Juniper Publishers
key to the Researchers

AUTHOR NAME
MARTHA ALVARADO IBARRA

ISBN: 978-1-946628-28-2

INTER-INSTITUTIONAL CONSENSUS 2018 OF VON WILLEBRAND DISEASE IN MEXICO

OPEN ACCESS BLOOD RESEARCH & TRANSFUSION JOURNAL

Inter-Institutional Consensus 2018 of Von Willebrand Disease in Mexico

Martha Alvarado Ibarra*

Centro Médico Nacional 20 de Noviembre ISSSTE

***Corresponding Author**

Martha Alvarado Ibarra, Servicio de Hematología, Centro Médico Nacional "20 de Noviembre", Ciudad de México, ISSSTE, México

Published By

Juniper publishers Inc.

United States

July 09, 2019

Authors names and Affiliations

Hernández Ruíz Eleazar: Hospital Regional Presidente Juárez del ISSSTE Oaxaca
Alcivar Cedeño Luisa María: Centro Médico Nacional 20 de Noviembre ISSSTE
Añorve Hernández Erika: Hospital Regional Lic. Adolfo López Mateos
Arana Luna Luara Luz: Centro Médico Nacional 20 de Noviembre ISSSTE
Cesarman Maus Gabriela: Instituto Nacional de Cancerología
Banda García Luisa Iztacihuatl: Hospital General de Zona II IMSS Xalapa, Veracruz
Bates Martin Ramón Alberto: Centro Médico Nacional 20 de Noviembre ISSSTE
Chargoy Vivaldo Euler: Hospital Regional Presidente Juárez del ISSSTE Oaxaca
Chávez Aguilar Lénica Anahí: Centro Médico Nacional 20 de Noviembre ISSSTE
Contreras Sánchez Sarahí: Hospital Civil de Culiacán
De la Peña Celaya José Antonio: Centro Médico Nacional 20 de Noviembre ISSSTE
Espitia Ríos María Eugenia: Centro Médico Nacional 20 de Noviembre ISSSTE
Estrada Domínguez Patricia: Centro Médico Nacional 20 de Noviembre ISSSTE
Fermín Caminero Denisse: Centro Médico Nacional 20 de Noviembre ISSSTE
Flores Villegas Luz Victoria: Centro Médico Nacional 20 de Noviembre ISSSTE
García Chávez Jaime: Centro Médico Nacional La Raza, Ciudad de México
García Lee María Teresa: Hospital Regional 1° de Octubre del ISSSTE
González Pérez María del Carmen: HIES Hospital Infantil del Estado de Sonora
Herrera Olivares Wilfrido: Hospital Regional ISSSTE, Puebla
Martínez Ramírez Mario Alberto: Hospital Regional ISSSTE Veracruz
Martínez Ríos Annel: Hospital Regional General Ignacio Zaragoza
Martínez Solar Marco Antonio: Hospital General ISSSTE Chiapas
Mena Zepeda Verónica: Centro Médico Nacional 20 de Noviembre ISSSTE
Merino Pasaye Laura Elizabeth: Centro Médico Nacional 20 de Noviembre ISSSTE
Morales Hernández Alba Edna: Centro Médico Nacional 20 de Noviembre ISSSTE
Orellana Garibay Juan José: Hospital Regional de Alta Especialidad Cuernavaca ISSSTE
Palma Moreno Orlando: Centro Médico Nacional 20 de Noviembre ISSSTE
Paredes Lozano Eugenia Patricia: Hospital Regional 1° de Octubre del ISSSTE
Peña Alcántara Paula: Centro Médico Nacional 20 de Noviembre ISSSTE
Pérez Zúñiga Juan Manuel: Hospital Regional General Ignacio Zaragoza
Ramírez Romero Eva Fabiola: Hospital Regional Presidente Juárez del ISSSTE Oaxaca
Reynoso Pérez Ana: Centro Médico Nacional 20 de Noviembre ISSSTE
Rojas Castillejos Flavio: Centro Médico Nacional 20 de Noviembre ISSSTE
Saavedra González Azucena: Hospital Regional de Alta Especialidad Bicentenario de la Independencia ISSSTE
Salazar Ramírez Óscar: Hospital General Dr. Darío Fernández Fierro ISSSTE
Scherling Ocampo Aldo Alfonso: Hospital Ángeles Acoxpa
Silva Vera Karina: Hospital General ISSSTE Tampico
Tapia Enríquez Ana Laura: Hospital General Lázaro Cárdenas Chihuahua

Tepepa Flores Fredy: Centro Médico Nacional 20 de Noviembre ISSSTE

Trejo Gómora Jorge Enrique: Hospital Regional Lic. Adolfo López Mateos

Vilchis González Shendel Paulina: Centro Médico Nacional 20 de Noviembre ISSSTE

Villela Peña Atenas: Centro Médico Nacional 20 de Noviembre ISSSTE

Alvarado Ibarra Martha: Centro Médico Nacional 20 de Noviembre ISSSTE

Summary

Von Willebrand Disease (vWD) is the most frequent coagulopathy. As such, it is a group of diseases characterized by a qualitative or quantitative deficiency of the von Willebrand factor (vWF). vWD manifests through mucocutaneous hemorrhages where severity depends on the disease subtype, and the hemostatic challenge. The diagnosis should be reached through the initial tests, and if necessary, supplementary tests should be performed for the right typification of the vWD. Regarding treatment for vWD, the choice among the different management types (desmopressin, vWF concentrates, topical agents, etc.) also depends on the vWD subtype and on the hemostatic challenge (e.g. minor or major surgery), which will define the specific treatment duration.

At a national level, there is a lack of resources and unified criteria for the vWD management. For this reason, a group of mexican experts carried out the vWD consensus directed to first contact physicians, specialists, and medical hematologists. The purpose of this consensus was to count on clearer and more opportune management and treatment lines for vWD.

Keywords: Von Willebrand Disease; Clinical guidelines; Diagnosis; Treatment; Mexico

Abbreviations: PT: Prothrombin Time; aPTT= activated Partial Thromboplastin Time; BT= Bleeding Time; vWD= von Willebrand disease; vWF= von Willebrand Factor; FvW:Ag= vWF binding to antigen test; FvW:RCo= ristocetin cofactor; FVIII:C= FVIII coagulant; vWF:CB= collagen binding test; FvW:FVIII= FVIII binding test; HMWM= High Molecular Weight Multimers; RIPA= Ristocetin Induced Platelet Aggregation at low doses.

Overview

Von Willebrand Disease (vWD) is the most frequent hereditary coagulopathy. It belongs to a group of diseases related to qualitative and quantitative defects of the von Willebrand Factor (vWF). The disease was initially identified by Dr. Eric von Willebrand in three families of the Åland Islands, where the index case was a five-year old girl known to Dr. Erik von Willebrand at the Deaconess Hospital, in Helsinki, Finland. As from this great job, it was evidenced that the hereditary pattern was different from that of hemophilias A and B (where heritage is linked to X), therefore Dr. von Willebrand called it initially "pseudohemophilia" [1]. vWD reported prevalence in the population is 0.6 to 1.3% (in the USA) [2], although only 0.01% present symptoms. On the other hand, in Mexico, there are no prevalence reports in the literature [3]. In the overall population, the vWF average value is 50 to 100 UI/dL. A partial or total reduction (quantitative defect), as well as a qualitative AFECTATION of the vWF results in a deficient platelet adhesion and aggregation, added to a possible reduction of the Factor VIII (FVIII) which stabilizes once bond to it in the bloodstream [2,4]. Also, other factors different from vWF, such as race, age, genetic factors, blood type, stress, inflammation and hormones (estrogens) may have influence on such levels.

vWF Physiology, Synthesis and Structure

vWF is a glycoprotein of 2,813 amino acids that is synthetized and stored in the vascular endothelial cells (Weibel-Palade bodies), megakaryocytes and platelets (alpha granules); it has an approximate half-life of 12 hours and it is codified by a gene of 178 Kba and 52 exons in the short arm of the chromosome 12 (12p13.3). Presently, more than 180 normal variants are known (highly polymorphic) [5] in the vWF gene structure, its transcription is regulated by specific transcription factors (proteins GATA and c-Ets-1), and there are also repressive transcriptional elements in the gene ascending sequence. The more relevant *Single Nucleotide Polymorphism* (SNP) is rs216303: T>C, located in the intragenic region of the gene. In a study of 7,856 subjects of European descent, in the ARIC (*Atherosclerosis Risk in Communities*) cohort, of three regions of the United States, Campos and cols. found that 18 out of 78 vWF SNP studied (equivalent to 23%) were significantly associated with the vWF levels. These SNP were found in a region of 50kb of the 180kb that form the vWF gene (equivalent to 27.8% of the gene). Likewise, these 18 SNP are found between exons 13 to 24, and include the introns of the mentioned interval, codifying the D2, D1 and D3 domains [5-7].

Besides the v*WF*, the genes associated with low levels of vWF in healthy people are ABO, STXBP5, STAB2, and *UFM1*. It is estimated that 75 to 85% of the vWF circulating freely in plasma is derived from the endothelium, and 15 to 25% left is found in circulating platelets. During the vWF synthesis a protein called pre-proVWF is formed, an initial product of 300-350 Kda containing a signaling peptide of 22 amino acids, a propeptide of 741 amino acids, and a mature protein of 2,050 amino acids. Afterwards, it is submitted to considerable processing which includes dimerization and multimerization (Figure 1).

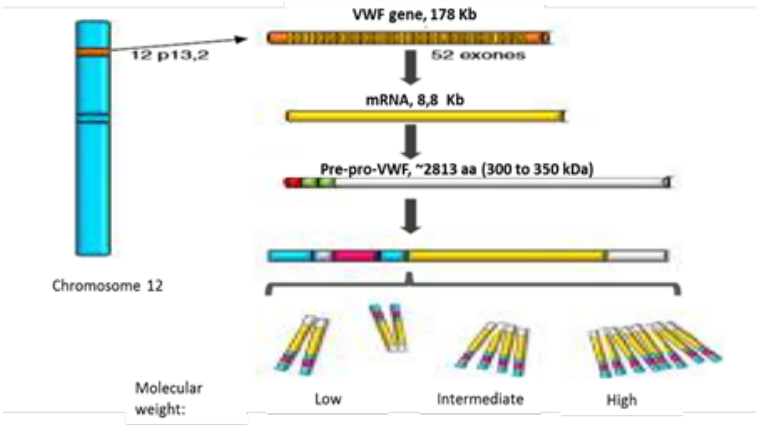


Figure 1: Representation of the gene, the transcript and the von Willebrand Factor protein. The location of the vWF gene in chromosome 12, the mature mRNA and the processing of the protein, from the von Willebrand pre-profactor to the formation of the high molecular weight multimers, are observed. Taken from: Hernández-Zamora et al. [9].

Dimerization occurs early during the protein processing, by the formation of disulfide bonds between the carboxyl-terminal ends of the propeptide within the endoplasmic reticulum. The addition of carbohydrate residues linked to the N-amino terminal portion also occurs in the endoplasmic reticulum, which is a critical process for the formation of dimers and the subsequent exit from this compartment. The pro-VWF dimers are transported to the Golgi apparatus, where greater glycosylation and sulfonation occur, forming multimers through disulfide bonds between the N-terminal amino ends of the prodimers. This process forms excessively large multimers, greater than 20 Mda. Both, the propeptide in a low pH environment and Ca+ ions are necessary for the formation of multimers (Figure 2). On the other hand, the glycans united by N and O-glycosidic bonds can carry carbohydrates that determine the ABO (H) group, but only in the mature vWF, not in the propeptide [8].

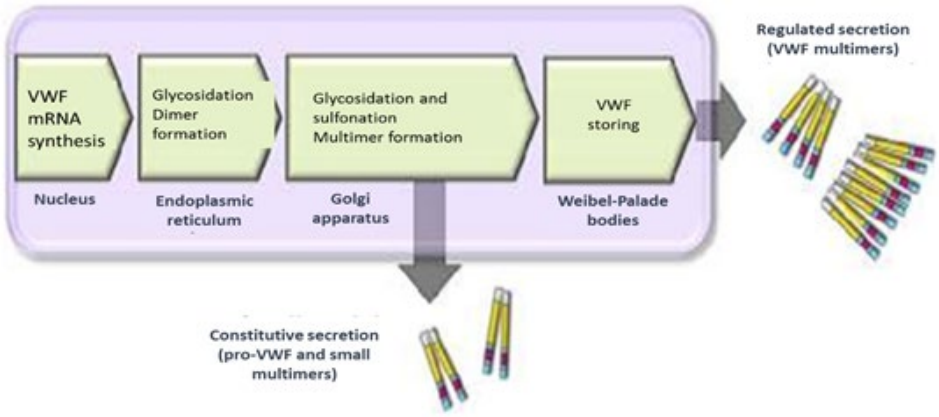


Figure 2: Scheme of the processing and secretion of von Willebrand Factor in endothelial cells. The vWF is formed in the endoplasmic reticulum, where it is dimerized and glycosylated. The dimers are transported to the Golgi apparatus and remain in the secretion granules (Weibel-Palade bodies), ending their maturation by forming multimers. A small amount of immature vWF (dimers and small multimers) is released constitutively. Taken from: Hernández-Zamora et al. [9].

There are two pathways involved in the secretion of the VWF constitutive pathway that represents 90-95% of the total and continuous secretion of small VWF multimers stored in the bodies of Weibel-Palade. The regulated pathway accounts for 5 to 10% of fully multimerized vWF secretion stored in alpha granules, megakaryocytes and platelets in response to physiological and pathological stimuli. The vWF shares these storage sites with other proteins that are released in response to physiological and pharmacological stimuli, including thrombin, shearing force and desmopressin. Within the conformation of the VWF there are different domains, arranged in the following order: D1-D2-D'-D3-A1-A2-A3-D4-C1-C2-C3-C4-C5-C6-CK.

The vWF propeptide is represented by the D1-D2 domains, the remaining domains make up the mature subunit of the vWF [8,9]. These domains belonging to mature VWF, have interactions with different molecules, providing them their key role in coagulation (Figure 3) [10]. Figure 3 Structure of the vWF precursor, its gene and Pseudogene. The schematic structure of the vWF precursor (pre-pro-FvW) consists of a signal peptide (1-22 residues), a propeptide (23-763 residues) and a mature unit (764-2,813 residues). The pro-vWF is organized into repetitions of homologous structural domains (A, C, and D). The binding sites of the vWF are shown with the FVIII, platelet glycoprotein (GP) Ib alpha, collagen, platelet glycoprotein GP IIb/IIIa (alphaIIbb3) and the cleavage site of the ADAMTS13 protein. The arrows show the positions of the mutations that cause von Willebrand Disease (EvW) type 2. The dark arrows show the location of mutations corresponding to the type 2A variants of the vWD with characteristic multimeric patterns due to the increase in proteolysis (IIA) or the defective alignment of the multimer caused by mutations in the propeptide (IIC), the domain of the cysteine knot (IID) or the D3 domain (IIE). Recessive variants of type 2 vWD are marked with an asterisk (*) [11].

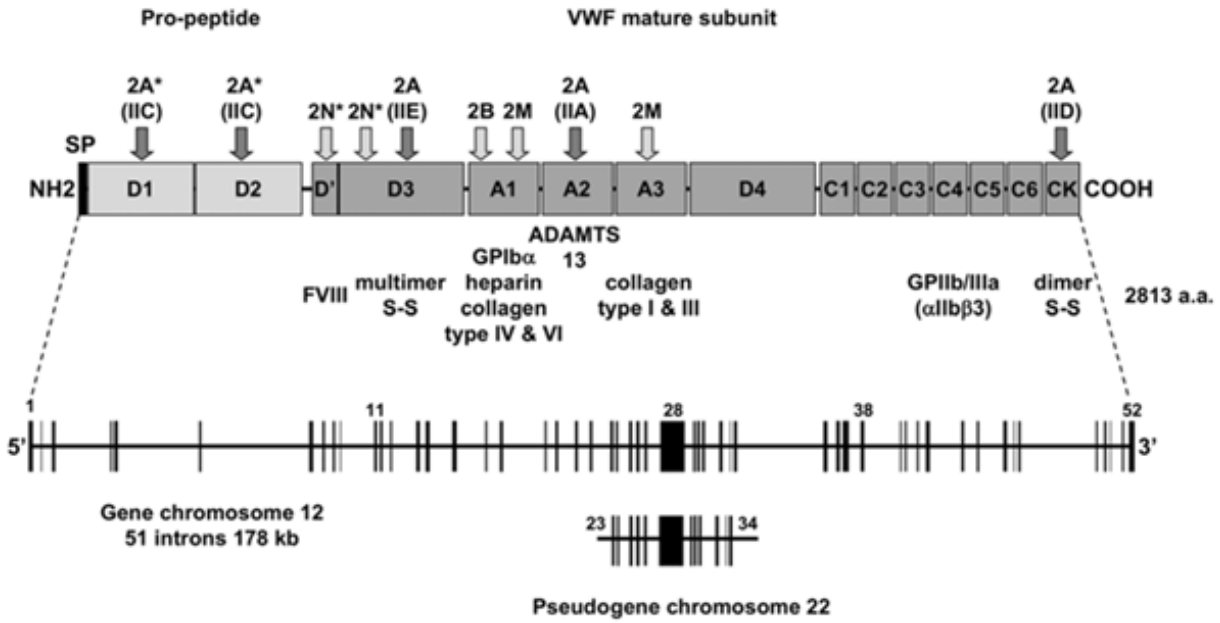


Figure 3: Structure of the vWF precursor, its gene and Pseudogene.

It has been shown that ADAMTS13 is constitutively released from the endothelial cells of the Golgi apparatus; merging along the entire length of the newly formed vWF molecule, where it is cleaved. Factor VIII plays a role in the acceleration of the proteolysis of these high molecular weight multimers by ADAMTS13. On the other hand, factor H, also released by endothelial cells, plays an inhibitory role in this cleavage [12-14] (Figure 4).

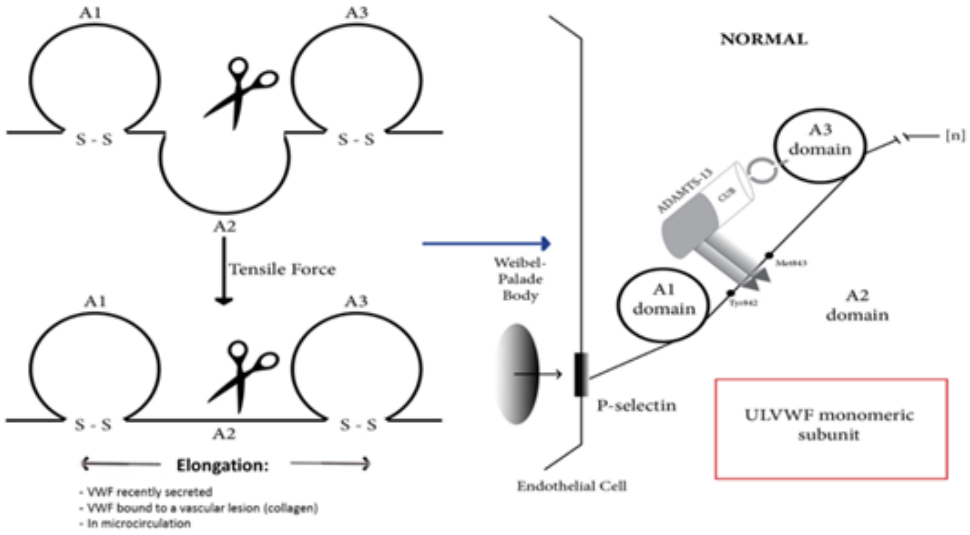


Figure 4: Scheme representing the interaction of vWF and ADAMTS13 with the endothelium. Modified from: Focosi et al. [14].

VWF Functions

The three vWF functions are to:

1. Mediate the adhesion of platelets to vascular damage sites, by binding to platelet receptor GP-Ib/IX and collagen in the vascular subendothelium.

2. Facilitate platelet aggregation through its interaction with the GPIIb/IIIa platelet receptor.

3. Join FVIII and protect it from proteolytic degradation caused by activated protein C in the bloodstream.

Platelet Binding

The binding of vWF to platelets and subendothelial components is critical for normal platelet adhesion and for platelet aggregation that occurs at high shear rates. Platelet binding requires an initial activation or alteration in the vWF structure, so that the binding sites in the A1 domain can compromise the platelet receptor complex GPIb-IX-V on the surface of the platelets. This binding occurs even in non-activated platelets. It has been shown that vimentin, a structural protein found in plasma and on the surface of platelets, improves the binding of vWF to the surface of platelets under high shear.

One or both of the following mechanisms may be important for the "activation" of circulating vWF:

i. When vWF binds to exposed subendothelial structures after endothelial damage, possibly immobilizing the protein, thus exposing multiple A1 domains of the VWF towards the lumen of the vessel where the platelets are present.

ii. It can also occur when the VWF is exposed to shear. In this context, the conformation of the vWF changes from a globular to a linear form, in which the A1 domains are available to bind to the GPIb platelet receptor. On the other hand, studies have shown that beta 2 glycoprotein acts to inhibit the binding of this "activated" vWF to GPIb, thus reducing platelet adhesion.

A second platelet receptor for VWF, the integrin αIIb-α3 (GPIIb/IIIa), does not bind to vWF unless the platelets are activated. With platelet activation, αIIb-α3 undergoes a conformational change and becomes accessible on the surface of the platelets. Platelet activation can be caused by a variety of agents, including activation induced by the binding of GPIb to immobilized VWF. GPIb-IX-V contains a mechano-sensitive domain that unfolds and transmits a signal within the platelet [15]. The platelet interaction αIIb-α3-vWF seems to contribute to the final and irreversible union of platelets to the subendothelium after the VWF has been linked to GPIb [16]. The αIIb-α3-VWF interaction may also contribute to platelet aggregation, especially in high shear conditions; under low shear conditions, platelet aggregation is mediated mainly by the binding of αIIb-α3 to fibrinogen. Finally, these contacts reach a threshold that signals the event of platelet activation. Then, the platelets stably adhere to the damaged vessel wall and undergo an aggregation response through an event mediated by GPIIb/IIIa (Figure 5).

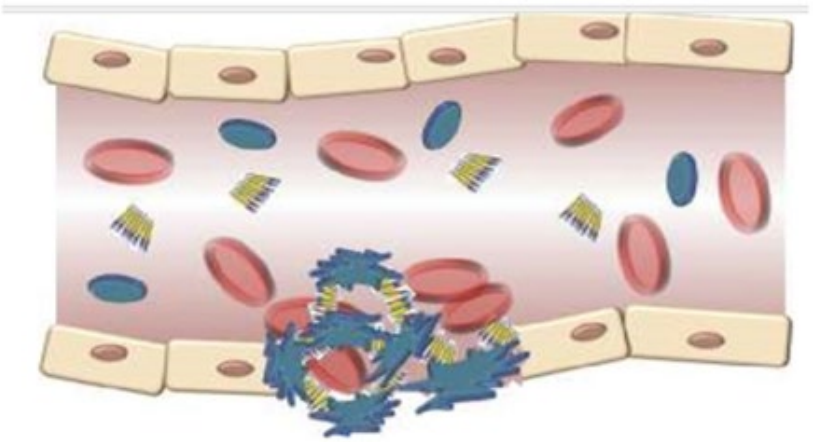


Figure 5: Schematic description of the vWF interaction with activated platelets during the formation of the hemostatic plug. Taken from: Hernández-Zamora et al. [9].

Clinical characteristics

The evaluation of von Willebrand disease (VWD) is based on the clinical history and physical examination that should include the search for mucocutaneous hemorrhages (bruising, ecchymosis, petechiae, mucosal bleeding), evaluating size, location and distribution. These signs and symptoms depend on the type and severity of the vWD (Table 1).

Table 1: Lists the most frequent hemorrhagic manifestations.

More frequent manifestations in vWD	
Localization	**Frequency**
Epistaxis	63%
Menorrhage	60%
Bleeding from dental procedures	52%
Ecchymosis	49%
Gingivorrhagia	35%
Post-traumatic hemorrhage	36%
Post-surgical hemorrhage	28%
Gastrointestinal hemorrhage	14%
Hemarthrosis (2N)	8%

There are different tools designed to objectively determine the severity of bleedings. One of them was published by Rodeghiero, in 2005, for the detection of vWD type 1 (Annex 1) [17]. However, the most useful tool for the vWD scrutiny is that validated by the ISTH (International Society on Thrombosis and Hemostasis) [18], which is relevant for both, pediatric population and adults. On the other hand, the recommended tool for evaluation of the severity of bleeding is the condensed MCMDM-1 (Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand Disease) (Annex 2) [19].

Annex 1:

Symptoms	Assigned Score
Epistaxis	0= Absent or negligible
	1= Present
	2= Clogging or cauterization
	3= Transfusion or replacement
Cutaneous symptoms	0= Absent or negligible
	1= Petechia or bruises
	2= Hematoma
	3= Medical consultation

Minor injuries	0= Absent or negligible
	1= Present (1-5 episodes per year)
	2= Medical attention
	3= Surgery/blood transfusion
Oral cavity bleeding	0= Absent or negligible
	1= Present
	2= Medical attention
	3= Surgery/blood transfusion
Gastrointestinal bleeding	0= Absent or negligible
	1= Present
	2= Medical attention
	3= Surgery/blood transfusion
Post-partum hemorrhage	0= Absent or negligible
	1= Present, iron therapy
	2= Blood transfusion, dilation-curettage, suture
	3= Hysterectomy
Muscle bruising or hemarthrosis	0= Absent or negligible
	1= Present
	2= Medical attention
	3= Transfusion, intervention
Dental extraction (extremely severe episode)	0= Absent or negligible
	1= Present
	2= Suture or tamponade
	3= Transfusion
Surgery (very severe episode)	0= Absent or negligible
	1= Present
	2= Suture or surgical re-intervention
	3= Transfusion
Menorrhagia	0= Absent or negligible
	1= Present
	2= Consultation, use of pills, iron therapy
	3= Transfusion, hysterectomy, dilatation-curettage, replacement therapy

Bleeding score used in the study.

Score for detection of von Willebrand disease. The detection of > 2 symptoms (regardless of severity) or a total score of 3 for men or 5 for women presented a sensitivity of 69.1% and specificity of 98.6%.

Taken from: Rodeghiero et al [17].

Annex 2: CONDENSED MCMDM-1 BLEEDING QUESTIONNAIRE:

Patient Information

Name _____

Address _____

_____

Phone Number _____ Email _____

Gender ☐ Male ☐ Female

Age _____ Date of Birth _____ (DD/MO/YYYY)

Ethnic Background _____

Presenting complaint of bleeding or bruising today ☐ Yes ☐ No

Personal history of bleeding or bruising ☐ Yes ☐ No

Ever been diagnosed with a bleeding disorder? ☐ Yes ☐ No

Diagnosis: _____

Family history of bleeding (at least one family member) ☐ Yes ☐ No

If yes, what was the diagnosis? _____

Are you currently taking Oral Contraceptive Pills? ☐ Yes ☐ No

If yes, brand name _____

Are you pregnant? _____ Gestation time _____

Specify any herbals and/or medications that you have taken in the past 30 days:

Name Dose Route Frequency Duration _____

_____

Nosebleeds ☐ Yes ☐ No

Number of episodes/year ☐ < 1 ☐ 6 - 12

☐ 1 – 5 ☐ > 1

Duration of average episode

< 1 minute

☐ 1 – 10 minutes

☐ > 10 minutes

Medical attention ☐ Yes ☐ No

Consultation only

☐ Cauterization/packing

☐ Antifibrinolytics

☐ DDAVP

☐ Transfusion/Replacement

Bruising ☐ Yes ☐ No

Location ☐ Exposed sites

☐ Unexposed sites

Size of average ☐ < 1 cm

☐ 1 – 5 cm

☐ > 5 cm

Minimal or no trauma ☐ Yes ☐ No

Medical attention ☐ Yes ☐ No

If yes, please specify _____

Bleeding from minor wounds ☐ Yes ☐ No

Number per year ☐ < 1

☐ 1 – 5

☐ 6 or more

Duration of average episode ☐ < 5 minutes

☐ > 5 minutes

Medical attention ☐ Yes ☐ No

☐ Consultation only

☐ Surgical hemostasis

☐ Blood transfusion/DDAVP/Replacement

Oral cavity bleeding ☐ Yes ☐ No

☐ Tooth eruption

☐ Gums, spontaneous

☐ Gums, after brushing

☐ Bites to lip and tongue

Medical attention ☐ Yes ☐ No

☐ Consultation only

☐ Surgical hemostasis/Antifibrinolytic

☐ Blood transfusion/DDAVP/Replacement

Post-dental extraction ☐ Yes ☐ No

☐ No bleeding in at least 2 extractions

☐ None done, or no bleeding in 1 extraction

Medical attention ☐ Yes ☐ No

☐ Consultation only

☐ Re-suturing or packing

☐ Blood transfusion/DDAVP/Replacement

Gastrointestinal Bleeding ☐ Yes ☐ No

☐ Ulcer, portal hypertension, hemorrhoids

☐ Spontaneous

☐ Surgery/Blood transfusion/DDAVP/Antifibrinolytic

Surgery ☐ Yes ☐ No

☐ No bleeding in at least 2 surgeries

☐ None done, or no bleeding in 1 surgery

Post-op medical attention ☐ Yes ☐ No

☐ Consultation only

☐ Surgical hemostasis/Antifibrinolytic

☐ Blood transfusion/DDAVP/Replacement

Menorrhagia ☐ Yes ☐ No

Duration of average menstruation _____ days

Duration of heavy menstruation _____ days

How often do you change your pads/tampons

on heaviest days _____ hours

on average days _____ hours

What type of feminine product do you use? (i.e. panty liner, super absorbency tampon etc.)_____

Medical attention ☐ Yes ☐ No

☐ Consultation only

☐ Pill use/Antifibrinolytics

☐ Dilatation & curettage

☐ Iron therapy

☐ Blood transfusion/DDAVP/Replacement

☐ Hysterectomy

Post-partum hemorrhage ☐ Yes ☐ No

☐ No bleeding in at least 2 deliveries

☐ No deliveries, or no bleeding in 1 delivery

Medical attention ☐ Yes ☐ No

☐ Consultation only

☐ D&C/Iron therapy/Antifibrinolytics

☐ Blood transfusion/DDAVP/Replacement

☐ Hysterectomy

Muscle hematomas ☐ Yes ☐ No

☐ Post-trauma, no therapy

☐ Spontaneous, no therapy

☐ Spontaneous or traumatic requiring DDAVP or Replacement

☐ Spontaneous or traumatic requiring surgical

☐ Intervention or transfusion

Hemarthrosis ☐ Yes ☐ No

☐ Post-trauma, no therapy

☐ Spontaneous, no therapy or replacement

☐ Spontaneous or traumatic requiring surgical

☐ Intervention or transfusion

Central Nervous System Bleeding ☐ Yes ☐ No

☐ Subdural, any intervention

☐ Intracerebral, any intervention

Other_____

Medical attention ☐ Yes ☐ No

☐ Consultation only

☐ Surgical hemostasis/Antifibrinolytic

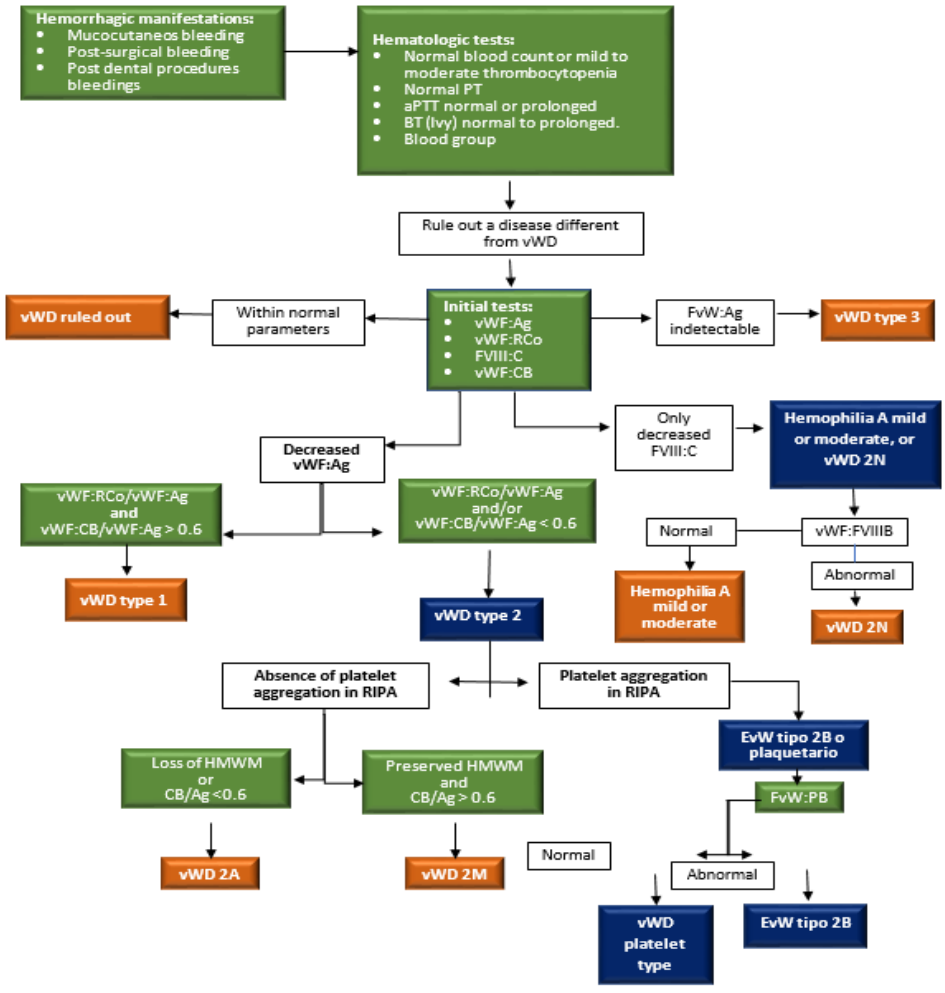
☐ Blood transfusion/DDAVP/Replacement

Punctuation keys

Scoring						
Symptom	**-1**	**0**	**1**	**2**	**3**	**4**
Epistaxis	--	Absent or negligible (less than 5)	> 5 or more than 10’	Consultation only	Clogging, cauterization or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Cutaneous	--	Absent or negligible (< 1cm)	> 1 cm without trauma	Consultation only	--	--
Bleeding due to minor injuries	--	Absent or negligible (less than 5)	> 5 or more than 5’	Consultation only	Surgical hemostasis	Blood transfusion, replacement therapy or desmopressin
Oral cavity	--	Absent	At least one referral	Consultation only	Surgical hemostasia or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Gastrointestinal bleeding	--	Absent	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, blood transfusion, replacement therapy, desmopressin, antifibrinolytics	--
Extracción dental	Without bleeding in at least 2 extractions	Never experienced or without bleeding in 1 extraction	Reported, without consultaiton	Consultation only	Surgical reintervention or tamponade	Blood trnasfusion, terapia de reemplazo o desmopresina

Surgery	No bleeding in at least 2 surgeries	Never experienced or without bleeding in 1 surgery	Reported, without consultation	Consultaiton only	Surgical haemostasia or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	--	Absent	Consultaiton only	Antifibrinolytics use of pills	Dilation and curettage, iron therapy, ablation	Blood transfusion, replacement therapy, desmopressin or hysterectomy
Postpartum hemorrhage	No bleeding in at least 2 deliveries	Never experienced or without bleeding in 1 surgery	Consultation only	Dilation and curettage, iron therapy, antifibrinolytics	Blood transfusion, replacement therapy, desmopressin	Hysterectomy
Muscle bruises	--	Never	Postrauma, sin terapia	Spontaneous, without therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention o blood transfusion
Hemarthrosis	--	Never	Postrauma, without therapy	Spontaneous, without therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requires surgical intervention of blood transfusion
Central nervous system bleeding	--	Never	--	--	Subdural, cualquier intervención	Intracerebral, any intervention

Scoring keys: Some small changes in the terminology of the original document MCMDM-1 scoring keys are indicated in the boxes. For dental extraction and surgery a score of 1 was previously shown as “Referred in <25% of cases”. For the category of menorrhagia we added ablation therapy (which was not included in the original) to the same level as D & C and iron therapy. Taken from Bowman et al. [18].



Diagnostic algorithm.

Abbreviations: PT= Prothrombin Time, **aPTT**= activated Partial Thromboplastin Time, **BT**= Bleeding Time, **vWD**= Von Willebrand Disease, **vWF**= Von Willebrand Factor, **FvW:Ag**= vWF binding to antigen test, **FvW:RCo**= Ristocetin Cofactor, FVIII:C= FVIII coagulant, **vWF:CB**= Collagen Binding Test, **FvW:FVIII**= FVIII binding test, **HMWM**= High Molecular Weight Multimers, **RIPA**= Ristocetin Induced Platelet Aggregation at low Doses [18].

For women in childbearing age, menorrhagia is the most frequent manifestation. However, the magnitude of the effect of vWD in this population is unknown, since 12% of women without the disease may have menorrhagia. For their study, there are visual scales that measure the intensity of bleeding, such as the Menstrual Assessment Chart (Figure 6) [20].

Day	1	2	3	4	5	6	7	8	9	10	11	12
Sanitary pad												
Lightly stained 												
Moderately soaked 												
Heavily soaked 												
Clots (small or large)												
Tampons												
Lightly soaked 												
Moderately soaked 												
Heavily soaked 												
Clots (small or large)												
Score												

Figure 6: Menstrual Assessment Chart. Taken from Higham et al. [20].

Indications: Keep a count of the number of sanitary pads or tampons you use each day of your cycle and your saturation level. Also take note of clots or overflow. Clots > 1 cm are considered large.

Score: Sanitary pads (score per pad)

Lightly stained: 1 point; Moderately soaked: 5 points; Heavily soaked: 20 points.

Tampons: (punctuation per tampon)

Lightly soaked:1 point; Moderately soaked: 5 points; Heavily soaked: 10 points

Clots: Small: 1 point; Large: 5 points

Interpretation: A score of ≥ 100 points indicates probable menorrhagia. Contact your doctor or the nearest bleeding disorder treatment center if you are concerned about your menstrual bleeding. (www.hemophilia.ca/en/treatmentcentres).

Classification

The criteria for the classification of the vWD were published by the International Society of Thrombosis and Haemostasis [ISTH] in 2006 [21].

i. **Type 1 (represents 75% of VWD diagnostics):** It is a quantitative partial deficiency with normal functions. In this type, all domains will be affected by decrease. In most cases, their inheritance pattern is autosomal dominant, and a small percentage is autosomal recessive [4]. Within this type is the vWD type 1C (including the Vicenza variant), in which there is a decreased survival or accelerated depuration of the vWF. In this variant there is an increased ratio of the vWF propeptide (FvWpp) in relation to the antigen (vWF: Ag) (see below) [22,23].

ii. **Type 2 (approximately 25% of patients diagnosed):** It is a qualitative deficiency that is subdivided into four variants (2A, 2B, 2M and 2N). The symptoms of bleeding are usually more severe than in type 1 [24]. Each of these variants has different pathophysiological characteristics, namely:

– A: Decrease in the proportion of functional large multimers of vWF, affecting the platelet adhesion capacity dependent on vWF.

– B: It affects <5% of patients with vWD [25]. It is due to mutations that abnormally increase the binding of vWF to platelets, causing depletion of large functional vWF multimers. The defect is located in the A1 domain. It can be confused with the platelet vWD-type (vWD-TP): in which there is an increase in the binding of the glycoprotein Ib (GPIb) platelet with the vWF, although in this case it is a mutation in the GPIb itself instead of the vWF itself [25]. Up to 10% of patients with vWD 2B can actually be vWD-TP.

– M: Mutations that decrease platelet adhesion dependent on vWF, where multimers are not diminished. The distinction between 2A and 2M requires the performance of electrophoresis of vWF multimers in gel. However, according to Favaloro, the test of multimers in agarose gel can be obviated if a VWF: CB is performed. The defect is located in domains A1 and A3 [25].

– N: It occurs in up to <5% of patients with vWD [25]. Level decreasing mutations affecting the binding with FVIII are observed. It is frequently confused with an autosomal recessive form of hemophilia A, the distinction may require vWF-FVIII binding assays. The defects reported have been located in domain D3.

iii. Type 3: (less than 1% of patients with vWD). The vWF levels are practically undetectable. On the other hand, FVIII levels are usually very low (<5 IU/dL). The inheritance pattern is autosomal recessive [24]. Patients with vWF levels of 0.01 to 0.05 IU/mL will invariably present this type of vWD [26] (Table 2).

Table 2: Summarizes the most distinctive characteristics of the different VWD types.

Classification of von Willebrand Disease	
Type	**Description**
1	Partial quantitative vWF deficiency
2	vWF qualitative defects
A	Decreased platelet and selective adhesion of large vWF multimers
B	Increased affinity of the platelet Ib glycoprotein
M	Decrease in platelet and non-selective adhesion of large VWF multimers
N	Significant decrease of the vWF/FVIII binding
3	Practically undetectable vWF

Acquired vWD

It is less common than congenital vWD [26] (incidence of 1/100,000 adults). The laboratory findings are similar. The mechanisms by which it is produced are [4]:

– Antibodies against vWF. Lymphoproliferative diseases, monoclonal gammopathies, autoimmune diseases.

– Conformational changes induced by turbulence that cause increased proteolysis. Examples: ventricular septal defects, aortic stenosis, obstructive hypertrophic cardiomyopathy, left ventricular assist device, primary pulmonary hypertension.

– Clonal thrombocytosis. Myeloproliferative neoplasms, being the most representative: essential thrombocythemia, polycythemia vera, primary myelofibrosis.

– Removal of vWF from the circulation by binding to tumor cells. Examples: Wilms tumor, some lymphoproliferative diseases and plasma cell neoplasms.

– Decreased synthesis, as in hypothyroidism.

– Associated with medicines: ciprofloxacin, valproic acid, griseofulvin, hydroxyethyl starch.

Diagnosis

The evaluation for a possible vWD should be considered in:

a. Patients with personal or family history of frequent mucocutaneous or postoperative bleeding.

b. Patients with autoimmune diseases, neoplasms, among others, presenting with a recent appearance of a hemorrhagic disorder.

c. Women with menorrhagia or abnormal bleeding during the puerperium without explainable cause.

Once the patient is assessed with a possible coagulopathy, general laboratory studies should be requested, these should include complete blood count, partial thromboplastin time, prothrombin time and, possibly, thrombin time and fibrinogen levels. These initial tests can exclude other causes of bleeding [3]. The bleeding time is measured as a scrutiny test for vWD, however, it presents certain drawbacks, the test can be affected by diverse factors, some of them might be: a crying patient (child), differences in the fitting of the sphygmomanometer cuff or

keloid scar formation in susceptible populations. Therefore, the test can be skipped [2]. The PFA-100 test has shown alterations, it is sensitive in almost all patients with vWD, except for the 2N type [2]. Although, according to the study by Sap et al. [27] the test presents a sensitivity of 21.4% despite a specificity of 100%, which makes this screening method unreliable with regards to von Willebrand disease, until more evidence is available. If other conditions that cause alterations in coagulation are ruled out, a specific vWD approach should be taken.

Initial diagnostic tests should ideally be performed in the absence of stress, recent physical activity, acute or chronic illness, pregnancy and elevated estrogen levels. This is due to the fact that these conditions raise the levels of vWF. These tests are:

Von Willebrand Factor antigen (vWF:Ag). It measures the concentration of the vWF protein in plasma. Recent evidence suggests <30 IU/dL as diagnostic level for detection of vWD; in levels between 30 IU/dL and 50 IU/dL the diagnosis is more complicated.

Ristocetin cofactor (vWD:RCo). It is the main functional test that evaluates platelet adhesion mediated by vWF and GpIb in the presence of the antibiotic ristocetin. The sensitivity of the test is not reliable when it is below 15 IU/dL [22].

Measurement of Factor VIII coagulant (FVIII:C). Evaluates the amount of FVIII in plasma with coagulometric techniques. FVIII is usually found to be decreased in patients with vWD, given that its half-life depends on the stabilization provided by the vWF.

Collagen Binding Assay (vWF: CB)

It measures the binding ability of the vWF to collagen. For authors such as Favaloro, the determination of the vWF:CB should be added to the initial diagnostic panel (difficult to find in public or private laboratories in Mexico), a failure could cause errors in the determination of type 1 vWD classifying it as type 2 in up to 20% of the cases, and 30% classified as 1 when in fact it is a type 2 vWD. Likewise, up to 5% of the patients could be classified as vWD being healthy subjects [25]. After the aforementioned studies, the quotients (ratios) of the different assays used as initial tests for the vWD should be considered. Namely, values <0.6 in the ratio FvW:RCo / FvW:Ag and FvW:CB / FvW:Ag suggest the presence of dysfunctional vWF (vWD type 2). However, the variability in the FvW:RCo test affects its usefulness. On the other hand, a FVIII/FvW:Ag ratio <0.6 also suggests vWD2N or hemophilia A [7]. Once the vWD diagnosis has been confirmed, it is advisable to carry out other complementary tests for a better typification in some cases (ie classification between the different types of type 2 vWD or distinction of vWD type 2B vs. vWD-TP).

Low dose RIPA (Ristocetin-Induced Platelet Aggregation)

Along with the platelet binding vWF assay (FvW:PB, platelet-binding), this is a test for the identification of vWD type 2B. In this type of vWD the test will induce platelet aggregation in platelet-rich plasma at a dose of ristocetin <0.6mg/mL, which is not usual in people without this diagnosis. When there is hyperaggregation with ristocetin, another hyper-aggregation with other agonists, such as ADP, should be ruled out. In vWD2B, hyperaggregation should not be general but exclusive to ristocetin [22]. Also, the RIPA assay at low doses would present aggregation in vWD-TP, so it should be discarded as indicated below.

Analysis of Multimers

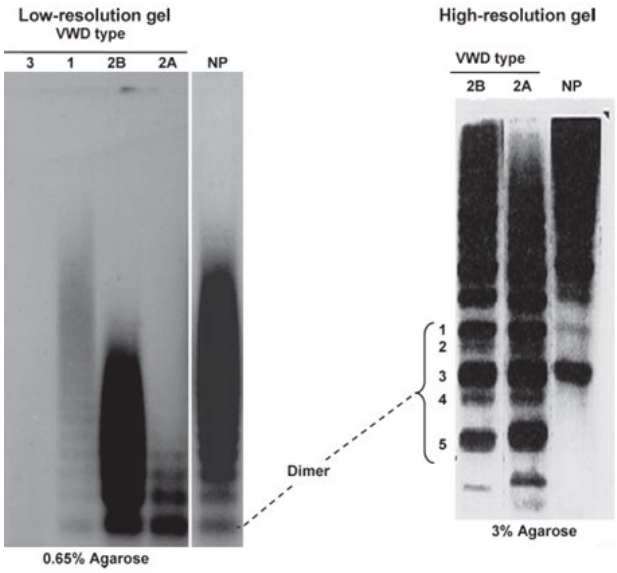


Figure 7: Right: analysis by low resolution multimers. Left: high resolution multimers showing the satellite bands in the lower part of the image. Abbreviation NP: Normal Patient. Modified from Nichols et al. [2].

In a simplified way, it is a qualitative assay in which the different concentrations of multimers of different sizes made by agarose gel electrophoresis are evidenced, using a polyclonal antibody or a combination of radiolabelled monoclonal antibodies. It is available only in

some large hospital centers and commercial laboratories [2]. The multimer analysis can be of low or high resolution. The low-resolution test is done initially. Here, the high molecular weight multimers (HMWM) are differentiated from the medium and small ones, making it possible to differentiate between types 1 and 3, from the type 2 vWD variants (A and B show a decrease in HMWM). On the other hand, in the high-resolution tests, the smallest multimers are shown in 3 to 8 satellite bands [2]. It is relevant to point out that in vWD type 1C there are ultra-large HMWMs, although vWF is diminished [2] (Figure 7).

Platelet Binding Assay (FvW:PB, platelet binding): [2] measures the binding of vWF to platelets fixed in paraformaldehyde at low concentrations of ristocetin (0.3-0.6mg/mL). Like RIPA, this test will only cause a binding in vWD type 2B; although, due to the use of platelets foreign to the patient, a vWD-TP bond will not take place.

FVIII Binding Assay (FvW:FVIIIB). It evaluates the binding of the patient's vWF with recombinant exogenous FVIII. Distinguishing patients with vWD type 2N, in whom this binding will not be achieved. Therefore, it is possible to make a differential diagnosis from mild hemophilia A.

Propeptide Assay (FvWpp). It assesses the activation intensity of the vWF and is useful for detecting vWD 1 of shortened half-life and acquired vWD [22]. In this case, as in the initial tests, the quotient FvWpp / FvW:Ag will also be used. Values > 1 indicate high vWF clearance, as a consequence of a mutation (congenital) or anti-vWF antibody [22].

Other Tests: genetic studies and antibodies against vWF are reserved for research purposes due to the high cost and need of adequate infrastructure in our environment (Tables 3 & 4).

Table 3: Summarizes the initial tests to discard a vWD, and tests complementing the diagnosis.

Lab tests for the vWD diagnosis
Initial management
VWF: Ag (vW antigen)
VWF: RCo (Ristocetin cofactor)
Factor VIII (FVIII:C)
VWF: CB (binding to collagen)
Complementary Studies
RIPA
Study of multimers in agarose gel of low and high resolution
FvW: PB (platelet binding test)
FvW: FVIII (Factor VIII binding)
FvWpp (propeptide)
Molecular biology

Modified from Menschengieser et al. [22].

According to the above-mentioned, the characteristics of the different types and sub-types of vWD may be grouped as follows in Table 4.

Table 4: Alterations of the different laboratory tests for the diagnosis and typification of VWD. Modified from Nichols et al. [2].

	Normal	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	PLT-VWD*
VWF: Ag	N	L↓ o↓↓	↓ o L	↓ o L	↓ o L	N o L	Absent	↓ o L
VWF:RCo	N	L ↓ o ↓↓	↓↓ o ↓↓↓	↓↓	↓↓	N o L	Absent	↓↓
FVIII	N	N o ↓	N o ↓	N o ↓	N o ↓	↓↓	1-9 IU/dL	N o L
RIPA	Absent	Absent	Absent	↓↓↓	Absent	Absent	Absent	↓↓↓
PFA-100 CT	N	N o ↓	↓	↓	↓	N	↓↓↓	↓
BT	N	N o ↓	↓	↓	↓	N	↓↓↓	↓
Platelet count	N	N	N	↓ o N	N	N	N	↓
vWF multimer pattern	N 	N 	Abnormal 	Abnormal 	N 	N 	Absent	Abnormal 

Genotypic Approach

The genotypic analysis is performed by direct sequencing (Sanger's method) of the fragments of interest previously amplified by PCR techniques. After sequencing, the electropherogram of the patient is compared to the normal sequence. It is possible to use screening methods such as the CSGE (Conformation Sensitive Gel Electrophoresis), which allows a quick check of several exons and patients.

Although diagnosis and classification do not require genetic analysis in general, there are situations where genotyping is essential to achieve the differential diagnosis between vWD2N and hemophilia A, vWD2B and PT-vWD, or vWD 2M and severe vWD1. It can also contribute to genetic counseling and improve clinical management (vWD3) (Table 5) (Figure 8).

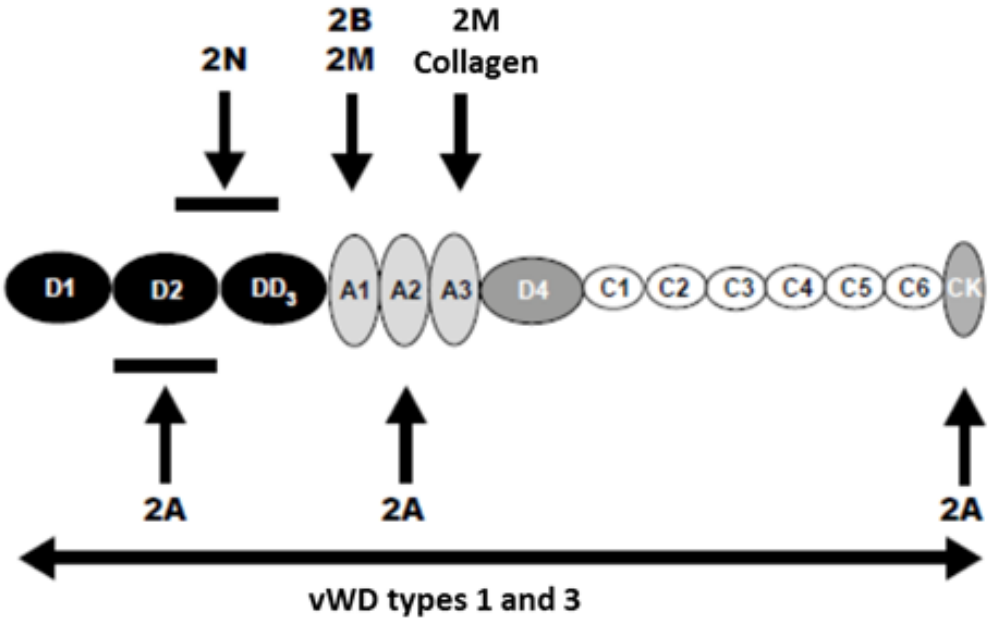


Figure 8: vWF affected interactions according to vWD types Woods et al. [7].

Table 5: Genotypic alterations in vWD.

Genotypic alterations in vWD	
Phenotype	**Genotype**
Type 1	The responsible mutations are located throughout the entire gene (from the promoter region to exon 52). Most of these mutations are changes of direction (up to 75%). However, the probability of finding them is limited to patients with vWF <30 IU/dL. It is associated with blood group O in 65% of cases. Likewise, the most frequent mechanism for decreasing the vWF: Ag is the intracellular retention of mutant vWF. Most of the cases present dominant inheritance with a single mutation and from 5 to 10% have more than one. Penetrance is incomplete, with phenotype expression in 50% of cases [24].
Type 2A	The genotypic alterations are located in different domains. Approximately 73% are located in the A2 domain, which alters the dimerization and multimerization of the vWF; 20% affect the A1 domain, which prevents its binding with platelet GPIb. A lower number of mutations affect the D3 domain (located in exons 22, 25 and 28), resulting in intracellular retention of vWF, loss of HWMW and reduction of ADAMST-mediated proteolysis [14]. Concerning the D2 domain, the mutations affect the propeptide and multimerization (inherited recessively and located in exon 11 to 16). Finally, mutations of the CK domain (exons 51-52) affect the dimerization, causing the formation of satellite bands in the multimer analysis [7].
Type 2B	All responsible mutations are in the A1 domain (which increases the affinity of the vWF for GPIb). The point mutation V1316M alters the platelet signals and leads to the inhibition of GP-IIB / IIIA [7].
Type 2N	Mutations occur in the D'-D3 domain (exon 17-25), resulting in alterations in the binding of vWF to FVIII. The inheritance pattern is recessive, therefore, at least one of the two alleles will cause affectation of the FvW and FVIII binding [7].
Type 2M	Approximately 76% of the mutations are in the A1 domain (exon 28, AA 1229-1439), which generates the inability to bind to the GP-IBA without loss of the HMWM. The underdiagnosed 2CB phenotype included in this group is characterized by mutations in the A3 domain (exons 28 to 32) [7].
Type 3	It is characterized by large deletions throughout the gene, although insertions have also been described, producing a change in the reading frame with the appearance of a stop codon (with loss and decrease in the synthesis of the vWF). Its prevalence is 10 to 20 times more common in consanguineous unions, with recessive inheritance.25 Genetic analysis can identify the causative mutation in almost all individuals, including prenatal diagnosis in carriers of vWD3 using chorionic villus sampling or amniocentesis in weeks 11 to 18 of gestation [24].

Treatment

The main objective of the management of patients with von Willebrand disease is to increase serum levels of vWF. The decision on which medicine to use will depend on the subtype of the disease, if indicated in acute bleeding or as prophylaxis by invasive procedure to be performed.

Desmopressin (DDAVP)

It is a synthetic derivative of the antidiuretic hormone that increases the levels of the vWF starting from the release of vWF stored in endothelial cells. It is indicated in subtypes 1, 2A, 2M and 2N (and contraindicated in subtype 2B due to exacerbation of thrombocytopenia). In subtype 3 due to the absolute absence of vWF, it lacks utility. DDAVP can be administered intravenously or subcutaneously at a standardized dose of 0.3 mcg/kg every 12 to 24 hours. It is also available in nasal spray at a dose of 150 mcg (one shot) in patients <50 kg of weight, or 300 mcg (two shots) in >50 kg. However, in Mexico, intranasal presentation is only available for diabetes insipidus and nocturnal enuresis, where lower doses are required (strength of 10 µg per shot), and not for von Willebrand disease. Intravenous or subcutaneous application is used as prophylaxis before undergoing invasive procedures; the intranasal route is limited to the management of minor (out of hospital) bleedings [28].

The response to DDAVP is variable and depends on the type of vWF mutation, in addition to the basal levels of vWF:Ag and vWFRCo [28]. Due to the variability of response to desmopressin of each individual, plasma levels of vWF and FVIII should be measured before application, 30-90 min and 4 hours after the application. A patient is a responder if the levels of vWF and FVIII increase 2 to 3 times more than the baseline and, in addition, are > 0.30 IU/ml at 30-90 min after the application, with persistence at 4 h after the dose [2,28]. Adverse effects with the use of DDAVP include facial erythema, hypotension, transient headache, symptomatic hyponatremia and cardiovascular events [2]. Therefore, it is recommended to restrict the water intake to 1500 ml in the 24 hours after administration [28].

DDAVP should be administered for short periods (48 to 72 hours, for not more than three days) and not as frequently due to tachyphylaxis (caused by the depletion of the vWF reserve in the endothelium [28]) and adverse effects. Therefore, if longer treatment or shorter intervals are required, the fluid balance and electrolyte levels should be monitored for possible symptomatic hyponatremia [4] (i.e., seizures [2]), being the use of vWF concentrates more appropriate in this case. In adult patients > 20 kg, DDAVP dose adjustments by weight are not necessary; also, it should be used with caution in patients with high cardiovascular risk, in children under 4 years of age, over 70 years of age and those who will undergo eye or central nervous system surgery. Its use in pregnant patients is controversial due to complications described as hyponatremia, preterm delivery and uterine contractions, so it is discouraged in this population [28]. Table 6 summarizes the doses according to DDAVP pharmaceutical form.

Table 6: Desmopressin recommended dose for VWD.

Desmopressin recommended dose for VWD	
Administration or intravenous infusion	0.3 mcg / kg diluted in 10 ml of 0.9% saline solution to pass in 15 min or diluted in 50 to 100 ml of 0.9% saline solution in 30 min infusion*
Subcutaneous	0.3 mcg/kg
Intranasal Spray	300 mcg per inhalation in> 50 kg, 150 mcg per inhalation in <50 kg
Dose interval (iv, sc and nasal)	Every 8 to 24 h depending on the clinical situation and the factors clearance
Time of the administration of desmopressin to the maximum peak of FVW / FVIII	30 to 60 min after the IV administration; 90 to 120 min after the subcutaneous or intranasal administration
*Rapid IV administration can cause tachycardia, tremor, and gastric discomfort.	

vWF Concentrates: Derivatives of human plasma, virus inactivated. They work on all types of vWD. Each of the different pharmaceutical forms also contain FVIII in different proportions, depending on the pharmaceutical company. Likewise, they differ in the content of high molecular weight multimers. Haemate® P, Wilate® and Alphanate® are the vWF concentrates approved by the Food Drug Administration (FDA). The duration of the application of the concentrate varies depending on the procedure (up to 14 days in major surgeries). In Mexico, only the Haemate® P (CSL Behring) and Wilate® (Octapharma) options are available. Regarding Haemate® P, strengths range between 250 IU of FVIII and 600 IU of vWF, or 500 IU of FVIII and 1200 IU of VWF, which are the only forms available in the country. On the other hand, Wilate® (Octapharma) contains 500 IU of vWF and 500 IU of FVIII per vial23. Monitoring of vWF levels during the administration is recommended: RCo and FVIII:C to achieve an adequate haemostatic effect (both with levels > 0.5 IU/mL) and to avoid overdosing with the risk of iatrogenic thrombotic events.

In some countries, recombinant vWF is already available, which requires the first dose to be administered along with a VIIIr Factor, reports a 96% control of the hemorrhage [28]. Tables 7 & 8 show the doses of vWF concentrates according to the procedures and/or situations to be found.

Table 7: Treatment of vWD in patients with very low vWF levels (<10 IU/DL) or who do not respond to desmopressin.

Treatment of vWD in patients with very low vWF levels (<10 IU/DL) or who do not respond to desmopressin			
Clinical situation	**FvW/FVIII Dose**	**Number of infusions**	**Desired vWF level**
Major surgery -Cardiothoracic surgery -Cesarean section -Craniotomy -Hysterectomy - Open cholecystectomy - Prostatectomy	40 to 60 UI/Kg	Every 12 hours initially, later on every 24 hours until improvement of the wound (14 days)	50 to 100 IU / dL, maintain levels of 3 to 10 days
Minor surgery -Biopsy (breast, cervical) - CVC placement - Complicated tooth extractions - Gingival surgery - Uncomplicated laparoscopic surgery	30 to 50 UI/Kg	Once every day (may require 1 to 5 days)	>30 UI/dl
Minor procedures. - Simple uncomplicated dental extraction - Cardiac catheterization - Cataract surgery - Endoscopy without biopsy -Hepatic biopsy - Laceration repair	20 to 40 IU/Kg	A single dose immediately before the procedure	>30 IU/Kg during 12 hours
Spontaneous or post-traumatic hemorrhage	20 to 60 IU/Kg or 20 to 40 IU/Kg	Once daily until remission and clinical monitoring	>30 IU/Kg
Childbirth, puerperium and/or epidural anesthesia	30 to 50 IU/Kg	One dose (once daily)	> 50 IU/dL and maintain levels for 3 to 4 days (take into account the type of vWD and if it increased during pregnancy)

Table 8: Prophylactic treatment with factor VIII concentrate in patients with severe von Willebrand factor deficiency.

Prophylactic Treatment with Factor Viii Concentrate In Patients With Severe Von Willebrand Factor Deficiency				
Bleeding type	**VWD type**	**FVIIII dose**	**Weekly dose**	**Initial dose**
Joints	Type 3	10 to 50 UI	1 – 3	After the first hemorrhage
Gastrointestinal	Type 2	20 to 50 UI	2 – 4	After 2 to 3 severe hemorrhages per year (requiring in-hospital treatment)
Nose/mouth	Type 3	20 to 50 IU	1 – 3	After 3 to 4 hemorrhages per year (requiring hospital treatment)
Menorrhagia	Type 3	20 to 50 IU	3 – 4	If disabling during menstruation
Dose calculated based on the pharmaceutical form of the Factor VIII/von Willebrand Factor (Haemate® P)				

Promotion of Hemostasis using Hemostatic Agents with Mechanisms other than the increase of vWF

Antifibrinolytics

They inhibit the activation of plasminogen, in addition to the inhibition of plasmin at high concentrations, avoiding the degradation of the fibrin clot [28]. Epsilon-aminocaproic acid and tranexamic acid are useful for mucosal bleedings, the latter being the most available in Mexico. They can be administered orally or intravenously for a systemic effect, or topical for local effect. The dose for systemic use (oral or intravenous) of tranexamic acid is 0.5 to 1 g, with a frequency of administration of 2 to 4 times a day in adults. The dose in children older than 1 year is 20 mg/kg/day divided into 2 to 3 applications. The presentation in suspension of tranexamic acid at a concentration of 50 mg/mL follows the same dose guidelines as the presentation in capsules or tablets, although it is not available in Mexico. On the other hand, the initial dose in adults for aminocaproic acid is 4-5 g (the intravenous application should be infused in 1 h). The maintenance dose in this population is 1 g/h

or up to 1.25 g/h orally, although in the latter you can choose 4-6 g every 4-6 h, with a maximum dose of 24 g per day. In pediatric patients the initial dose is 100 mg/kg or 3 g/m^2 (intravenous administration will also be infused in 1 h), with maintenance dose of 33.3 mg/kg/h or 1 g/m^2/h and maximum dose of 18 g/m^2/day or 600 mg/kg/day. Contraindications to the use of antifibrinolytics would be disseminated intravascular coagulation, as well as hematuria of unknown origin, renal origin or in urethral bleeding due to possible coagulation in ureters with episodes of painful colic and the risk of obstruction [28]. They can be used as monotherapy or as an adjuvant with desmopressin and/or von Willebrand Factor concentrates. Table 9 shows the doses of the antifibrinolytics according to the route of administration and population.

Table 9: Antifibrinolytic agents for VWD treatment.

Antifibrinolytic agents for VWD treatment		
Formulation	**Available strength**	**Dose**
Tranexamic acid IV	10 mg/ml	0.5 to 1 g in 2 to 3 times a day (1 ml/min) Children > 1 year: 20 mg/kg per day, divided into 2 to 3 doses per day
Tranexamic acid oral	650 mg	0.5 to 1 g in 2 to 4 doses per day Children> 1 year: 20 mg/kg per day, divided into 2 to 3 doses per day
Tranexamic acid oral wash	50 ml/ml	0.5 to 1.5 (15 to 25 mg/kg/d), in 2 to 3 doses per day (rinse and swallow or spit) Children> 1 year: 20 mg/kg per day, divided into 2 to 3 doses per day
Aminocaproic acid IV	250 mg/ml.	Initial dose: 4 to 5 g slowly during the first hour, followed by continuous infusion of 1 g/h. Children: 100 mg/kg or 3 mg/m2 slowly (> 1h), followed by a continuous infusion of 33.3 mg/kg/h or 1 g/m2/h
Aminocaproic acid oral	500 mg and 1000 mg.	Initial dose: 4 to 5 g, followed by 1 to 1.25 g/h or 4 to 6 g every 4 to 6 hours, maximum dose of 24 g/day. Children: Start with 100 mg/kg, followed by 3 g/m2 during the first hour, followed by 33.3 mg/kg or 1 g/m2 every hour
Maximum dose: 18 g/m2/day or 600 mg/kg/day Aminocaproic acid oral wash	250 mg/ml.	Initial dose: 4 to 5 g, followed by 1 to 1.25 g/h with a maximum dose of 24 g/day (rinse and swallow or spit). Children: Start 100 mg/kg, followed by 3 g/m2 during the first hour, followed by 33.3 mg/kg or 1 g/m2 every hour Maximum dose: 18 g/m2/day or 600 mg/kg/day

Topical Agents

Fibrin sealants, also called coagulable protein complexes, currently available are:

i. Tissucol® [Baxter]: combination of fibrinogen, factor XIII, plasma fibronectin and plasminogen.

ii. Tisseel® [Baxter]: containing human fibrinogen, synthetic aprotinin and human thrombin.

iii. Beriplast P® (CSL Behring), are useful in local hemorrhage (oral cavity and wounds). Components: human fibrinogen, human Factor XIII, aprotinin from bovine lung and human thrombin.

Cryoprecipitates

Cryoprecipitates are plasma derivatives, historically used to treat Hemophilia A and von Willebrand disease; each unit has 80 IU of Factor VIII and a variable amount of von Willebrand Factor (72-102 IU per cryoprecipitate) [29]. This consensus discourages its routine use as a replacement for vWF, so it should only be used in extraordinary situations to treat vWD (i.e., hemorrhagic emergency treatment in the absence of vWF concentrates, as recommended by the World Federation of Hemophilia [2]).

Special Situations

Menorrhage: Hormonal and anatomic alterations should be ruled out as the cause of bleeding. After this, hormonal contraceptives combined with progesterone and estrogen can be used if pregnancy is not desired, which significantly reduces uterine bleeding [28] due to an increase in fibrinogen, prothrombin, FVII, FVIII and vWF [2]. Likewise, the possible complications of a spontaneous rupture of an ovarian cyst are reduced. Bleeding days are drastically reduced when they are administered continuously (≥28 days). Desmopressin has been used as effectively as hormone therapy [2].

Other hormonal treatments such as the intrauterine device (IUD) with levonorgestrel can suppress the growth of the endometrium and the spiral arteries and increase capillary thrombosis without affecting the activity of FVIII in the endometrium, as with the copper IUD. Complications from device insertion do not occur in the presence of adequate hemostasis with replacement therapy [28].

In addition, in women with menorrhagia the combination of antifibrinolytic (recommended dose: tranexamic acid 0.5 to 1 g every 6 h for 3 to 4 days, starting even before bleeding) and hormonal therapy can be offered. Despite the possible prothrombotic risk of the tranexamic acid combination and hormonal therapy, no cases of thromboembolism are reported, therefore it is considered a safe therapy [28]. Dilatation and curettage are not useful in severe menorrhagia; On the other hand, one study showed that the induction of endometrial ablation reduced menorrhagia in 6/7 patients [30]. Some women may require hysterectomy (Figure 9).

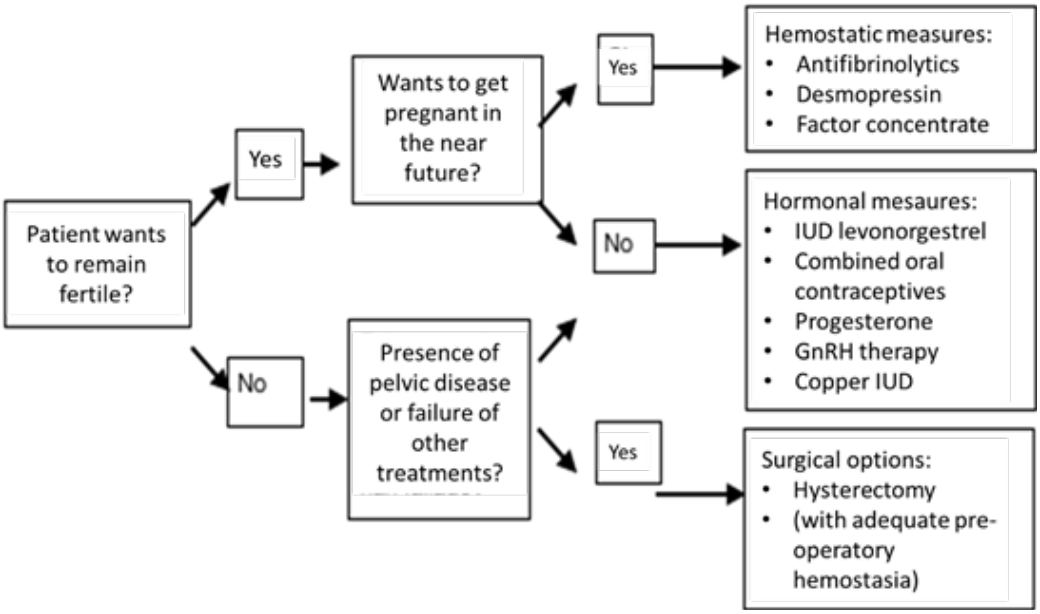


Figure 9: Hypermenorrhea management in vWD.

Treatment in childbirth and pregnancy

VWD is not associated with low fertility, but with an increased risk of spontaneous abortions. Therefore, it is suggested to refer patients to genetic counseling. In addition, the newborn should be evaluated as soon as possible by a pediatric hematologist. Vaccination for hepatitis A and B virus should also be promoted before pregnancy [2]. In addition to the above, patients must attend a perinatal center with a hemophilia treatment area or a haematologist with experience in haemostasis. Prior to any invasive procedure, women should be subjected to FVIII and FvW:RCo tests to determine the need and amount of appropriate prophylaxis, especially prior to the use of analgesia with epidural block, as well as before the removal of an epidural catheter. In the vWD type 1 and 2, the levels of vWF must be monitored: Ag, FVW: RCo, FVIII:C at 12, 30 and 34 SDG. If the vWF and FVIII levels are less than 0.5 U/ml between week 30 and 34, a treatment plan should be established to include dosage of the factor and/or antibrinolytic concentrate during labor and hospitalization, depending on the type of anesthesia and the indication for atraumatic delivery. In patients who have previously responded to desmopressin, administration of desensitization after cord clamping should be considered [28]; However, it should be used with caution during labor (vaginal or cesarean) due to risk of water retention, secondary hyponatremia and seizures, associated with the use of intravenous fluids [2,4]. Tranexamic acid does not cross the placental barrier and no adverse fetal effects have been reported. Aminocaproic acid has been used in a limited way without adverse effects reported [2].

In case of spontaneous abortion or interruption of pregnancy, the VWF:RCo levels should be measured, offering prophylactic treatment if they are less than 50 U/dL. It is recommended to reach levels greater than 50 U/dL of FVIII and VWF:RCo before delivery and maintain them for at least 3 to 5 days after the event. There is no consensus on the levels needed for regional anesthesia, but it is considered that with levels > 50 U/dL and normal coagulation studies, the procedure can be considered safe [2].

Generally, in type 1 vWD, vWF and FVIII factor levels reach normal values in the third trimester of pregnancy, so maternal problems during delivery are not expected. Historically, guidelines have suggested target levels of vWD and FVIII greater than 0.5 U/ml prior to delivery. However, it has been seen that there is an increased risk of postpartum hemorrhage despite specialized treatment in women with vWD, suggesting that they are decreased during delivery [28]. Pregnancy can exacerbate thrombocytopenia and hemorrhagic tendencies in women with type 2B vWD. Epidural anesthesia, vaginal delivery and caesarean section can be safe in type 1 vWD when the VWF:RCo is greater than 0.5 U/ml. In types 2 and 3, restoration of hemostasis is not always achievable despite replacement therapy, so neuraxial anesthesia is not recommended in types 2 and 3 despite having apparently normal levels [31].

To determine the indication for atraumatic delivery, invasive prenatal diagnosis can be performed at weeks 33 and 34 of pregnancy, if the mutation of the vWF gene is known. If the maternal FVIII or vWF is less than 0.5 U/ml, treatment with factor concentrate is indicated during these procedures. When a child potentially has type 3 vWD or a severe type 1 or clinically severe 2 vWD, an atraumatic delivery should be attempted; vaginal delivery is preferable; forceps can be used only in case of emergency, and vaginal breech delivery or expulsion with a duration longer than 1 h is not allowed. When there is evidence of complications, cesarean section should be chosen before replacement therapy [28]. Perianal hematoma is a rare complication of vaginal delivery, but it occurs more frequently in women with vWD [2].

Postpartum bleeding lasts from 21 to 27 days in healthy women; women with vWD have a 15 to 20 times higher risk of postpartum hemorrhage, since the coagulation factors return to their pre-pregnancy level within 14 to 21 days after delivery. Therefore, more frequent

evaluations are required, considering prophylaxis even for two weeks or more after delivery [2,4], maintaining vWF levels greater than 50 U/dL for at least three days in the case of vaginal delivery, or five days in case of cesarean section. It is also suggested to supplement with tranexamic acid four times a day at doses of 500 to 1000 mg, or aminocaproic acid at doses of 4 to 6 grams every 4 to 6 hours orally during the first seven days postpartum [28].

The measurement of vWF:RCo and FVIII in cord blood of the newborn is indicated in type 1 and 2 severe vWD and in type 3 vWD. Due to the high relative levels of vWF:RCo and FVIII by blood activation in the cord after birth, should be re-measured a few weeks later if they are doubtful [28]. Intramuscular injections in neonates with unknown levels of vWF:RCo and FVIII should be avoided or replaced by subcutaneous injections. In case of a possible severe vWD (vWF <0.05 U/ml and/or FVIII <0.05 U/ml), it is indicated to keep the newborn under observation during the first 24 h. Routine ultrasound is not essential but should be performed immediately in case of symptoms suggestive of intracranial bleeding. If ultrasound is not available, replacement therapy in the neonate is indicated prior to the image in case of symptoms of high suspicion [31].

Pain Management in Patients with Von Willebrand Disease

Drugs that may interfere with platelet aggregation and increase the risk of bleeding, such as NSAIDs and acetylsalicylic acid, should be avoided, with the exception of celecoxib and paracetamol which can be used safely and are effective for pain control and, in the case of paracetamol, fever. Opioid or narcotic derivatives such as tramadol and buprenorphine are also useful [32] (Table 10).

Table 10: Drugs to be avoided in patients with WVD James AH et al. [31].

Drugs to be avoided in patients with WVD	
Class	**Examples**
Analgesics	Ibuprofen Naproxen Aspirin Alka-Seltzer, Pepto Bismol (contains Aspirin) Ketorolac
Antidepressants	Citalopram Venlafaxine Paroxetine Fluoxetine Sertraline
Anticoagulants and anti-aggregants (individualized for each case and need)	Acenocoumarin Warfarin Clopidogrel Enoxaparin Dalteparin Non-fractioned heparin
Dietary or herbal supplements	Oral arnica Cranberry extracts Bromelain extracts Cat's claw Coenzyme Q10 Forskolin (weight reduction) Sage *Dong Quai* (Angélica China) Matricaria Garlic capsules Ginkgo biloba

	Ginger Ginseng Horse chestnut Pau d´arco (Lapacho rosado) *Red Clover* Turmeric *Melilotus officinalis* Vitamin E at high doses Sweet asperis (coumarin derivatives)

Physical Activity

Some sports in patients with moderate to severe disease present a higher risk of hemorrhage, therefore they should be avoided:

i. Contact sports (e.g., boxing, martial arts, wrestling)

ii. Football

iii. Skiing (water and snow)

iv. Jaripeo

v. Diving

vi. Olympic gymnastics

vii. Hockey

viii. Climbing

ix. Weightlifting

x. Motorcycling

References

1. Von Willebrand EA (1999) Hereditary pseudohaemophilia. Haemophilia 5(3): 223-231.
2. Nichols WL, Hultin MB, James AH, Manco-Johnson MJ, Montgomery RR, et al. (2008) von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemophilia 14(2): 171-232.
3. Zavelia Padilla-Romo MG, Jaloma-Cruz AR (2015) Diagnostic algorithm for von Willebrand Disease (vWD) in a Mexican population. Gac Med Mex 151(3): 399-402.
4. Ywan BP, Nichols WL, Rick ME (2009) Diagnosis and Management of von Willebrand Disease: Guidelines for Primary Care. Am Fam Physician 80(11): 1261-1268.
5. Campos M, Sun W, Yu F, Barbalic M, Tang W, et al. (2011) Genetic determinants of plasma von Willebrand factor antigen levels: a target gene SNP and haplotype analysis of ARIC cohort. Blood 117(19): 5224-5230.
6. van Loon J, Dehghan A, Weihong T, Trompet S, McArdle WL, et al. (2016) Genome-wide association studies identify genetic loci for low von Willebrand factor levels. Eur J Hum Genet 24(7): 1035-1040.
7. Woods AI, Blanco AN, Kempfer AC, Paiva J, Bermejo EI, et al. (2016) Factor von Willebrand y Enfermedad de von Willebrand: nuevos enfoques diagnósticos. Acta Bioquím Clín Latinoam 50(2): 273-289.
8. Lenting PJ, Christophe OD, Denis CV (2015) von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends. Blood 125(13): 2019-2028.
9. Hernández-Zamora E, Zavala-Hernández C, Quintana-González S, Reyes-Maldonado E (2015) von Willebrand disease. Molecular biology and diagnosis. Cir Cir 83(3): 255-264.
10. Gogia S, Neelamegham S (2015) Role of fluid schear stress in regulating VWF structure, function and related blood disorders. Biorheology 52(5-6): 319-335.
11. Baronciani L, Goodeve A y Peyvandi F. Diagnóstico molecular de la enfermedad de von Willebrand. Haemophilia 23: 188-197.
12. Zander CB, Cao W, Zheng XL (2015) ADAMTS13 and von Willebrand factor interactions. Curr Opin Hematol 22(5): 452-459.
13. Cao W, Krishnaswamy S, Camire RM Lenting PJ, Zheng XL (2008) Factor VIII accelerates proteolytic cleavage of von willebrand factor by ADAMTS13. Proc Natl Acad Sci U S A 105(21): 7416-7421.
14. Focosi Daniele (2018) Homo Sapiens Diseases - Alterations in Platelets.