ACQUIRED VON WILLEBRAND SYNDROME (AVWS)

TERM DEFINITION

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder caused by a reduced concentration and/or function of von Willebrand factor (vWF) that is not directly inherited, but rather is a consequence of other medical disorders.

CLASSIFICATION

ACCORDING TO TYPE OF VON WILLEBRAND DISEASE

- **Type 1:** Quantitative decrease in vWF
- **Type 2:** Qualitative decrease in vWF
- **Type 3:** Complete absence of vWF

Majority of AVWS cases are type 1 or type 2

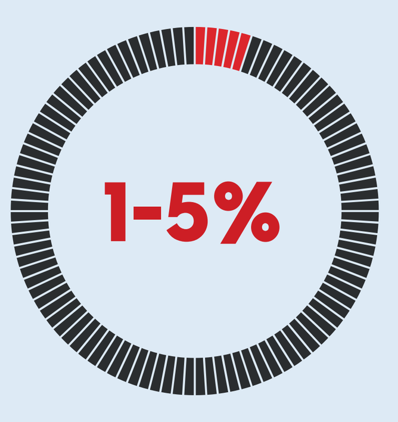
ACCORDING TO PATHOPHYSIOLOGY

- Autoimmune clearance or inhibition of vWF
- Increased shear-induced proteolysis of vWF
- Increased binding of vWF to platelets / other cell surfaces
- Decreased synthesis of vWF

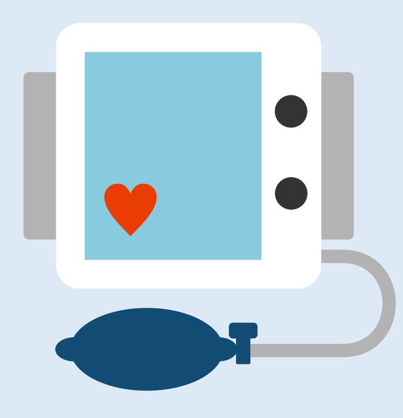
ACCORDING TO UNDERLYING CAUSE

- **Lymphoproliferative disorders**
  - Waldenstrom's macroglobulinemia
  - Lymphoma
- **Myeloproliferative neoplasms**
  - Essential thrombocythemia
  - Polycythemia vera
- **Plasma cell dyscrasia**
  - Multiple myeloma
  - Monoclonal gammopathy of unknown significance (MGUS)
- **Cardiac conditions**
  - Aortic stenosis
  - Congenital cardiac defects
  - Left ventricular devices (LVAD)
  - Extracorporeal membrane oxygenation (ECMO)
- **Drugs**
- **Autoimmune disorders**
- **Hypothyroidism**

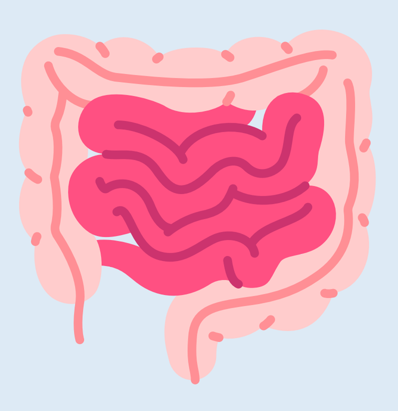
FACTOIDS



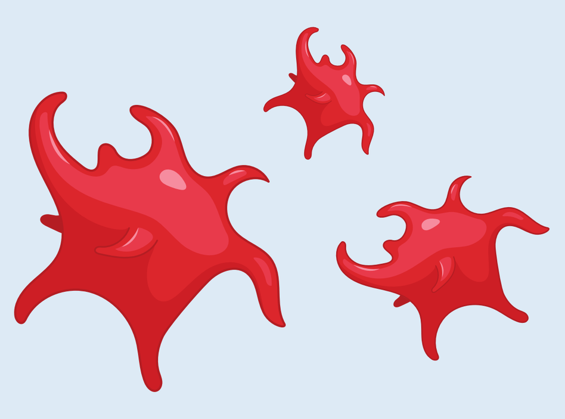
AVWS is rare. It comprises 1%-5% of all cases of von Willebrand disease (VWD).



Increasing incidence of AVWS due to increased use of ECMO & LVAD devices.



AVWS associated with angiodysplasia in the intestines and aortic stenosis is called Heyde syndrome.



Patients with essential thrombocythemia and elevated platelet counts may bleed owing to AVWS.

DIAGNOSIS

CONSIDER

Consider the diagnosis in a patient with:

- Bleeding and laboratory results suggesting abnormal von Willebrand factor (vWF) activity
- Underlying disease known to cause AVWS
- Negative family history of bleeding diathesis

CONFIRM

Lab values supporting diagnosis include:

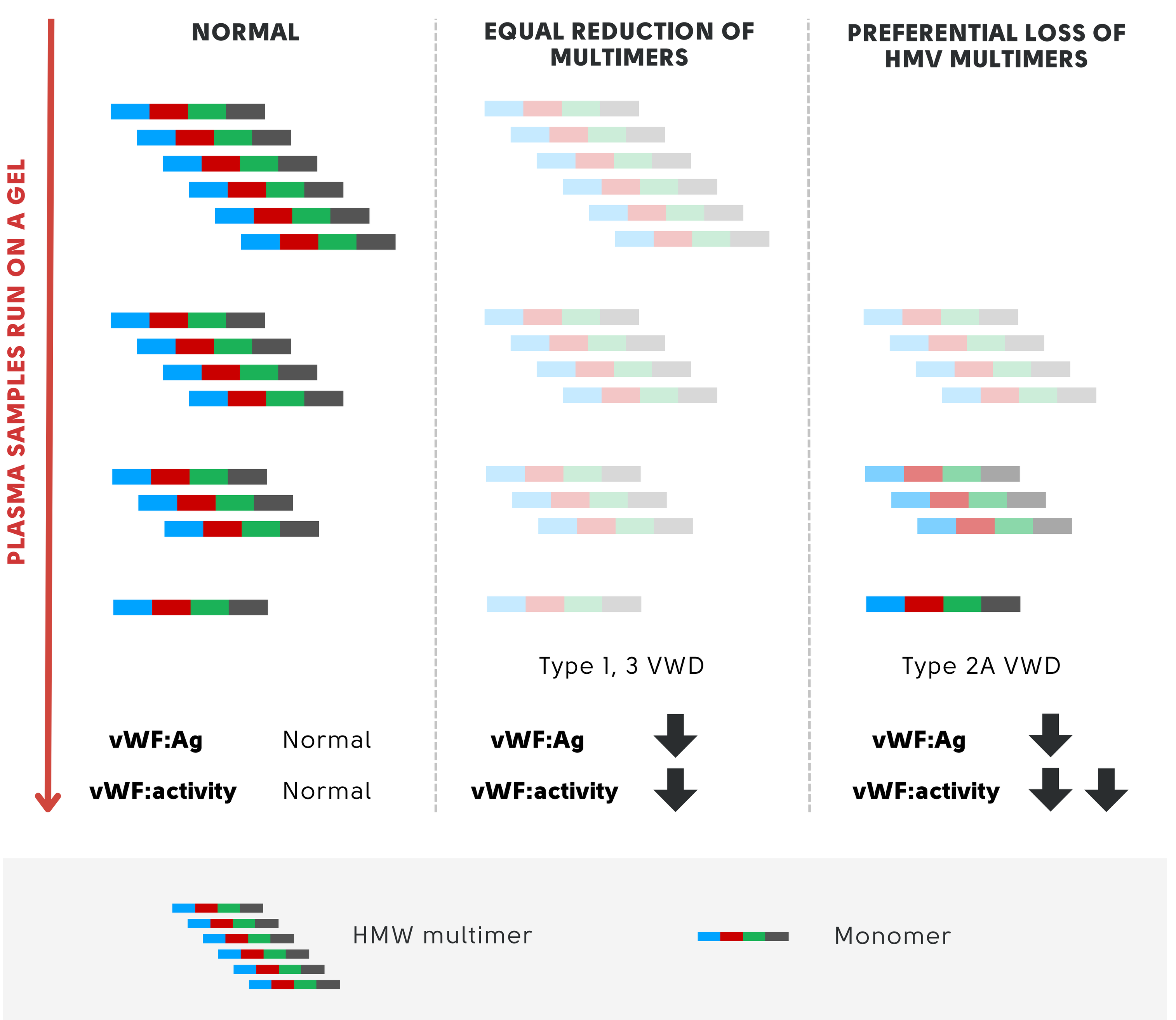
- Reduced von Willebrand factor antigen (vWF:Ag)
- Reduced von Willebrand factor ristocetin cofactor (vWF:RCo), often disproportionately low relative to vWF:Ag
- Reduced Factor VIII levels

Additional supporting labs include:

- Decreased von Willebrand factor collagen binding (vWF:CB)
- Reduced vWF:CB/Ag ratio
- Abnormal multimer pattern - decreased high molecular weight multimers found in one-third or more of patients with AVWS
- Decreased vWF propeptide
- Antibodies to vWF (detected in < 20% of patients)

VWF MULTIMER ANALYSIS

Normally, there is an abundance of high molecular weight vWF multimers in the blood. These are more hemostatically active than smaller multimers and monomers. In von Willebrand disease (VWD), there may be a proportional reduction in multimers of all sizes. As a result, vWF:Ag and activity levels are proportionally low (type 1 and type 3 VWD). In other cases, there is a disproportionate loss of high molecular weight WVF multimers, either from decreased assembly, increased clearance or increased binding to cell surfaces (type 2A VWD). Most cases of acquired von Willebrand syndrome follow a type 1 or 2A pattern.



DIFFERENTIAL DIAGNOSIS
of isolated increase in aPTT

AVWS may be associated with an isolated prolongation of the activated partial thromboplastin time (aPTT). **Isolated elevation of the aPTT** is caused by deficiency of, or inhibitors against clotting factors in the intrinsic pathway:

- Heparin (also inhibits components of common pathway, but predominant effect of aPTT)
- Lupus anticoagulant (inhibitors components of all pathways but predominant effect on aPTT)
- Deficiency of inhibitor against:
  - FXII
  - FXI
  - FIX
  - FVIII

PROXIMATE MECHANISMS

Various mechanisms are implicated in the pathophysiology of AVWS; the majority of them leading to the increased degradation or clearance of circulating vWF.

Mechanisms of reduced vWF in AVWS include:

- **Immune:**
  Antibody-mediated clearance of vWF
  Antibody-mediated inhibition of vWF
- **Shear stress-induced proteolysis:**
  High shear stress results in unfolding of vWF, thereby increasing its susceptibility to proteolysis by ADAMTS-13.
- **Adsorption onto platelets or tumor cells:**
  An inverse relationship exists between the platelet count and vWF multimer size, probably because increased encounters with platelets promote increased cleavage of vWF by ADAMTS13.
- **Decreased vWF synthesis**

Cause of AVWS	Mechanism of reduced vWF antigen / activity
Aortic stenosis	Elevated shear stress around stenotic valve
Congenital heart defects	Elevated shear stress around a septal defect
Hypertrophic obstructive cardiomyopathy	Shear forces
ECMO / LVAD	Shear forces
Myeloproliferative neoplasms	Increased binding of vWF to platelets, especially high molecular weight multimers
Lymphoproliferative disorders	Antibody-mediated clearance of vWF or inhibition of vWF functions
Monoclonal gammopathy of unknown significance	Antibody-mediated clearance of vWF or inhibition of vWF functions
Autoimmune disorders	Antibody-mediated clearance of vWF or inhibition of vWF functions
Medications	Multiple mechanisms including decreased production of vWF
Hypothyroidism	Decreased production of vWF
Solid tumor	Adsorption of vWF on maligant cells

LVAD, left ventricular devices (LVAD); ECMO, extracorporeal membrane oxygenation

TREATMENT

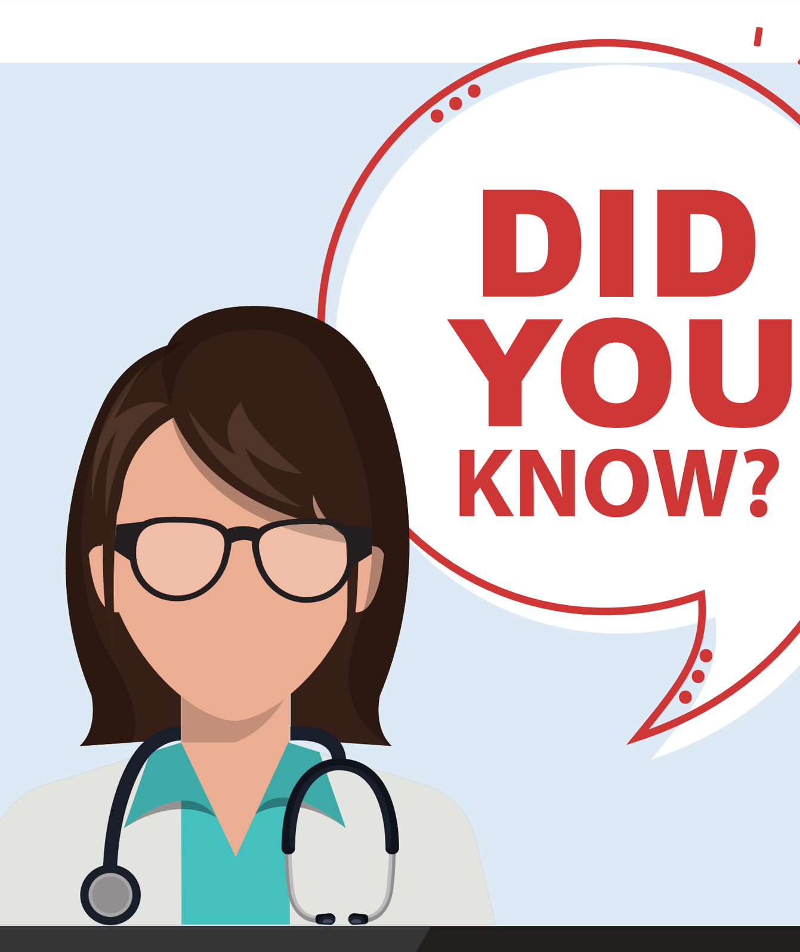
HEMOSTATIC TREATMENT

- vWF/FVIII concentrates
- Desmopressin (DDAVP)
- Intravenous immunoglobulin (IVIG)
- Antifibrinolytics

***Note:** vWF/FVIII concentrates and DDAVP may be less efficacious in AVWS vs. congenital VWD because there is often increased clearance of vWF.*

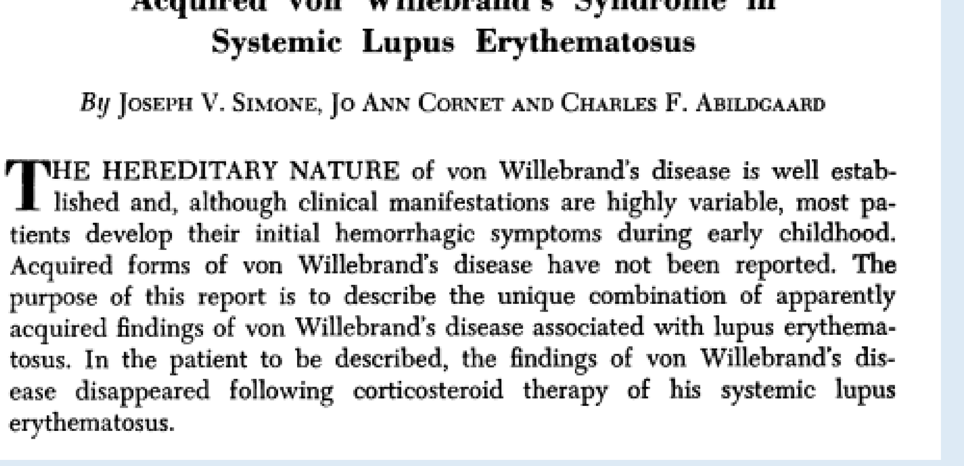
TREATMENT OF UNDERLYING DISEASE (IF PRESENT)

- For example, treat underlying systemic lupus erythematosus, hematological malignancy, or hypothyroidism



HISTORY OF MEDICINE

Acquired von Willebrand syndrome was first reported in 1968 in a patient with SLE (*Blood*. 1968;31:806-812).



Acquired von Willebrand's Syndrome in Systemic Lupus Erythematosus

By Joseph V. Simone, Jo Ann Cornet and Charles F. Abildgaard

THE HEREDITARY NATURE of von Willebrand's disease is well established and, although clinical manifestations are highly variable, most patients develop their initial hemorrhagic symptoms during early childhood. Acquired forms of von Willebrand's disease have not been reported. The purpose of this report is to describe the unique combination of apparently acquired findings of von Willebrand's disease associated with lupus erythematosus. In the patient to be described, the findings of von Willebrand's disease disappeared following corticosteroid therapy of his systemic lupus erythematosus.

NOTES

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