AMPATHCHAT No. 100

VON WILLEBRAND DISEASE- AN UPDATE

PUBLISHED: DECEMBER 2025

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BACKGROUND

In 1926, Erik von Willebrand identified a hereditary bleeding disorder in the Asland islands that affected both males and females, distinguishing it from haemophilia. Research conducted in the 1950s determined that the condition was due to a deficiency of von Willebrand factor (vWF), a plasma protein subsequently isolated in the 1970s. von Willebrand Disease (vWD) is currently recognized as the most prevalent genetic bleeding disorder and is classified into multiple types based on quantitative or qualitative defects in vWF. Approximately 1% of the population exhibits low vWF, and 1 in 1,000 individuals with low vWF experience symptoms that may range from mild to severe mucocutaneous bleeding.[1] The prevalence of vWD remains relatively consistent across various racial and ethnic groups. Patients exhibiting similarly low circulating vWF levels may demonstrate differing bleeding tendencies, indicating the potential influence of disease modifiers such as vWF release and platelet content (or "cargo" release with platelet degranulation), particularly platelet factor 4 content in platelets[2].

FUNCTION OF VON WILLEBRAND FACTOR

vWF is a large adhesive multimeric glycoprotein produced by endothelial cells and megakaryocytes which is cleaved by the enzyme ADAMTS13 into smaller and less active forms. VWF has two primary roles, namely:

- Binding to FVIII and thus stabilizing and protecting it from degradation in the bloodstream (FVIII Carrier)
- Forming a bridge between platelets and exposed collagen at exposed sites of endothelial injury (adhesion and aggregation of platelets)

Therefore, when von Willebrand factor (VWF) is deficient or defective, both platelet plug formation and the coagulation cascade are impaired, resulting in extended bleeding episodes.

VWF interacts with more than 60 distinct ligands and has several proposed functions. These encompass roles in angiogenesis—where angiodysplasia, particularly within the gastrointestinal tract, is recognized as a complication in individuals with either inherited or acquired von Willebrand disease (VWD)—as well as involvement in wound healing, tumour cell biology, malaria and other infectious diseases, and atherosclerosis.[3]

CLINICAL PICTURE OF VON WILLEBRAND DISEASE

There are three primary types of vWD, each characterised by different clinical presentations (refer to Table 1). Common symptoms include easy bruising, frequent or prolonged epistaxis, gingival bleeding, and menorrhagia. Gastrointestinal bleeding (GIB) and haematuria occur less frequently. Notably, GIB accounts for up to 53% of hospitalisations related to vWD-associated haemorrhage and tends to be recurrent, often as a result of angiodysplasia.

The incidence of gastrointestinal bleeding is higher among younger patients, individuals of African ethnicity, and males with vWD. Significant risk factors for GIB include angiodysplasia, diverticulitis, Hepatitis C infection, and tobacco use.[4]

Joint and muscle haemorrhage is frequently observed in patients with more severe types of vWD. Postoperative bleeding following surgical or dental interventions is common, as is haemorrhage resulting from minor trauma. In neonates, clinical manifestations may include umbilical stump haemorrhage, cephalohematoma, and conjunctival bleeding, and in childhood as post-circumcision bleeding.

DIAGNOSIS OF VON WILLEBRAND DISEASE

The broad spectrum of normal vWF values within the population, coupled with the variability in clinical manifestations among patients, can present considerable diagnostic challenges. A combined guideline, as suggested by ISTH, ASH, NHF and WFH[5] suggest the specific steps in confirming the diagnosis of vWD (see figure 1). Recently, given the complexity of diagnosing von Willebrand disease (vWD), which may impede timely recognition of the disorder, it is recommended that evaluative measures in low-income countries include assessment of vWF antigen, activity levels, FVIII concentration, and, where appropriate, a test dose of DDAVP—except in cases where thrombocytopenia is present.[6]

TREATMENT OF VON WILLEBRAND DISEASE

Therapeutic strategies for vWD are individualized based on the disease type, severity, and clinical context. The primary objective of treatment is to prevent or manage bleeding episodes. Available modalities[7] are shown in Table 2. Special care should be taken to diagnose and treat iron deficiency in these patients.[8]

DIFFERENTIAL DIAGNOSIS OF INHERITED VON WILLEBRAND DISEASE

Acquired vWD: Diagnosed at older age, without bleeding previously; associated with lymphoproliferative disorders, autoimmune diseases, or cardiac conditions (aorta valve stenosis).

Haemophilia A, B or C: Deficiency of factor VIII, IX or XI, respectively; distinguished by normal vWF levels and abnormal factor VIII/IX/XI assays.

Platelet function defects: Inherited and acquired disorders (e.g. Bernard-Soulier syndrome, anti-platelet drug ingestion, platelet-type (pseudo) vWD (platelet GPIba defect, which mimics type 2B vWD).

Fibrinolytic defects: Disorders affecting clot stability.

Vascular defects: Ehlers Danlos syndrome, Marfan syndrome, Hereditary Haemorrhagic Telangiectasis, Vitamin C deficiency.

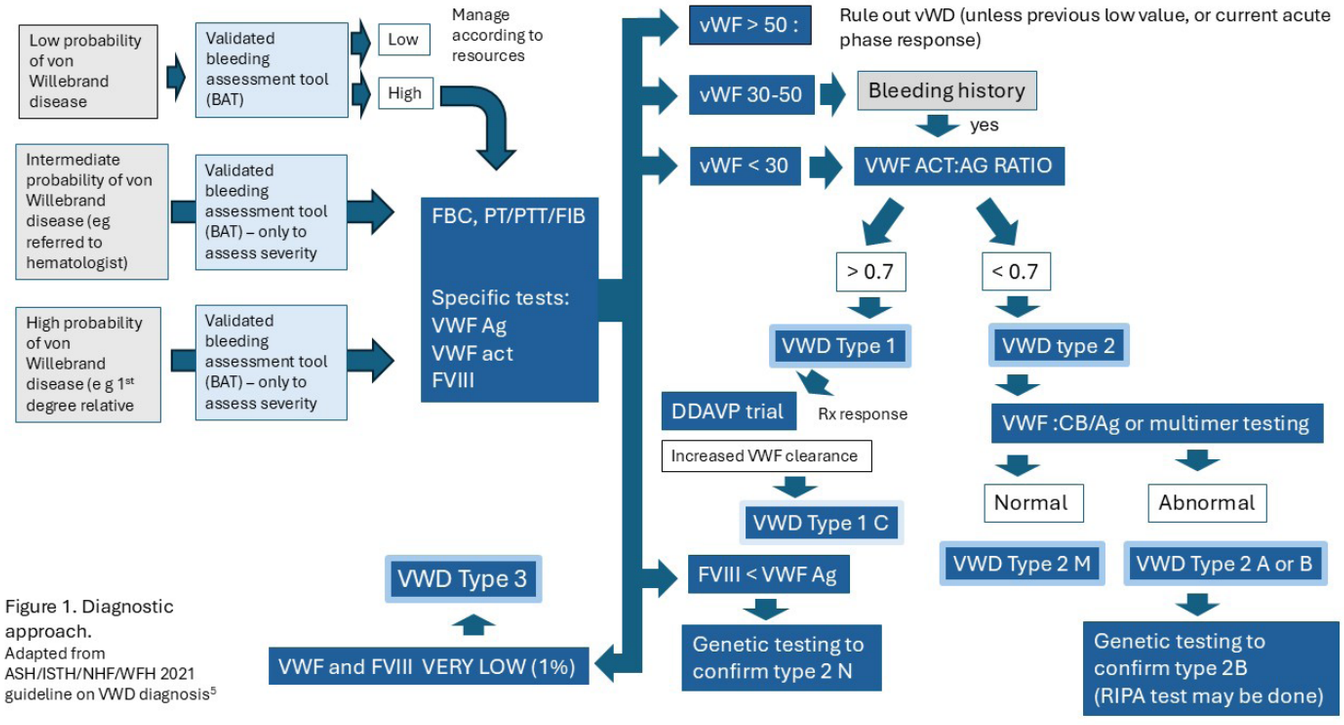

Figure 1. Diagnostic approach.
Adapted from ASH/ISTH/NHF/WFH 2021 guideline on VWD diagnosis[5]

Figure 1: Diagnostic approach. Adapted from ASH/ISTH/NHF/WFH 2021

Type	Inheritance	Prevalence	Clinical Picture	Laboratory diagnosis	Treatment (see table 2)
Type 1	AD	75% of vWD patients	Mild-moderate mucocutaneous bleeding. Variable bleeding tendency	↓vWF antigen & ↓vWF activity uniformly deceased; normal multimer present with electrophoresis; normal or mild ↓FVIII; ↓RIPA (Normal in disease). Increased vWF clearance at 4h with DDAVP test in Type 1C	DDAVP; tranexamic acid; vWF concentrates
Type 2 A	Mostly AD, occasional AR	10-20% of vWD patients	Moderate to severe mucocutaneous bleeding	↓vWF activity >↓antigen; loss of HMW multimers on multimer electrophoresis; FVIII normal or decreased; RIPA decreased	vWF concentrates; tranexamic acid
Type 2 B	AD	5% of vWD patients	Moderate to severe mucosal bleeding + thrombocytopenia	↓vWF activity >↓antigen; FVIII normal or decreased; ↓Platelets; abnormal RIPA (increased); loss of HMW multimers	Avoid DDAVP; vWF concentrates; tranexamic acid
Type 2 M	AD or AR	Uncommon	Bleeding similar to type 1/2A	↓vWF activity > ↓antigen; FVIII normal or decreased; normal multimers, RIPA decreased; normal multimers present, uniformly decreased	DDAVP or vWF concentrates
Type 2 N	AR	Uncommon	Haemophilia-like bleeding (joint, soft tissue, urinary bleeding)	Low FVIII (5-15%) normal antigen vWF an vWF activity; FVIII binding assay abnormal, normal multimer electrophoresis; RIPA normal	vWF/FVIII concentrates-monitor levels; DDAVP (sometimes)
Type 3	AR	Rare	Severe mucocutaneous + joint bleeds	vWF antigen & activity nearly absent; very low FVIII (1-10%), RIPA absent or low, multimers faint/undetectable on electrophoresis	Regular vWF/ FVIII replacement; Tranexamic acid

AD: Autosomal dominant
AR: Autosomal resessive

RIPA: Ristocetin-induced platelet aggregation
HMW: High mollecular weight

Table 1: Types of von Willebrand disease. Adapted from Uptodate (accessed 24/11/2025) and ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease.[5]

	Action	Indication	Side effects/monitoring	Pregnancy
Desmopressin (DDAVP)	Increases the release of endogenous von Willebrand Factor (vWF) and Factor VIII.	Managing bleeding episodes and minor surgical procedures. Extended haemostatic coverage (three days or longer) is not feasible; in such cases, replacement therapy with FVIII/vWF concentrates is required. Tranexamic acid may serve as adjunctive therapy, particularly in instances of mucosal bleeding.	With repeated administration, monitor FVIII and vWF activity. Restrict fluid intake and closely monitor urinary output and serum electrolytes in adults receiving frequent doses. Avoid use in children younger than two years due to the risk of hyponatremia. Exercise caution in elderly patients, especially those with atherosclerosis, owing to potential ischemic complications.	vWF often increase during pregnancy. Can be used at time of delivery (0.3 µg/kg for 2–3 days) after umbilical cord section if FVIII or VWF is not >50 U/dL. May also be used during the first trimester for invasive procedures.
Replacement vWF	Replaces vWF (and FVIII in Hemosolvate)	When extended haemostatic coverage is needed, or patients unresponsive to DDAVP, also those with severe forms of vWD. Minor surgery: Daily or every other day doses of 30–60 IU/kg of vWF to achieve FVIII:C level > 30 U/dL for 2–4 days. Monitoring FVIII and vWF not strictly required. Dental extractions or invasive procedures: Single dose of 30 IU/kg of vWF to maintain FVIII:C level > 50 U/dL for 12h. Major surgery: Daily doses of 50–60 IU/kg of vWF to maintain preoperative FVIII:C and vWF:RCo levels of 100 U/dL until 36–48 h postoperatively and then >50 U/dL for 5–10 days. Measure plasma levels of FVIII:C and VWF:RCo 6–12 h after surgery and then every 24 h. Usual thrombo-prophylactic treatment with LMWH is advised in patients at high risk of venous thrombosis. Spontaneous bleeding episodes: Single or daily doses of 30–60 IU/kg of VWF to maintain FVIII:C levels >30 U/dL until bleeding stops. Ideally, vWD concentrates devoid of FVIII should be used for major elective surgery, high risk for thrombosis (old age, cancer surgery, orthopedic surgery), and long-term prophylaxis (i.e., for target joints, recurrent gastrointestinal bleeding, recurrent epistaxis in children), alternatively FVIII level should be monitored.	vWF type 3 patients with alloantibodies against vWF should not be treated with concentrates containing vWF (risk of anaphylactic reactions). Recombinant FVIII or recombinant activated Factor VII to be used instead. Emicizumab could be useful (little experience at present).	Delivery and puerperium: Daily doses of 30–50 IU/kg vWF to maintain FVIII:C and vWF level > 50 U/dL for 3–4 days or longer in more severe cases.
Adjunctive therapies				
Tranexamic acid	Antifibrinolytic agents	Can be used for mucosal bleeding		Oral Tranexamic acid should be considered to lessen bleeding during post-postpartum period, starting soon after delivery (usually 1 g every 8 h).
Hormonal therapy	Regulating the menstrual cycle	Menorrhagia may be addressed		
Iron therapy	Treat iron deficiency	Chronic bleed with iron loss		

Table 2: Treatment of vWD. Adapted from *Castaman G. How I treat von Willebrand disease. Thromb Res*. 2020 Dec;196:618-625.

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