for AVWS in 60 children with congenital aortic or pulmonary stenosis found evidence of the disease in seven (12 percent) [55].
- In a 2014 series of 50 children with congenital heart disease who underwent cardiac catheterization or cardiac surgery, 26 had high-grade intracardiac or extracardiac stenoses [56]. Significantly diminished VWF levels were documented in 13 of the 26 (50 percent); by comparison, none of the remaining 24 children without high grade stenosis had reduced VWF. None had major clinically significant bleeding, and surgical blood loss was similar between those with and without AVWS, suggesting AVWS was mild. In those with AVWS, the alterations in VWF resolved completely with surgical or interventional repair.
- A 2014 study that included 192 adults with congenital heart disease found laboratory evidence of AVWS in 21 percent, with the highest prevalence in those with the most complex defects [57].

Aortic stenosis — AVWS is common in individuals with aortic stenosis (AS).

- In a 2003 series of 42 consecutive adults with severe AS, nine (21 percent) had at least one episode of bleeding, most frequently from skin or mucosal sites [58]. High molecular weight VWF multimers were reduced in 33 patients (79 percent)with severe AS; this resolved by day 1 after corrective valve surgery.

- In a 2015 series of 31 consecutive adults with severe AS, 21 (68 percent) had loss of large VWF multimers [59]. There was a trend towards a correlation between the peak aortic gradient and the loss of large multimers, but there was no cutoff below which VWF was unaffected in this cohort. All of the individuals had a reduced hemoglobin level, with hemoglobin <9 g/dL in 12 (39 percent). Endoscopy was performed in four, and in each case showed angiodysplasia. Seven of the patients with AVWS had aortic valve replacement, which resulted in resolution of AVWS in all cases.

The association between aortic stenosis and bleeding from gastrointestinal angiodysplasia has been designated Heyde syndrome. In some cases this is attributed to AVWS, although some patients with the syndrome have normal VWF levels, and other mechanisms of angiodysplasia such as decreased gastrointestinal perfusion have been implicated [60]. (See "Clinical manifestations and diagnosis of aortic stenosis in adults", section on 'Bleeding tendency'.)

Severe mitral regurgitation — Patients with severe mitral regurgitation may develop AVWS by mechanisms identical to aortic stenosis, including Heyde syndrome [61].

Left ventricular assist device or extracorporeal membrane oxygenation — Left ventricular assist devices (LVAD) are mechanical circulatory devices used in patients with cardiogenic shock or end-stage heart failure. Extracorporeal membrane oxygenation (ECMO) devices are used to provide circulatory support, including during cardiac surgery. (See "Treatment of advanced heart failure with a durable mechanical circulatory support device" and "Extracorporeal life support in adults in the intensive care unit: Overview".)

LVAD and ECMO can be associated with increased bleeding risk for several reasons, including the coagulopathic effect of extracorporeal circulation, anticoagulant therapy used to reduce the risk of pump thrombosis, platelet dysfunction, and shear stress induced by continuous flow across the device. The shear stress may damage VWF, and increased binding to platelets may enhance proteolysis by ADAMTS13 [24]. (See 'Mechanisms of reduced VWF' above.)

Bleeding within the first week after implantation is often attributed to mechanisms other than AVWS such as surgical bleeding or anticoagulation, but laboratory testing often shows that AVWS is also present at that time and may be an additional contributing factor [24,62]. The changes in VWF resolve rapidly upon removal of the device.

- **LVAD** – The overall bleeding risk (from any cause) may be as high as 40 percent for some LVAD devices [24]. All patients with continuous flow LVADs are assumed to have AVWS and are not routinely tested. However, only a small proportion of individuals with an LVAD have clinically significant bleeding due to AVWS [24]. (See "Management of long-term mechanical circulatory support devices", section on 'Bleeding'.)

- **ECMO** – In a 2015 series of 18 adults receiving ECMO, all had AVWS [63]. Bleeding was often present, typically as diffuse mucosal or bronchial bleeding or bleeding at puncture sites. The VWF abnormalities were detectable within 24 hours of starting ECMO and resolved after removal of the device.

As with other cardiovascular conditions, gastrointestinal bleeding may be seen with these devices. The frequency of gastrointestinal bleeding in patients with an LVAD has been estimated to be on the order of 17 to 30 percent, and up to one-third of this bleeding appears to be due to gastrointestinal angiodysplasia. (See 'Consequences of reduced VWF' above.)

Wilms tumor — Series of children with Wilms tumor have documented AVWS in four to eight percent [64,65]. In the larger series, which included 185 children, all had resolution of the VWF abnormalities within two to four weeks of starting chemotherapy for the tumor [64]. The authors reported that based on these findings they have initiated testing for AVWS in all patients with suspected Wilms tumor at their institution. We recommend testing for AVWS in any patient with Wilms tumor who has a bleeding history or who requires surgery or other invasive procedure. (See "Treatment and prognosis of Wilms tumor".)

Hypothyroidism — Hypothyroidism can cause AVWS, although the prevalence of AVWS in hypothyroidism is unknown and it appears to be uncommon. Most individuals are treated with thyroid hormone replacement and have resolution of the AVWS [34,35].

In a 2014 series of 90 consecutive adults with clinically overt untreated hypothyroidism, laboratory evidence of AVWS was present in 29 (32 percent) [66]. Of these, 20 had some bleeding symptoms, which often included mild petechiae, bruises, or mucosal bleeding (epistaxis, oral bleeding, heavy menstrual bleeding). Most had moderate reductions in VWF:antigen and VWF:ristocetin cofactor levels (range, 10 to 50 percent). VWF levels correlated positively with the levels of free T4. The authors suggested that this prevalence is likely an overestimate since the cutoff for mild VWD using the 97.5 percentile will result in the inclusion of 2.5 percent or more of the general population.

The main mechanism of AVWS in hypothyroidism is reduction of VWF synthesis in the setting of low thyroid hormone levels. Autoantibodies against VWF have also been reported in autoimmune thyroiditis [48]. (See 'Mechanisms of reduced VWF' above.)

Valproic acid and other medications — Multiple medications have been implicated in causing AVWS, including valproic acid, ciprofloxacin, griseofulvin, hydroxyethyl starch (also called hetastarch; used as a plasma expander) and dextrans [6,67-70]. Their mechanisms are also diverse and include reduced synthesis (valproic acid), accelerated proteolysis (ciprofloxacin), and precipitation of the protein (hydroxyethyl starch) [6]. (See 'Mechanisms of reduced VWF' above.)

In a group of 83 children taking valproic acid for epilepsy, 63 and 23 percent had a history of bleeding or a prolonged bleeding time, respectively [70]. In those patients whose VWF was assessed, 83 and 66 percent had mild reductions in VWF antigen (VWF:Ag) and VWF ristocetin cofactor activity (VWF:RCo), respectively.

TYPICAL PRESENTATIONS

The two major settings in which AVWS is suspected are in a patient with an underlying condition known to predispose them to having reduced VWF levels, and in an individual with new-onset unexplained bleeding, usually involving mucosal surfaces [8].

- **Individual with a known associated condition** – AVWS may present in any of a number of associated conditions (table 1) (see 'Associated diseases' above), either as a known underlying disorder, or, less commonly, as the presenting finding in the absence of another recognized illness.

  An international registry was created in 2000 and identified 186 new cases of AVWS, with the following distribution of associated conditions [5]:

  - Lymphoproliferative disorders – 48 percent
  - Cardiovascular disorders – 21 percent
  - Myeloproliferative disorders – 15 percent
  - Other cancers – 5 percent
  - Immunologic disorders – 2 percent

  In a different international cohort of patients with AVWS in association with a lymphoproliferative, myeloproliferative, or autoimmune disorder, the median age of presentation was 69 years, consistent with the epidemiology of these underlying conditions [40].

- **New-onset unexplained bleeding** – For a patient without an underlying condition known to cause AVWS, new onset of mucosal or skin bleeding raises the possibility of an acquired disorder or a mild hereditary disorder that was previously unappreciated [45].

- **Children** - Some of the disease associations found in adults are not common in children. The more usual causes for AVWS in children include congenital heart disease, autoimmune diseases, neoplasia (Wilms tumor), and hypothyroidism [44].

DIAGNOSTIC EVALUATION

The diagnosis of AVWS requires a thorough history and clinical assessment supplemented by laboratory tests [71]. The best screening remains the patient's medical history, including personal and family history of abnormal bleeding and hemostatic challenges. A personal history for underlying conditions known to cause AVWS should also be obtained, as well as a history of any medications that might cause bleeding.

If the patient is bleeding, it may be necessary to intervene before the diagnostic evaluation has been completed. An antifibrinolytic agent may be given in some cases even if the underlying cause of bleeding has not been identified, since these agents work independently of a specific coagulation factor or platelet disorder. (See 'Treatment of acute bleeding' below.)

Laboratory testing — A complete blood count (CBC) with platelet count and coagulation testing including a prothrombin time (PT) and an activated partial thromboplastin time (aPTT) should be obtained if they are not already available.

- **CBC, PT, and aPTT** – In an individual with AVWS, the aPTT may be prolonged due to low factor VIII levels (see 'Consequences of reduced VWF' above); however, a normal aPTT does not eliminate the possibility of AVWS, because this test becomes prolonged only when the factor VIII level is below approximately 20 to 30 percent, depending on the laboratory. The platelet count and PT are unaffected in AVWS (although the platelet count may be abnormal due to an associated condition).

- **VWF levels** – VWF levels are appropriate in individuals with a high suspicion of AVWS based on clinical findings or screening laboratory results, especially if there is bleeding or need for a surgical procedure. This testing may also be appropriate for individuals with an MPN or other disorder before administration of aspirin or other platelet inhibitory drug, even if the individual does not have current bleeding. Additionally, patients with AVWS-associated diseases who will be treated with therapies that may reduce the platelet count below 40,000 to 50,000/microL should be evaluated for AVWS.

  Since most patients with an LVAD or EMCO are considered to have AVWS of varying severity, it is not necessary to obtain VWF levels unless the patient has bleeding that is not explained by other possible causes, or if treatment for other possible causes of bleeding is not effective. If VWF levels are extremely low, this information should be incorporated into the treatment plan.

  We obtain the following tests:

- VWF antigen (VWF:Ag)
- Platelet-dependent VWF activity (VWF:RCo or VWF:GPIbM)
- Factor VIII activity (FVIII:C)

Additional details are presented separately. (See "Clinical presentation and diagnosis of von Willebrand disease", section on 'VWD screening tests'.)

Definitive reference ranges that specifically define AVWS have not been established. Most experts use the same cut-off values for AVWS and inherited VWD, and we consider this to be a reasonable approach.

A number of factors may affect VWF measurements [72-79]:

- VWF is an acute phase reactant, increasing in the setting of physiologic stress or inflammation.
- VWF levels are affected by blood type. Type O individuals have plasma levels 25 to 30 percent lower than type A, B, or AB.
- Estrogens increase VWF levels (eg, during pregnancy and use of oral hormonal contraceptives).
- Genetic polymorphisms in some populations (eg, African Americans) cause reduced VWF values in laboratory tests without affecting function.

If the above tests are not definitive, further testing may be helpful:

- VWF multimers
- VWF:propeptide
- VWF:collagen binding

Decreased collagen binding, decreased high molecular weight multimers (found in one-third or more of patients with AVWS), and/or a high ratio of VWF propeptide to VWF:Ag (eg, ratio >2) may be found in patients with AVWS. The high VWF:propeptide to VWF:Ag ratio indicates increased clearance of VWF, which can be helpful in both the diagnosis and in confirming remission after treatment [80]. While none of these tests is definitive for distinguishing AVWS from inherited VWD, they may at least help to establish the diagnosis of VWD and suggest the diagnosis of AVWS in the correct clinical setting. Other information may be more useful in distinguishing AVWS from inherited VWD, such as the response to initial treatment and a measurement of the half-life of infused VWF. (See 'Distinguishing acquired from inherited disease' below.)

Results of testing for autoantibodies to VWF using functional tests (mixing studies) often are negative, even if such an antibody exists [10,14,15]. This may be because the antibody is completely bound to the VWF protein (and hence not present in the plasma) or because the antibody decreases VWF levels by causing increased clearance of the VWF protein rather than inhibiting VWF function (and hence does not affect the results of the mixing study). If the mixing study is easily available, it is helpful when it is positive and therefore can be a reasonable option.

A number of ELISA assays for autoantibodies to VWF have been developed in research laboratories, but none have been broadly standardized or widely used, and they are not widely available.

Distinguishing acquired from inherited disease — Distinguishing AVWS from inherited VWD is important in planning treatment, especially if an intervention directed at AVWS such as immunosuppressive therapy is planned. Other reasons for distinguishing AVWS from inherited VWD include other treatment decisions, judgments about whether to search for an associated condition, and decisions about testing and counseling of relatives. (See 'Post-diagnostic testing' below and "von Willebrand disease (VWD): Treatment of major bleeding and major surgery".)

There are no screening tests that distinguish congenital VWD from AVWS. For individuals with low VWF levels, findings that favor AVWS over congenital VWD include the following [8]:

- Onset of bleeding later in life; history of prior uneventful surgery or trauma without excessive bleeding prior to bleeding episode(s)
- Negative family history for VWD
- Presence of an inhibitor to VWF or VWF-binding antibodies
- Ratio of VWF:RCo to VWF:Ag <0.7 and loss of high molecular weight (HMW) multimers (not always present; one must distinguish from VWD type 2A) [81]
- Remission of bleeding after treatment of an underlying AVWS-associated disorder
- Response to treatment with intravenous immune globulin (IVIG), suggesting an IgG monoclonal gammopathy-associated AVWS
- Response to VWF-containing concentrates (usually short-lived) or desmopressin

In cases in which it is difficult to determine whether VWD is acquired or inherited (children, or adults with an unclear bleeding history), there may be value in testing first degree relatives for VWD [20]. The presence of VWD in first degree relatives is strongly suggestive of inherited disease.

Differential diagnosis — The differential diagnosis of AVWS includes inherited VWD and other inherited and acquired bleeding disorders. Some of the conditions associated with AVWS are

also associated with higher risks of other bleeding disorders.

- **Inherited VWD** – Inherited VWD is the most common inherited bleeding disorder. Like AVWS, patients may have bleeding or bruising of variable severity. Like AVWS, reduced VWF levels and function are seen on laboratory testing, and several patterns of VWF multimers may be seen on multimer analysis. Unlike AVWS, in inherited VWD, some relatives are likely to be affected and to have similar laboratory abnormalities (except in cases of de novo mutations or uncertain parentage). Unlike AVWS, inherited VWD is due to genetic variations and thus does not respond to immunosuppressive therapies or treatments directed at reducing shear stress. (See "Clinical presentation and diagnosis of von Willebrand disease".)

- **Other inherited bleeding disorders** – Other inherited bleeding disorders include hemophilia (inherited deficiency of factor VIII [hemophilia A], factor IX [hemophilia B], or factor XI [hemophilia C]), rare deficiencies of other coagulation factors, hereditary hemorrhagic telangiectasia (HHT), and platelet disorders. Unlike AVWS, these disorders are associated with different laboratory abnormalities of coagulation and/or platelets rather than abnormal VWF levels or function.(See "Clinical manifestations and diagnosis of hemophilia" and "Factor XI (eleven) deficiency" and "Rare inherited coagulation disorders" and "Clinical manifestations and diagnosis of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)".)

- **Acquired inhibitors to other coagulation factors** – Acquired factor inhibitors are autoantibodies to coagulation factors that interfere with hemostatic function. Autoantibodies to factor VIII are the most common acquired inhibitor. Like AVWS, acquired factor inhibitors may be seen in individuals with increased autoantibody production, such as systemic lupus erythematosus (SLE), other autoimmune disorders, and certain malignancies. Unlike AVWS, other acquired factor inhibitors are generally associated with a more severe prolongation of the aPTT or a prolongation of the PT (depending on the factor involved), a reduction of the involved specific factor level, usually evidence of a factor inhibitor on mixing studies, and normal levels of VWF. Although factor VIII may be decreased in AVWS, factor VIII function usually corrects in a factor VIII mixing study. (See "Acquired hemophilia A (and other acquired coagulation factor inhibitors)".)

- **Platelet disorders** – Acquired platelet disorders may occur in the setting of uremia, liver disease, and a number of medications. Inherited platelet disorders are uncommon. Like AVWS, platelet disorders may cause petechiae and mucosal bleeding with a normal platelet count. Unlike AVWS, these disorders do not alter VWF levels or function. (See "Inherited platelet function disorders (IPFDs)".)

- **Antithrombotic therapies** – Bleeding in a patient with any of the above conditions may be exacerbated by an antithrombotic agent (anticoagulant or anti-platelet agent). Like AVWS, patients receiving one of these agents may present with mucosal bleeding or soft tissue bleeding. Unlike AVWS, the antithrombotic therapies have predictable effects on coagulation and platelet testing, they do not affect VWF level or function, and the primary intervention for bleeding is to reverse and/or stop the drug. (See "Heparin and LMW heparin: Dosing and adverse effects" and "Fondaparinux: Dosing and adverse effects" and "Direct oral anticoagulants (DOACs) and parenteral direct-acting anticoagulants: Dosing and adverse effects" and "Warfarin and other VKAs: Dosing and adverse effects".)

MANAGEMENT

There are a number of management decisions to be made for patients with AVWS, including the selection of the best treatment for acute bleeding, the need for chronic (prophylactic) therapy, the role of treatment for the underlying condition, and the best way to manage individuals with AVWS who require antithrombotic therapy for their underlying disorder.

Our approach discussed in the following sections is largely consistent with several review articles [8,46,82,83].

Post-diagnostic testing — There are no additional required tests in an individual diagnosed with AVWS. However, the following may be appropriate in selected individuals:

- Evaluation of any abnormal findings on the complete blood count (CBC) and coagulation testing. This may include testing the levels of additional coagulation factors in the intrinsic pathway (factors IX and XI) when the presence of bleeding and prolongation of the activated aPTT is out of proportion to any observed decrease in the factor VIII level. Depending on the severity of bleeding, platelet function screening may also be undertaken. (See "Platelet function testing".)

- Evaluation for an underlying disorder associated with AVWS, if such a condition has not already been diagnosed [8,71]. In many cases a thorough history and physical examination will be sufficient to identify one of the causative conditions described above. For those without a diagnosed associated condition, limited laboratory testing may include review of the CBC and blood smear for findings associated with hematologic disorders, thyroid stimulating hormone (TSH), and serum protein electrophoresis (SPEP) to detect monoclonal gammopathy, with subsequent testing guided by the results.

- If an associated condition is not identified, it may be appropriate to revisit the family history and/or test family members for inherited von Willebrand disease (VWD). (See "Clinical presentation and diagnosis of von Willebrand disease".)

Treatment of acute bleeding — The treatment of bleeding varies depending on its severity, the reversibility of the underlying cause, and other coexisting hemostatic abnormalities (for which appropriate treatment should be administered).

For the most severe bleeding, von Willebrand factor (VWF) concentrates are used alone or in combination with other modalities; these are summarized in the table (table 2).

Treatment of the underlying condition — If possible, treat the underlying condition responsible for the AVWS. Conditions that lead to consumption or reduced half-life of VWF will also shorten the half-life of VWF concentrates and make them less effective at usual doses and intervals. However, for many of the conditions, treatment is not immediately possible, and it may take days to weeks to become effective if treatment is available. Thus, for clinically important bleeding, treatment of the underlying condition is important but must be accompanied by other therapies. The following may be appropriate in specific diseases:

- Surgical correction for congenital heart defects or aortic stenosis.
- Cytoreductive therapy for myeloproliferative neoplasms with very high platelet counts (eg, >1 million).
- Immunosuppressive therapy or intravenous immune globulin (IVIG) for conditions with autoantibodies to VWF such as SLE, monoclonal gammopathy of undetermined significance (MGUS), or chronic lymphocytic leukemia (CLL).
- Plasmapheresis – Uncommonly, plasmapheresis has been used in cases with autoantibodies and serious bleeding to rapidly, though transiently, reduce antibody levels; this is most effective with IgM autoantibodies [8].
- Agents to treat angiodysplasia – Octreotide, thalidomide, lenalidomide, and atorvastatin have been used to treat gastrointestinal angiodysplasia in inherited VWD and should be useful in AVWS as well [83].

Therapies for bleeding — Specific treatments used initially for active bleeding associated with AVWS include DDAVP (desmopressin) and VWF concentrates, alone or in combination (table 2).

DDAVP — The rationale for the use of DDAVP initially is that bleeding may respond rapidly to DDAVP without exposure to foreign proteins in VWF preparations, and DDAVP may be more readily available than VWF concentrates. Overall, the response rate is said to be approximately 30 percent, depending on the distribution of causes in any series of patients with AVWS [33].

DDAVP is usually avoided in individuals with cardiovascular disease and/or a history of thrombosis, as well as older, fragile patients who may be at high risk for thrombosis.

Treatment with DDAVP may be rapidly effective, and it has the theoretical advantage over VWF concentrates of causing a transient release of ultrahigh molecular weight, very prothrombotic VWF multimers [20].DDAVP is often administered when VWF concentrates are not immediately available. DDAVP should not be used (or used with great caution) in patients with a high risk of thrombosis [20].

DDAVP is given every 12 to 24 hours for a maximum of three doses; it should be administered intravenously for active bleeding in a newly diagnosed AVWS patient. It can be administered intranasally, subcutaneously, or intravenously (table 3) once the patient has been shown to have a sufficient increase in VWF and factor VIII activity levels after the initial intravenous administration. (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'DDAVP'.)

With rare exceptions, these patients will not have been given a DDAVP trial in the non-bleeding state, but the first administration of DDAVP in this setting acts as a therapeutic trial; if the patient does not have a satisfactory response, no further doses of DDAVP are given. Tachyphylaxis occurs with DDAVP after the initial three to five doses of administration; for this reason and because of side effects, it is not generally used beyond three to five days in a given treatment session.

DDAVP can cause hyponatremia, which can be severe and can lead to seizures. Serum sodium levels should be monitored with repeated doses, and free water intake should be limited.

The efficacy of DDAVP depends on the cause of AVWS. In a study that compared the efficacy of DDAVP in 25 individuals with AVWS due to different underlying conditions, DDAVP was effective in correcting VWF levels in 15 of 16 patients without an autoantibody to VWF and in only 4 of 8 with an autoantibody to VWF [10].

DDAVP may be administered in addition to VWF concentrates, if the patient first receives a VWF concentrate and the VWF concentrate fails to sufficiently stop the bleeding.

VWF concentrates — For clinically significant bleeding, VWF concentrates are administered intravenously, either after a poor response to a therapeutic trial with DDAVP (see 'DDAVP' above) or sometimes initially, depending on availability and circumstances.

Plasma-derived and recombinant VWF products are available.

- **Dosing** – A dose of plasma-derived VWF/FVIII concentrate of 40 to 60 international units per kg of body weight is given initially to attempt to reach a plasma level of 50 to 100 international units/dL.

  Subsequent doses will depend on the response of the patient. Subsequent doses of 20 to 40 international units per kg of body weight every 12 hours usually maintains the plasma concentration at 50 to 100 percent in a patient without a shortened VWF half-life. Patients with AVWS may require higher and more frequent doses (eg, 50 to 100 international units/kg) to maintain desired VWF levels. The dose given is also dependent upon the degree of bleeding, as shown in the table (table 4).

  Continuous infusion of factor has been used in a few patients whose factor levels cannot be maintained with intermittent infusions and who continue to bleed; the doses have varied between 2 and 15 international units per kg per hour [84-86].

Recombinant VWF (rVWF) — rVWF treatment for AVWS has shown good results, although there is not widespread experience. Theoretically it may be very useful due to its longer half-life, lack of factor VIII content (for patients who may already have high factor VIII levels), and inclusion of ultra-high molecular weight multimers [87].

- **Monitoring** – It is important to obtain levels of VWF and factor VIII activity immediately before and following infusion to determine the half-life of the infused products. Post-infusion levels can be measured at 4, 8, and 12 hours after the first infusion to obtain half-life information, with less frequent testing performed subsequently (every twelve hours or once daily) depending on the patient's clinical status.

  In general, the goal is to maintain the activity of factor VIII and of VWF (generally measured as VWF:RCo or VWF:GPIbM) between 50 to 100 percent for 3 to 14 days for more serious bleeding or major surgery. Factor VIII activity should be monitored to ensure that it does not rise above 200 international units/dL, which increases the risk of thrombosis.

- **Supporting data** – An in vitro study comparing rVWF and plasma-derived VWF concentrate indicated that rVWF yields higher levels of VWF activity and antigen and does not result in an increase in endogenous thrombin potential as the plasma-derived

concentrate did [88]. The usual starting dose is 80 international units/kg intravenously. Examples of successful use of rVWF include a pediatric patient with AVWS who had a good response and a patient with an IgM paraproteinemia who had a good response [89,90].

Additional information about available VWF products and their administration is discussed in detail separately. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'VWF concentrates for major bleeding'.)

Antifibrinolytic therapy and topical agents — Bleeding can also be treated with antifibrinolytic agents, especially bleeding from mucosal sites such as epistaxis, dental bleeding, or heavy menstrual bleeding.

Available agents include tranexamic acid and aminocaproic acid.

Topical agents such as Gelfoam or Surgicel soaked in topical thrombin can be used for nasal or oral bleeding. The antifibrinolytic and topical medications are frequently used in conjunction with other therapies for AVWS. Administration is similar to other bleeding conditions. (See "Management of bleeding in patients receiving direct oral anticoagulants", section on 'Antifibrinolytics and other pro-hemostatic therapies' and "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'Antifibrinolytic agents'.)

Recombinant activated factor VII (rFVIIa) — Case reports have described the successful use of rFVIIa in patients with AVWS who have life-threatening bleeding not controlled by other measures [91-93].

rFVIIa does not raise VWF or factor VIII levels, but in cases of extreme or life-threatening bleeding that cannot be controlled by other means, it has been effective. (See "von Willebrand disease (VWD): Treatment of major bleeding and major surgery", section on 'Refractory bleeding'.)

IVIG — Intravenous immune globulin (IVIG) is effective in some cases of AVWS, especially those due to anti-VWF autoantibodies (table 2); this often applies to patients with associated diseases such as SLE, monoclonal gammopathies such as MGUS, multiple myeloma, and some lymphoproliferative disorders [10,33,94,95].

In a report of 10 patients with AVWS due to MGUS, IVIG produced a more sustained response in VWF levels than VWF concentrates or DDAVP, and IVIG prevented perioperative bleeding [96]. The benefits of IVIG in individuals with MGUS were mostly limited to those with IgG MGUS (not IgM MGUS).

Dosing of IVIG is similar to that used in other autoimmune disorders (eg, 1 g/kg intravenously once daily for two days), and it is repeated at approximately three to four week intervals if needed [33]. IVIG may be used in conjunction with VWF concentrates and/or DDAVP in patients with a suboptimal response to these medications [33]. (See "Overview of intravenous immune globulin (IVIG) therapy".)

Therapies to decrease autoantibody levels — The following may be appropriate in addition to therapies listed above:

- **Immunosuppressive therapy** – Immunosuppressive therapy may be useful for reducing autoantibody production in individuals with disorders associated with autoantibodies to VWF. Besides glucocorticoids, this may include cyclophosphamide or other immune modifying medications, including the monoclonal antibody rituximab, which targets B cells [94,97]. A 2016 case report described effective use of lenalidomide in two patients with AVWS, one due to MGUS and one to smoldering myeloma [43]. Both had bleeding that did not respond to other therapies such as VWF concentrates and DDAVP, and both had a sustained response to lenalidomide, even after the dose was reduced or the drug discontinued. Consultation with a specialist in rheumatologic disorders or hematologic malignancies may be indicated.

- **Plasmapheresis** – Plasmapheresis is used to remove autoantibodies on a temporary basis and is particularly helpful in patients with IgM autoantibodies.

Reversal of anticoagulation or antiplatelet therapy — Individuals with AVWS who develop clinically important bleeding while they are being treated with an anticoagulant or an antiplatelet agent may require reduction or reversal of anticoagulation. For those receiving antiplatelet agents, platelet transfusion may be appropriate for serious bleeding. (See "Heparin and LMW heparin: Dosing and adverse effects", section on 'Reversal' and "Management of warfarin-associated bleeding or supratherapeutic INR" and "Platelet transfusion: Indications, ordering, and associated risks", section on 'Antiplatelet agents'.)

Treatment of bleeding associated with gastrointestinal angiodysplasia — Bleeding from gastrointestinal angiodysplasia can occur in patients with AVWS (see 'Consequences of reduced VWF' above). Management can be challenging, and high quality evidence is lacking to support a specific approach. The following may be appropriate in selected patients, with the choice among them individualized according to the individual's underlying medical condition(s) and the site(s) and severity of bleeding:

- Local endoscopic procedures or embolization if the number of lesions and anatomy are amenable. (See "Angiodysplasia of the gastrointestinal tract", section on 'Treatment'.)

- Systemic VWF therapies such as those described above, especially if lesions are more numerous or anatomically inaccessible [36]. In some cases, prophylaxis with VWF concentrates may be effective, but higher doses at more frequent intervals might be needed (typical dose, 40 to 60 international units/kg intravenously two to three times per week). (See 'Treatment of acute bleeding' above.)

- Thalidomide and its immunomodulatory (IMiD) derivatives. A 2015 report described the use of thalidomide in eight individuals with LVAD-associated AVWS and bleeding from gastrointestinal angiodysplasias [62]. All treated patients had cessation of bleeding (five patients) or reduction in bleeding (two patients); one died of sepsis within one week of starting the drug. Lenalidomide and thalidomide have also been shown to be effective in the gastrointestinal angiodysplastic bleeding in inherited VWD and may be effective in AVWS [83,98]. We would use this approach if other measures were ineffective. Contraindications to these medications must be taken into account.

- Rituximab was used successfully to maintain remission in a 78-year-old male who had responded to IVIG for continuous bleeding from gastrointestinal angiodysplasia [99]. He had received multiple other therapies, including thalidomide and local ablation, before IVIG and subsequently rituximab was administered.

- Octreotide, a somatostatin analogue, has been used successfully in patients with AVWS and gastrointestinal bleeding [100,101].

- Statins, especially atorvastatin, may have antiangiogenic effects in some individuals. Case reports have described dramatic improvements with reduced transfusion requirements [102,103]. A review that summarized the efficacy of various treatments for angiodysplasia identified 17 individuals treated with statins, with five (29 percent) reporting a good response [104].

  Once bleeding has been controlled, it is important to establish a plan for treating and preventing future bleeding.

Bleeding prophylaxis and perioperative management — The correlation between VWF levels and clinical bleeding is weak. Thus, decisions about prophylaxis and perioperative management should not be based solely on laboratory values but should also incorporate clinical features for each patient.

Individuals with AVWS who require surgery should have a plan for prophylaxis and treatment of bleeding available to all clinicians involved in the patient's care. For elective surgery, delaying the procedure until the patient receives treatment of the underlying disorder causing AVWS

may be the best approach. If this is not possible, hemostatic therapies as described above may be required (table 2), with the choice of agent and dosing dependent on the severity of the AVWS and the bleeding risk of the procedure. (See 'Therapies for bleeding' above.)

In unusual cases, especially those in which definitive therapy for the underlying cause of AVWS is not undertaken, patients may require long-term prophylaxis against bleeding. An example is aortic stenosis with angiodysplasia (Heyde syndrome) in a patient who does not undergo aortic valve surgery [36]. In such a patient, one might consider administering VWF concentrates two or three times weekly, following clinically for evidence of a change in the quantity of gastrointestinal blood loss.

Specific prophylactic strategies for surgery follow:

- DDAVP can often be used successfully for minor procedures, as long as the patient has demonstrated a VWF response to a DDAVP test dose several days earlier (see 'Post-diagnostic testing' above). This should not be done in the one to two days before the procedure because there will be insufficient time for VWF stores to be replenished. The first perioperative dose of DDAVP is administered approximately one hour before the procedure, and subsequent doses can be given 6 to 12 hours after surgery and then every 24 hours. It is important for all patients to have VWF concentrates available in case DDAVP is ineffective. (See "von Willebrand disease (VWD): Treatment of minor bleeding, use of DDAVP, and routine preventive care", section on 'DDAVP'.)

- VWF concentrates are often required for major and high-bleeding-risk procedures. It is prudent to measure the response to VWF concentrates, including the half-life of the infused concentrate, the day before surgery if possible. The schedule and dosing is similar to that described above (see 'Treatment of acute bleeding' above), keeping in mind the possible use of continuous infusion.

- Antifibrinolytic therapies may be especially useful for dental procedures and other procedures involving sites with high intrinsic fibrinolytic activity. Caution should be used in patients who have any danger of ureteral obstruction.

Administration of these therapies is discussed in more detail above. (See 'Treatment of acute bleeding' above.)

Patients who require antithrombotic therapy — Management is especially challenging in patients with AVWS who also require antithrombotic therapy. Examples include those on a left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO) device.

Individuals who are not bleeding can be treated with anticoagulants judiciously. Common sense suggests that a short-acting agent that can be reversed should be used.

If bleeding occurs, the risks and benefits of discontinuing anticoagulation are individualized according to the severity of bleeding and thromboembolic risk. Antithrombotic therapy should be discontinued for any serious or life-threatening bleeding; treatment with VWF concentrates may be appropriate (see 'VWF concentrates' above); and consideration should be given to removal of the LVAD or ECMO if possible.

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: Acquired bleeding disorders" and "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 topics (see "Patient education: von Willebrand disease (The Basics)")
- Beyond the Basics topics (see "Patient education: von Willebrand disease (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Mechanisms** – A number of conditions can reduce levels of von Willebrand factor (VWF) and cause acquired von Willebrand syndrome (AVWS). Mechanisms include autoantibodies to VWF, high shear with unfolding and subsequent cleavage of VWF (especially the most hemostatically active high molecular weight multimers), adsorption of VWF to cells, and decreased VWF production. (See 'Pathophysiology' above.)

- **Prevalence** – The prevalence of AVWS is unknown, but it is likely to be 20- to 100-fold less common than heritable von Willebrand disease (VWD). The prevalence in certain disease populations is higher. (See 'Epidemiology' above.)

- **Causes** – Major causes of AVWS include lymphoproliferative disorders, myeloproliferative disorders, autoimmune disorders, cardiovascular conditions with vessel stenosis or high flow, left ventricular assist device (LVAD), extracorporeal membrane oxygenation (EMCO), Wilms tumor, hypothyroidism, and certain medications (table 1). (See 'Associated diseases' above.)

- **Evaluation** – AVWS may be suspected in a patient with a recognized associated underlying condition or with new-onset unexplained bleeding and no personal or family history of bleeding. A physical examination should focus on findings of associated conditions. Laboratory testing should include complete blood count (CBC), platelet count and screening coagulation testing. If the history and preliminary laboratory testing suggest AVWS, additional testing includes VWF antigen and activity and factor VIII activity. (See 'Typical presentations' above and 'Laboratory testing' above.)

  If an underlying cause is unknown, limited evaluation for possible hematologic disorders is appropriate (blood smear review, serum protein electrophoresis [SPEP]), as is testing for thyroid disease. Individuals not expected to have the underlying condition corrected soon may have a DDAVP test dose. (See 'Post-diagnostic testing' above.)

- **Differential** – The differential diagnosis includes hereditary VWD, platelet abnormalities, and other hereditary bleeding disorders; acquired coagulation factor inhibitors; and effects of antithrombotic therapies. (See 'Differential diagnosis' above.)

- **Management**

  - **Bleeding** – Treatment of acute bleeding may include treatment of the underlying condition and administration of DDAVP, VWF concentrates (plasma-derived or recombinant), antifibrinolytic and topical therapies, and/or others noted in the table (table 2) and discussed above. (See 'Treatment of acute bleeding' above.)

Antithrombotic therapies may need to be discontinued in actively bleeding patients. Bypassing agents are rarely used. (See 'Reversal of anticoagulation or antiplatelet therapy' above.)

- **IVIG and immunosuppression** – Individuals with autoantibodies to VWF may be treated with intravenous immune globulin (IVIG) and may receive longer term benefit from immunosuppressive therapy. IVIG may be given concomitantly with other therapies. (See 'Therapies to decrease autoantibody levels' above.)

- **GI lesions** – Local or systemic therapies may be indicated depending on the number and anatomy of the lesions. (See 'Treatment of bleeding associated with gastrointestinal angiodysplasia' above.)

- **Perioperative** – Prophylaxis against bleeding and perioperative management may comprise DDAVP, VWF concentrates, and/or IVIG, depending on the bleeding risk for the individual patient (table 2). (See 'Bleeding prophylaxis and perioperative management' above.)

- **Concurrent thrombotic risk** – Some individuals may have an increased risk for thrombosis and may require antiplatelet therapy (essential thrombocythemia [ET]) or an anticoagulant (cardiovascular conditions). AVWS by itself is not a contraindication to these therapies, but close consultation with appropriate specialists regarding the timing of therapy, need for intensive monitoring, and available reversal strategies is advised. (See 'Patients who require antithrombotic therapy' above.)

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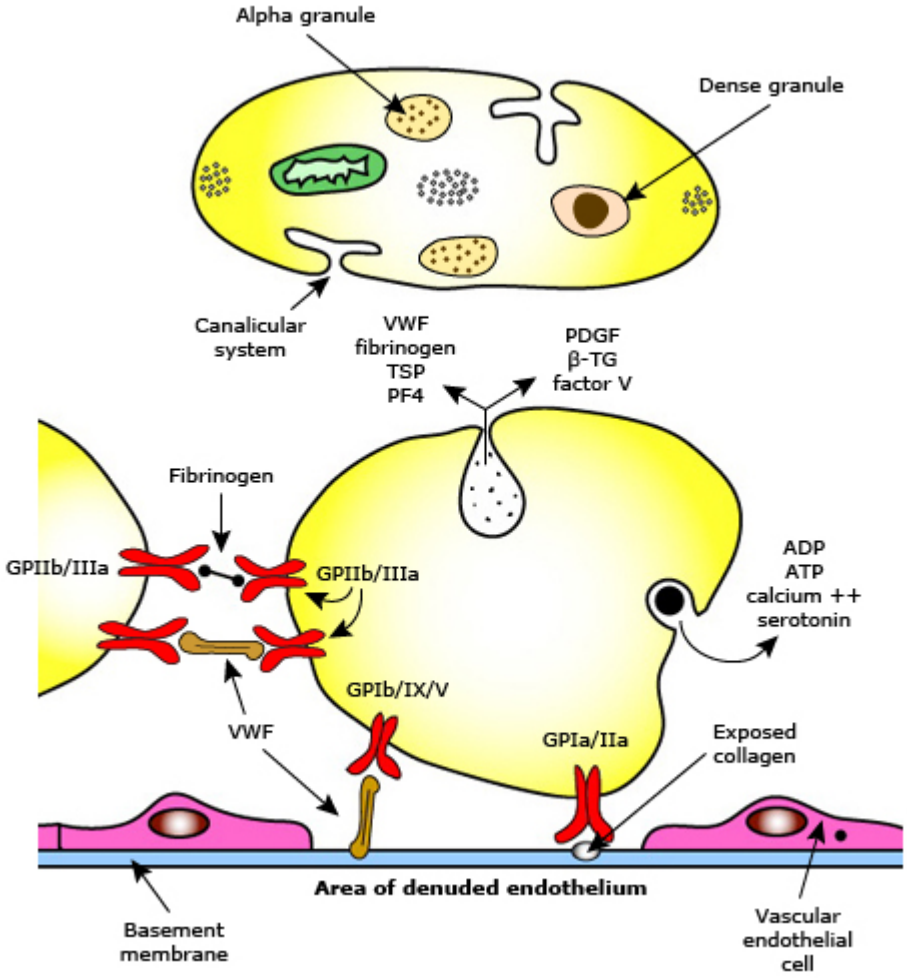
Topic 110531 Version 23.0

GRAPHICS

The platelet and its interactions



Schematic drawing of the platelet (top figure), showing its alpha and dense granules and canalicular system. The bottom figure illustrates the platelet's major functions, including secretion of stored products, as well as its attachment, via specific surface glycoproteins (GP), including von Willebrand factor (VWF), to denuded epithelium (bottom) and other platelets (left).

VWF: von Willebrand factor; TSP: thrombospondin; PF4: platelet factor 4; PDGF: platelet derived growth factor; β-TG: beta thromboglobulin; ADP: adenosine diphosphate; ATP: adenosine triphosphate.

Courtesy of Steven Coutre, MD.

Graphic 81908 Version 4.0

Disorders associated with acquired von Willebrand syndrome

Malignancies
Lymphoproliferative disorders
▪ Monoclonal gammopathy of undetermined significance (MGUS)
▪ Multiple myeloma
▪ Non-Hodgkin lymphoma (NHL)
▪ Chronic lymphocytic leukemia (CLL)
▪ Waldenström macroglobulinemia
Myeloproliferative neoplasms (MPNs)
▪ Essential thrombocythemia (ET)
▪ Polycythemia vera (PV)
▪ Chronic myeloid leukemia (CML)
▪ Primary myelofibrosis (PMF)
Wilms tumor
Other cancers
Immune disorders
Systemic lupus erythematosus (SLE)
Other autoimmune diseases
States of high vascular flow
Ventricular septal defect
Congenital heart disease with high flow state
Aortic stenosis
Severe mitral valve prolapse or mitral regurgitation
Ventricular assist device (LVAD)
Extracorporeal membrane oxygenation (ECMO) device
Other disorders
Hypothyroidism
Gastrointestinal angiodysplasia

Drugs and other agents
Valproic acid
Hydroxyethyl starch
Antibiotics: Griseofulvin, ciprofloxacin

The table lists selected causes of AVWS for which there were three or more reports in the literature on its association; other causes are also possible.

AVWS: acquired von Willebrand syndrome.

Adapted from:

1. *Veyradier A, Jenkins CS, Fressinaud E, et al. Acquired von Willebrand syndrome: from pathophysiology to management. Thromb Haemost 2000; 84:175.*
2. *Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost 2000; 84:346.*

Graphic 54202 Version 11.0

Therapies for acquired von Willebrand syndrome (aVWS)

Therapy	Dose	Comments
Therapies directed at treatment of bleeding (or prevention of surgical bleeding)		
DDAVP (desmopressin)	▪ Intravenous dose: 0.3 mcg/kg (maximum dose 20 mcg) in 50 mL saline over 20 min	▪ Can be repeated every 12 to 24 hours, but tachyphylaxis occurs after 3 to 5 doses. ▪ Follow response at 1 and 4 hours (assay VWF and factor VIII activities). ▪ Follow serum sodium after 2 to 3 doses to avoid hyponatremia (may need to discontinue). ▪ Use with caution in patients with cardiovascular disease
VWF concentrate (plasma-derived or recombinant)	▪ Plasma-derived: Usual starting dose, 40 to 60 units/kg intravenously ▪ Recombinant: Usual starting dose, 80 units/kg intravenously	▪ Follow response (VWF and factor VIII activities) at 1 and 4 hours to estimate half-life. ▪ Adjust dose and frequency of infusion depending on clinical course. ▪ Consider continuous infusion if therapy is effective but half-life is short.
Antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid)	▪ TXA: 10 mg/kg intravenously 3 times per day **or** 25 mg/kg orally every 6 to 8 hours ▪ EACA: 25 to 50 mg/kg orally 4 times per day	▪ Either agent may be used. ▪ Generally given as adjunctive therapy with other treatments. ▪ Reduce dose in patients with kidney failure.
Recombinant activated factor VII (rFVIIa)	▪ NovoSeven RT*: Usual dose, 90 mcg/kg intravenously every 4 to 6 hours	▪ Use for life-threatening bleeding after other therapies fail. ▪ Avoid in patients with cardiovascular risk.
Therapies directed at increasing VWF levels and decreasing the levels of autoantibodies¶		

IVIG	▪ 1 gram/kg intravenously over several hours, once per day for 2 days (total dose, 2 grams/kg)	▪ Most effective in IgG MGUS and in other autoantibody-mediated disease. ▪ May take 2 to 3 days to prevent clearance of VWF and raise VWF activity levels in patients with a response.
Plasmapheresis	▪ One exchange every 2 to 3 days, with each exchange consisting of 1 to 1.5 plasma volumes	▪ May use as a temporizing measure (with other treatments) in patients with multiple myeloma or other disorders with high paraprotein levels. ▪ In most cases, a total of 3 to 5 procedures. ▪ Use albumin as replacement fluid.

The underlying disorder responsible for aVWS should be treated whenever possible. Use specific treatments for bleeding. Medications can be combined in many cases. Other therapies with other mechanisms of action have been described in case reports; examples include rituximab (immunosuppressive), lenalidomide (anti-angiogenic), or octreotide (reduce portal blood flow). We generally do not use these therapies, as experience is very limited and they are not approved for aVWS. Refer to UpToDate for a more comprehensive discussion of the diagnosis and treatment of aVWS.

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aVWS: acquired von Willebrand syndrome; VWF: von Willebrand factor; TXA: tranexamic acid; EACA: epsilon aminocaproic acid; rFVIIa: recombinant activated factor VII; IVIG: intravenous immune globulin; Ig: immunoglobulin; MGUS: monoclonal gammopathy of undetermined significance.

* An alternative rFVIIa product, SevenFact, is available but not approved for aVWS. Dosing for NovoSeven RT and Sevenfact are not interchangeable; refer to the product information for details.

¶ Therapies directed at lowering autoantibody levels and preventing immune destruction of VWF are only appropriate for individuals with immune-mediated aVWS.

Graphic 129086 Version 4.0

Administration of DDAVP for hemostasis

Administration	Caveats and comments
Uses and limitations	▪ Adequate response to a test dose is ideally established before use, but a patient with AVWS and acute bleeding may receive the first dose as a therapeutic trial ▪ Do not use in children <2 years of age ▪ Avoid or use with extreme care in individuals with cardiovascular disease ▪ Avoid or use with extreme care in pregnant women
Dosing	▪ May be repeated once daily for 3 to 5 days. Beyond 5 days, tachyphylaxis renders it ineffective
Intravenous or subcutaneous	▪ Intravenous: 0.3 mcg/kg (maximum 20 mcg) diluted in 50 mL of normal saline and infused over 20 to 30 minutes ▪ Subcutaneous (not approved for use in the United States): 0.3 mcg/kg (maximum 20 mcg) subcutaneously
Nasal spray	▪ Use the formulation intended for hemostasis (concentration of 1.5 mg/mL; dose 150 mcg/spray), **not** the formulation for enuresis (concentration of 0.01%) ▪ Weight <50 kg: One spray in one nostril (total dose 150 mcg) ▪ Weight ≥50 kg: One spray in each nostril (total dose 300 mcg)
Adverse events	
Hyponatremia	▪ Avoid excess free water intake (oral or intravenous) ▪ Avoid NSAIDs ▪ Monitor serum sodium
Thrombotic events	▪ Especially of concern in individuals with pre-existing increased risk factors such as cardiovascular disease
Headache, flushing, hypotension, hypertension	▪ Usually alleviated by slowing the infusion

Administration of DDAVP causes release of stored von Willebrand factor and factor VIII from endothelial cells and platelets. Refer to UpToDate for details of the management of VWD, hemophilia, and uremic bleeding. Refer to Lexicomp drug information on desmopressin (DDAVP) for additional prescribing information.

AVWS: acquired von Willebrand syndrome; DDAVP: 1-desamino-8-D-arginine-vasopressin; NSAIDs: nonsteroidal antiinflammatory drugs; VWD: von Willebrand disease.

Graphic 110532 Version 9.0

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 ▪ **Minor bleeding or surgery:** Initial dose 40 to 50 international units/kg, followed by 40 to 50 international	▪ 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 differing ages and severities of VWD and in specific clinical settings

	units/kg every 8 to 24 hours as needed clinically	
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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