Review Article

Acquired von Willebrand Syndrome: An Update

ABSTRACT

Acquired von Willebrand Disease (AvWD) is an uncommon bleeding disorder resulting from the development of decreased quantities of circulating functional von Willebrand factor (vWF). The condition may occur due to a number of pathogenic mechanisms, and is invariably associated with an underlying disorder such as congenital heart disease, neoplasms, and autoimmunity or with the use of certain drugs. While its manifestations are similar to that of inherited von Willebrand disease (vWD) in terms of clinical signs and laboratory results, it differs in that the patient lacks a personal or family history of bleeding and presents later in life. Management of the disorder is based on treatment of the underlying condition, which usually results in resolution of the bleeding diathesis. Acute hemorrhage usually requires vWF concentrates and in some cases immunosuppression. Other options involve use of Intravenous Immunoglobulins (IVIg) or plasmapheresis. Recently, immunotherapies and novel agents such as Emicizumab, Lenalidomide and Rtiuximab have been tried as off-label options.

Keywords:*Acquired von Willebrand syndrome, Clinical Presentation, Diagnosis, Hemorrhagic Diathesis, Management, Pathophysiology.*

INTRODUCTION

The von Willebrand factor (vWF) is a glycoprotein multimer involved in the process of hemostasis: it accumulates at the site of endothelial injury and functions as a bridge between adhered platelets, as well as serving as a carrier molecule for circulating factor VIII (FVIII), increasing its plasma half-life by preventing its breakdown by activated Protein C.[1-3] Acquired von Willebrand syndrome (AvWS) is a rare bleeding diathesis resulting from a quantitative defect in the levels of circulating vWF.[4] The global prevalence of the disease is estimated to be between 0.04% and 0.13%, which is thought to be an under-representation as these patients are often misdiagnosed with other disorders.[5,6] Studies report that AvWS is increasing in prevalence both due to increased recognition of the disorder as a cause of bleeding, as well as an increase in underlying precipitants.[4,7]

AvWS is most commonly seen in the older adult population.[8] Clinical manifestations and lab work-up demonstrates features similar to inherited von Willebrand disease (vWD) but without a past or family history of bleeding.[4] Patients often present with excessive bleeding following trauma/surgical procedures, or unprovoked mucocutaneous oozing; Hemorrhage associated with AvWS is not usually fatal, but may require acute management.[3, 9] Although AvWS was first recognized in 1968 (in a patient with systemic lupus erythematous (SLE), it has received more attention in recent years due to the discovery of its association with various underlying disorders.[1,10] The bleeding diathesis is usually triggered by a causal condition: it is commonly associated with the presence of lympho- and myeloproliferative disorders, solid neoplasms, cardiovascular and autoimmune diseases, as well as the use of certain drugs.[9,11]

While the pathophysiology is multifactorial, *the synthesis and release of vWF is usually normal* (except in cases with hypothyroidism) with most cases occurring due to increased *clearance* of vWF from the blood stream.[12] Accelerated clearance may be attributable to the presence of specific and non-specific immunoglobulins, vWF adsorption onto neoplastic cells, or destruction of Large multimers of vWF (LvWF) as a result of shear stress or proteolytic degradation, however, multiple mechanisms may exist concurrently in a single patient.[12] The diagnosis of AvWS is frequently confounded by the requirement for extensive testing to differentiate it from other causes of bleeding, especially the inherited and more common vWD, while management is often complicated due to the underlying precipitant or its therapy, which usually requires complete treatment before AvWS resolves.[4,8]

This review article explores contemporary knowledge on the pathophysiology and clinical presentation, as well as the diagnosis and management of patients with AvWS.

PATHOPHYSIOLOGY

Physiology:

The vWF is synthesized as dimeric subunits, which undergo multimerization to become a large precursor protein in the endoplasmic reticulum and Golgi apparatus of endothelial cells (stored in and secreted from Weibel-Palade bodies) and in megakaryocytes (alpha granules). [13,14] This glycoprotein undergoes several processing steps post-translation before being secreted into the circulation, and its release is regulated by several stimuli, including thrombin, histamine, and epinephrine.[14, 15] Its molecule is composed of several domains, including a signal peptide, propeptide, D domains, A1-A3 domains, B domains, and a C-terminal domain. The propeptide is

cleaved during processing, and the mature vWF molecule is composed of identical subunits linked by disulfide bonds.[13, 16] It is a multimeric molecule with a size as large as 20,000 kDa, while its subunits may be as small as 250 kDa.[17, 18]

This factor has several important functions in hemostasis, including platelet adhesion, aggregation and stabilizing FVIII in the blood.[2, 18] Platelet adhesion occurs when vWF binds to the glycoprotein Ib/IX/V receptor complex on the surface of platelets. This interaction is critical for platelet plug formation and the initiation of hemostasis.[19] In addition, vWF also binds to collagen, which is exposed when the endothelial lining is damaged, which helps to anchor platelets at the site of injury and promotes platelet activation and aggregation.[19, 20] Higher multimers are more efficient at binding platelets and are more haemostatic.[21]This factor also plays a crucial role in stabilizing FVIII in the blood.[16] FVIII is a co-factor for the intrinsic pathway of coagulation and is rapidly degraded in the absence of vWF by activated Protein C.[1-3] The vWF binds to and protects FVIII from degradation, thereby increasing its half-life in plasma.[16,22,23]

The activity of vWF is regulated by several mechanisms, including proteolysis, cleavage, and clearance.[24] Proteolysis occurs when vWF multimers are cleaved by the metalloprotease ADAMTS13 (as well as other metalloproteinases, plasmin and leukocyte-derived proteases), which cleaves vWF between the A2 and A3 domains. This cleavage is important for regulating vWF activity, as larger vWF multimers are more active than smaller ones.[25, 26] Cleavage can also occur through the action of thrombin, which cleaves vWF at the N-terminus of the A1 domain. This cleavage reduces the ability of vWF to bind to platelets and collagen.[4] Clearance of vWF from the circulation occurs via receptor-mediated endocytosis, where endothelial cells and hepatocytes take up vWF. [4, 14]

Pathology: AvWS was previously thought to be an uncommon cause of bleeding diatheses, however, the determination of its association with structural heart disease (valvular abnormalities, septal defects) in recent times established that the disease appears to be more common than previously proposed.[5, 6,27] It is now understood to be invariably associated with an underlying disorder. These include common causes such as cardiovascular disorders, lymphoproliferative diseases (LPDs) including chronic lymphocytic leukemia and plasma cell dyscrasias such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma and Waldenström macroglobulinemia.Less frequent provoking disorders include myeloproliferative neoplasms (MPNs) such as essential thrombocythaemia, polycythemia rubra vera, chronic myeloid leukemia, primary myelofibrosis, solid tumors (such as Wilms tumours), autoimmune disease (for e.g., systemic lupus erythematous) and certain drugs (sodium valproate, griseofulvin. ciprofloxacin, hydroxyethyl starch). [4,28-30]

AvWS has a complex, multifactorial pathophysiology which commonly revolves around the increased clearance of vWF from plasma secondary to shear stress, proteolysis, development of autoantibodies or cell surface adsorption, consistently occurring secondary to a provoking disorder.[31, 32] Less commonly, such as in cases with hypothyroidism, patients develop AvWS due to a decrease in production of vWF (the factor itself is qualitatively normal). Hypothyroidism may also be associated with impaired release of vWF into circulation.[33]

Shear stress can result in the degradation of LvWF due to mechanical destruction in patients with valvular heart disease, left ventricular assist devices (LVADs), extracorporeal membrane oxygenation (ECMO) or areas of vascular stenosis.[32] Moreover, LvWF undergoes a

tumbling motion as it moves through circulation which applies force on its structure causing it to elongate and unfold making it susceptible to degradation by enzymes.[34]

LvWF can also undergo increased rates of degradation secondary to proteolysis by the enzyme ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), especially in cases with MPNs.[4, 35] Additionally, patients with LPDs (particularly plasma cell dyscrasias) and those with autoimmune diseases may develop autoantibodies against domains (both functional and non-functional) within the structure of vWF. These immune complexes are then removed from blood circulation by the reticulo-endothelial system.[28,36] Direct inhibitors of vWF's interaction with circulating platelets may also occur, however, these are a rare occurrence.[4]

Lastly, adsorption of LvWF on malignant cells in cases with LPDs (Waldenström macroglobulinemia, non-Hodgkin lymphoma, Multiple Myeloma), MPNs and solid tumors (such as Wilms tumours) results in increased clearance from blood circulation, which results in the development of AvWS, especially in patients with high cell loads.[37,38] Furthermore, certain tumour cells, such as the clonal plasma cells found in MGUS, exhibit an anomalous expression of glycoprotein Ib (GPIb) which allows vWF to bind to it, resulting in decreased circulating levels. This is also true for MPNs such as essential thrombocythaemia as well as reactive thrombocytosis, as GP1b is also expressed on platelets, and hence patients with thrombocytosis may have low circulating vWF levels.[4,39-41] The frequency of association of different underlying conditions with the development of AvWS, and the likely precipitating mechanisms, is displayed in **Table I**.

Table-I: The frequency and likely mechanism of Acquired von Willebrand Disease

Disorder	Frequency	Mechanism
Lymphoproliferative disorders		
Chronic lymphocytic leukaemia	Anecdotal[42]	Likely immune-mediated[42]
Multiple myeloma	7 - 15%[43,44]	Autoantibody, adsorption[43-45]
Lymphoplasmacytic lymphoma	13%[46]	Increased degradation[46]
Waldenström macroglobulinemia	Anecdotal[28]	Increased degradation[28]
Monoclonal gammopathy of undetermined significance	Anecdotal[47]	Increased clearance, increased degradation[48]
Solid tumours		
Wilms tumor	8%[49,50]	Likely adsorption[50]
Cardiovascular disorders		
Congenital valvular stenosis	12%[51]	Shear stress[51]
Congenital heart disease	21%[52]	Likely shear stress[53]
Left ventricular assist devices	100%[54]	Shear stress, increased degradation[54]
Extra-corporeal membrane oxygenation	100%[55]	Likely shear stress[53,55]
Myeloproliferative neoplasms		
Essential Thrombocythaemia	20 - 55%[56,57]	Adsorption, increased degradation[56]
Polycythaemia rubra vera	17 - 49%[57,58]	Adsorption, increased degradation[56-58]
Chronic myeloid leukaemia	Anecdotal[59]	Unknown
Primary myelofibrosis	15 - 33%[58,60]	Adsorption, increased degradation[56-58]
Other Disorders		
Autoimmune disease	2%[61]	Immune-mediated[61]
Hypothyroidism	32%[62]	Low production[62]

CLINICAL PRESENTATION

Patients with AvWS usually present in late adult life, with a median age at diagnosis of around 60 years, and typically do not have a past or family history of a bleeding diathesis.[63] The clinical presentation can vary widely depending on the underlying cause of the condition, as well

as its severity. Bleeding is usually mucosal, as in vWD, and involves the nasal, oral, uterine, vaginal and/or gastrointestinal mucosae. Patients may also present with easy bruisability, menorrhagia, or prolonged bleeding after injury or surgery. They may present with symptoms and signs related to the underlying medical condition, such as an autoimmune disease, LPDs, MPNs, or cardiovascular disease.[4,8,64] The ISTH registry reports that patients with AvWS secondary to LPDs have a greater tendency to have more severe episodes of hemorrhage compared to those who suffer from other underlying conditions; however, this may simply be attributable to the higher incidence with which AvWS occurs in LPDs.[61] It should be noted here that death secondary to hemorrhage precipitated by AvWS is a rare occurrence.[61]

The association of vWD with the formation of angiodysplasias is well described, and these lesions also form in AvWS. It is estimated to occur in 12% of all cases of vWD.[65] The most common sites involved are the caecum and ascending colon, but patients may have multiple lesions affecting different parts of the gastrointestinal tract. Angiodysplasias are delicate and mild insults can lead to intractable bleeding.[66] While the exact mechanism of formation is unclear, angiodysplasias are thought to form due to impaired platelet adhesion and aggregation caused by vWF deficiency, resulting in blood vessel wall weakness and dilatation. In addition, an imbalance between circulating vWF and factors involved in angiogenesis may result in an overgrowth of blood vessels that are prone to rupture and bleeding.[66]

DIAGNOSIS

The diagnosis of AvWS is suspected in adult patients with a new-onset bleeding diathesis, in the absence of a past or family history of bleeding disorders.[4-8] A number of general and specific investigations which help in establishing a diagnosis, and are discussed as follows:

General Investigations:

a. **Complete blood counts:** These counts, including the platelet count, are usually normal, unless the patient has an underlying platelet disorder such as essential thrombocythaemia.[8]
b. **Prothrombin time:** Prothrombin Time (PT) is usually normal, unless deranged by an underlying condition.[4]
c. **Activated partial thromboplastin time:** Patients who have low circulating FVIII levels have prolonged activated Partial Thromboplastin Time (aPTT), but this only occurs when FVIII levels are below 30%.[67]
d. **Bleeding time:** Bleeding time is prolonged in patients with altered vWF due to poor platelet aggregation.[5,68]

Specific Investigations:

a. **Platelet function analyser-100 closure time:** Platelet Function Analyser-100 Closure Time (PFA-100 CT) is also prolonged, while a normal PFA-100 CT carries a 99.3% sensitivity in predicting the absence of a bleeding diathesis secondary to vWF dysfunction but cannot differentiate between vWD and AvWS.[69]

b. **vWF: Antigen levels:** No cut-off levels have been described for vWF: Antigen (vWF:Ag), and those for vWD are used.[3,4] Levels of vWF:Ag <30 IU/dL are considered indicative of vWD, while levels between 30 – 50 IU/dL are suspicious of it.[70] The vWF:Ag levels in plasma may be normal or decreased in patients with AvWS, depending on etiology.[4,8] However, it should be noted that a number of factors such as race and blood group O individuals, among others, can affect the levels of circulating vWF:Ag, and may not be adequately reflective of the presence of AvWS.[71,72]

c. **vWF: Ristocetin Cofactor activity:**The vWF: Ristocetin Cofactor (vWF:RCo) activity is markedly reduced in patients with AvWS, and the vWF:RCo/vWF:Ag ratio is typically below 0.7.[73]

d. **vWF: Collagen Binding activity:** The vWF: Collagen Binding (vWF:CB) activity is also very low, but this test is only employed when the aforementioned tests do not yield conclusive answers.[74]

e. **vWF multimer electrophoresis:** This assay will help to detect a quantitative decrease in LvWF, which can be seen in patients with AvWS, especially when the primary pathology causes shear destruction of LvWF.[51-55,75]

f. **Plasma vWF propeptide:** Plasma vWF propeptide (vWFpp) indicates the degree of biosynthesis of vWF and a vWFpp/vWF:Ag ratio of >2 indicates that there is an increased clearance of vWF, which can occur in AvWS.[76]

g. **FVIII activity levels:** FVIII levels are low in AvWS, as less vWF is available to protect FVIII from degradation.[4-8]

While the aforementioned tests are useful in establishing whether there is a pathology in the function of vWF, none of them help distinguish AvWS from vWD. Diagnosis may be further

complicated by the use of antithrombotic/anticoagulation therapy for underlying disorders. Diagnosing AvWS may be based on the algorithm displayed in **Figure 1**.

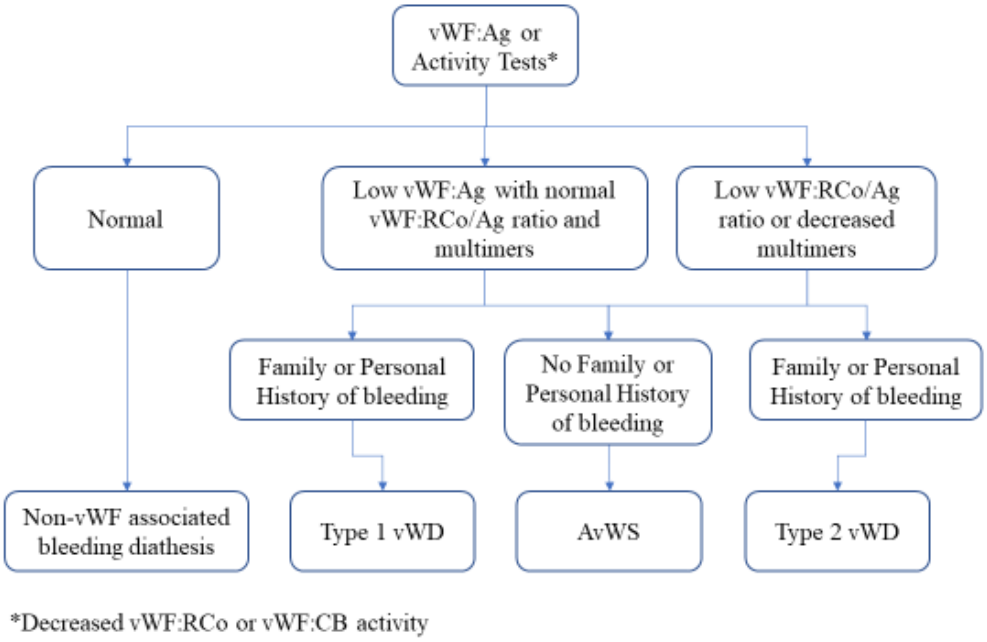

Figure-1: Diagnosing acquired von Willebrand syndrome and differentiating it from inherited von Willebrand disease.

Testing for autoantibodies against vWF have a limited role in the diagnostic evaluation of AvWS, as such cases account for only a minority of patients.[37,77] However, since such patients are known to have a higher tendency to have more severe episodes of bleeding (as autoantibodies bind to and inactivate LvWF preferentially), they should be tested in each patient of AvWS, as their presence provides valuable information with regards to clinical course/prognosis.[78] Such

testing is based on mixing studies wherein patient plasma is mixed with normal plasma and incubated at body temperature followed by the estimation of vWF:RCo and vWF:CB levels.[79] The presence of an inhibitor will result in low activity of these two compounds. However, it should be noted that this test is limited by the inability to detect autoantibodies that increase the clearance of vWF from plasma without decreasing its activity.[4,79,80] More advanced techniques such as Enzyme-Linked Immuno-Sorbent Assays (ELISA) may be utilized to detect such antibodies, however, such methods are not routinely employed.[80]

In short, establishing a concrete diagnosis of AvWS is problematic as it is difficult to differentiate vWD from AvWS because of similar clinical and laboratory pictures, and a combination of high clinical suspicion and suggestive laboratory workup should be considered before labeling a patient with AvWS, particularly when a patient presents with mild symptoms and at a young age. Furthermore, differentiating AvWS from vWD is of paramount importance as the management modalities are quite different.

MANAGEMENT

Management of AvWS involves identifying and treating the precipitating condition, controlling bleeding once it occurs, and preventing future hemorrhagic episodes:

Treating underlying condition/Inhibitor eradication: Identification and management of the underlying precipitant is the only process by which a durable cure can be achieved, such as with immunosuppression, chemotherapy or withdrawing offending drug etc..[1-8] It is pertinent to note here that patients with hypothyroidism may develop a resolution of AvWS following adequate treatment with thyroxine.[1-8]

Managing bleeding symptoms: Hemorrhages may range from mild to severe. The management of bleeding symptoms may involve the administration of specific drugs to promote clotting, and/or replacement of plasma vWF:

a. **Desmopressin:** This is an intravenously/subcutaneously/intransally administered synthetic analog of 1-Deamino-8-D-Arginine Vasopressin (DDAVP) which works by rapidly releasing endothelial vWF.[38,77] It is given at a dose of 0.3 mg/kg every 12 to 24 hours (maximum three doses due to tachyphylaxis) to manage active bleeding, as well as for prevention, in AvWS.[38,81] Patients receiving DDAVP while suffering from MGUS have demonstrated a significant increase in levels of plasma vWF after administration, but the effect was short-lived. This may be due to the presence of circulating anti-vWF antibodies, especially in cases precipitated by LPDs, which results in rapid deactivation and clearance of DDAVP-released vWF.[82] The effect was also transient in certain MPNs due to the enzymatic degradation of released vWF, or its adsorption of the neoplastic cell surface.[43] Previously, the ISTH registry declared that approximately a third of patients treated with DDAVP had an adequate response, but this greatly varied with the underlying disorder: patients with cardiovascular disease and MPNs had a lower response rate compared to those who suffered from autoimmune or LPDs.[61]

b. **vWF concentrates:** These concentrates are derived from donor plasma and also usually contain other clotting factors such as FVIII, which can be employed in the treatment of AvWS. The ISTH registry recorded that the frequency of a positive response to vWF/FVIII concentrates was 40%, when vWF is administered at dosages ranging from 30-100 units/kg.[61] However, the half-life of factors infused in this manner, including

vWF, is shorter in cases with AvWS compared to patients with vWD, thus increased doses need to employed to attain therapeutic plasma levels.[43,82,83]

c. **Antifibrinolytic agents:** Drugs such as aminocaproic acid and tranexamic acid act by inhibiting the activation of plasminogen, thus prolonging the half-life of the fibrin meshwork essential for a stable clot.[84] Both these medications can be given orally, locally or intravenously, and serve as useful adjuncts to the treatments mentioned previously, both for prophylaxis and for patients with acute bleeding.[4,84] However, as a single agent these drugs can only be used for minor bleeding episodes. Aminocaproic acid is given at a dose of 50-60 mg/kg every 4-6 hours, while tranexamic acid is dosed at 20-25 mg/kg every 8-12 hours.[4,31]

d. **Recombinant Activated Factor VII:** Recombinant Activated Factor VII (rFVIIa) works by bypassing the FVIII/IX coagulation pathway via two mechanisms: i) at low concentrations, rFVIIa overwhelms the inhibitory action of zymogen factor VII which increases thrombin generation, an action which requires the presence of tissue factor, or ii) at high concentrations, rFVIIa binds to activated platelets activating factor X in sufficient quantities to facilitate a spike in thrombin generation, which is tissue factor independent.[85,86] It is administered at a dose of 90 µg/kg, usually in about three doses and has been used effectively in patients with AvWS who have failed to respond to DDAVP and vWF/FVIII concentrates.[4,7]

Preventing Future Episodes:

a. **Intravenous Immunoglobulins:** Intra-Venous Immunoglobulins (IVIg) may be effective in cases of AvWS via a variety of mechanisms including: i) neutralizing autoantibodies and inhibiting their secretion, ii) neutralizing circulating immune complexes and iii)

blocking Fc receptors and preventing internalization of vWF by endothelial cells.[4] IVIg is administered at a dose of 1 g/kg/day for two days or 0.4 g/kg/day for five days in patients with AvWS.[4,87] Response is usually noted between one to two days after administration which is seen as an increase in circulating vWF and FVIII:C levels. The response may last for up to three to four weeks, necessitating repeat dosing after three weeks of administration to maintain efficacy.[4,87] However, it is appropriate to note here improvement in plasma levels of these factors lags behind administration of IVIg making it of limited utility in patients with an acute hemorrhage, necessitating the administration of fast-acting agents, such as those mentioned above.[4,87]

IVIg is reported to produce a successful response in one-third patients suffering from AvWS according to the ISTH registry, and has been seen to be chiefly useful in patients suffering from solid tumors, autoimmune diseases and LPDs, particularly in cases with AvWS secondary to MGUS.[61] A trial comparing IVIg to DDAVP and VWF/FVIII concentrates in patients suffering from AvWS secondary to MGUS demonstrated that IVIg produced more sustained increments in levels of circulating vWF and FVIII.[88] However, this benefit was not seen in patients suffering from MGUS where the antibody class involved was IgM. Furthermore, prophylactic infusions of IVIg every three weeks was associated with a significant reduction in gastrointestinal bleeding in patients with AvWS secondary to IgG-MGUS.[88]

b. **Plasmapheresis:** Plasmapheresis can be employed in cases where autoantibodies are suspected to be responsible for reduced levels of circulating vWF in patients with AvWS, and is noted to be particularly useful in patients suffering from IgM-MGUS, who typically are non-responsive to other treatments such as IVIg.[4,89]

Novel Therapies: While traditional therapies such as IVIg and plasmapheresis can be effective in the management of AvWS, novel therapies are also being explored for its management with varying degrees of response:

a. **Recombinant vWF:** Recombinant vWF (rvWF) represents a potential treatment modality that can replace traditional plasma-derived vWF concentrates in managing patients with AvWS, however, experience in this setting is limited. It is associated with a longer half-life compared to plasma-derived vWF and contains LvWF. The standard dose is 80 IU/kg intravenously.[90]

b. **Rituximab:** This is a monoclonal anti-CD20 antibody that targets B-lymphocytes, which play a role in the production of anti-vWF autoantibodies. It has been seen to be effective at doses of 150 mg to 375 mg/m^2 weekly for three to four doses in some patients with AvWS, resulting in a substantial improvement in coagulation profiles.[7,91]

c. **Lenalidomide:** Lenalidomide treatment has been seen to be associated with an increase in plasma vWF antigen (vWF:Ag) and vWF ristocetin cofactor (vWF:RCo) levels in patients with AvWS secondary to MGUS, which may be sustained for up to two years post-treatment. Furthermore, this effect may be ascribed not just to its action on plasma cells but also due to decreased plasma clearance of vWF.[92,93]

d. **Emicizumab:** This is a bispecific, FVIII-mimetic antibody that mimics the in-vivo function of FVIII, which is deficient in hemophilia A. A shorter half-life of FVIII in patients with AvWS compounds bleeding tendencies of such patients and Emicizumab has been shown to improve bleeding symptoms in patients with acquired hemophilia A associated with vWD, and its use may be extrapolated to patients with AvWS in future.[94]

Adjunctive Management: Patients may develop bleeding severe enough to warrant transfusions of red cell concentrates.[95] Furthermore, drugs that interfere with coagulation such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), direct oral anticoagulants (DOACs), warfarin and parental anticoagulants should be avoided as they increase the risk of bleeding.[96] Patients should be managed by a multidisciplinary team to manage AvWS as well as its underlying cause for effective management. This may involve collaboration between hematologists, oncologists, rheumatologists, and other healthcare professionals. Moreover, patients should remain on regular monitoring and follow-ups to monitor their bleeding symptoms and adjust treatment as needed.[4] Additionally, the treatment modalities mentioned above should be used with caution in patients who are at risk for the development of thrombosis, especially rapidly acting agents like DDAVP.[97,98] Bleeding secondary to gastrointestinal angiodysplasia and patients of AvWS due to undergo surgery represent a unique challenge to manage: a number of different modalities, in addition to conventional methods (like DDAVP and vWF concentrates), such as thalidomide, rituximab, octreotide, and the use of statins have been described in literature.[95,99,100]

CONCLUSION

AvWS is becoming an increasingly common bleeding diathesis, with a multifactorial etiology, and is almost universally linked with an underlying disease. The disorder itself is usually associated with mild to moderate symptomatology, but can rarely be life-threatening. Patients typically present in late adulthood with laboratory findings suggestive of vWD but without a past or family history of a hemorrhagic diathesis. This makes establishing a diagnosis quite challenging as there is no specific gold-standard investigation; diagnoses are made on clinical suspicion and should be established in consultation with clinical hematologists and

hematopathologists. Screening for this bleeding disorder in patients with neoplastic or autoimmune disease presenting with a hemorrhagic diathesis is advisable. Treatment involves control of acute hemorrhage with short-term hemostatic measures such as DDAVP, factor concentrates and anti-fibrinolytics, intermediate-term control can be obtained with modalities like IVIg and plasmapheresis and long-term strategies such as chemo-immunotherapy for underlying Lymphoma or Waldenstrom's. Novel agents such as immunotherapies require further investigation before they can be prescribed more frequently.

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