VON WILLEBRAND DISEASE

Module 2

How to screen for von Willebrand disease?

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What will you learn in this micro e-learning programme about von Willebrand disease?

This micro e-learning programme consists of **three modules** aiming to increase awareness, knowledge and understanding of the existence, diagnosis, treatment and implications of von Willebrand disease among healthcare professionals outside of haematology.

Upon completion of the three modules, you will:

- be aware of the potential **existence of von Willebrand disease** in your patient population
- be able to **recognise the signs and symptoms** of von Willebrand disease
- understand **how to search for von Willebrand disease**, effectively using the screening tools available and signposting patients towards earlier diagnosis
- be aware of the **impact** of von Willebrand disease on other care

AFTER MODULE 1 YOU WILL

- be aware of the potential **existence of von Willebrand disease** among your patient population
- be able to recognise the **signs and symptoms** of von Willebrand disease

AFTER MODULE 2 YOU WILL

Current Module

- understand you can **help diagnose** von Willebrand disease
- be able to effectively use the **screening tools** available
- understand the **next steps** to take when suspecting von Willebrand disease

AFTER MODULE 3 YOU WILL

- be aware of the **impact of von Willebrand disease on provision of general care**
- understand the key **aspects of von Willebrand disease affecting your clinical practice**
- understand the importance of a **multidisciplinary approach** in von Willebrand disease care

This micro e-learning module has been developed by a **multidisciplinary panel of experts**

Dr. Alison Dougall

IRELAND

- **Dental** consultant medically complex patients at Dublin Dental Hospital
- Director of doctorate programme in special care dentistry, Trinity College Dublin
- Former chair of World Federation of Haemophilia Dental Committee
- Medical advisory board member of European Haemophilia Consortium (EHC)
- President of International Society for Disability and Oral Health

Dr. Vickie McDonald

UK

- Consultant **Haematologist** at the Royal London Hospital, London
- Honorary senior lecturer at Queen Mary University of London
- National chief investigator for the UK immune thrombocytopenia (ITP) registry

Dr. Gianluigi Pasta

ITALY

- **Orthopaedic** consultant at the Haemophilia Centre at Fondazione IRCCS Policlinico San Matteo di Pavia
- Chair of the Musculoskeletal Committee of the World Federation of Haemophilia (WFH)
- Coordinator of Musculoskeletal Group of Italian Haemophilia Centres Association

Dr. Med. Rosa Sonja Alesci

GERMANY

- **Haematology** consultant and health economist
- Director of the IMD Blood Coagulation Centre in Bad Homburg/Frankfurt/Wiesbaden
- Active member of German Society of Haematology and Oncology
- Member of medical advisory board German Alliance for Security of Haemophilia

Prof. Ana Boban

CROATIA

- Head of **Haemophilia** Centre at the University Hospital Centre Zagreb
- Professor of **internal medicine** at the School of Medicine of the University of Zagreb, Croatia
- Specialist degrees in internal medicine and haematology
- Executive committee member of the European Association for Haemophilia and Allied Disorders (EAHAD)

Dr. Jonathan C. Roberts

USA

- Associate medical director and associate research director at the Bleeding & Clotting Disorders Institute (BCDI)
- Assistant professor of **Paediatrics** and Medicine at the University of Illinois College of Medicine at Peoria in Peoria, IL
- Haematologist with BCDI

Dr. Michael A. Mazzeffi

USA

- Cardiothoracic **anaesthesiologist** and **intensive care** physician
- Executive vice chair and director of cardiac intensive care at George Washington University School of Medicine in Washington, DC

Prof. Jan Blatný

CZECH REPUBLIC

- Consultant **Haematologist**, director of Haemophilia Comprehensive Care Centre and medical director of **Paediatrics** at University Hospital in Brno
- Associate professor of paediatrics at Masaryk University in Brno
- Active member of International Society on Thrombosis and Haemostasis (ISTH), Vice president of EAHAD and MAG member of EHC
- Paediatric coordinator of the Czech National Haemophilia Programme

The views expressed in this slide deck are the personal opinions of the experts.
They do not necessarily represent the views of the experts' institutions or the rest of the HEMOSTASIS CONNECT group.

When to suspect von Willebrand disease
Module 1 summary

Module 1 of this micro e-learning programme described how von Willebrand disease is the most common inherited bleeding disorder, occurring in men, women, and children. **Signs and symptoms** of von Willebrand disease include:

General

- **Family history** of a bleeding disorder
- Notable **bruising** without injury
- **Prolonged/excessive bleeding**, even from minor wounds

Dental

- Prolonged bleeding following invasive **dental procedures**
- Prolonged **bleeding from the gums** following deep cleaning
- **Recurrent ulcers and pallor** of the mucosa associated with anaemia

Paediatric

- **Nosebleeds**
- Bleeding **during teething** in small children
- Notable **bruising without injury**
- **Excessive bleeding** from minor wounds

ENT

- **Nosebleeds**
- Severe (potentially life-threatening) bleeding after **tonsillectomy/ adenoidectomy**

Gynaecological

- Heavy **menstrual bleeding**, especially since menarche
- Bleeding during **ovulation**
- Primary and late **post-partum haemorrhage**

Surgical

- **Joint pain** and/or bleeds
- Prolonged and/or severe bleeding after **minor or major surgery**

Gastrointestinal

- **Bleeding of gastrointestinal tract** with or without an obvious anatomic lesion in adults

ENT, ear, nose, and throat
This slide is based on the clinical experience of the authors

Next steps
when suspecting von Willebrand disease in your patient

1

The key first step is taking a **thorough bleeding history, including a detailed family history.**[1]

- The personal bleeding history and family history will guide you in determining the likelihood of an underlying bleeding disorder and provide justification for performing further laboratory testing
- **Use a validated bleeding assessment tool** (BAT) for this, such as the ISTH-SSC BAT[2]

Practical tips:

Be mindful of bias. Bleeding symptoms may be seen as normal in families with (undiagnosed) bleeding disorders, leading patients to underestimate or trivialise their symptoms.

Note that the ISTH-SSC BAT lacks specificity for bleeding disorders in patients with oral bleeding.[3] This may reinforce the inaccurate perception that gum bleeding is related to bleeding disorders rather than gingivitis.

2

The second step is **laboratory assessment.**[1]

- In patients with a **low probability** of von Willebrand disease (e.g., in the primary care setting), initial screening with a validated BAT helps determine who needs specific blood testing
- In patients with a **high probability** of von Willebrand disease (e.g., because they have an affected first-degree relative), laboratory assessment should be performed regardless of their BAT score

BAT, bleeding assessment tool; ISTH, International Society on Thrombosis and Haemostasis; SSC, Scientific and Standardization Committee

1. James PD, et al. Blood Adv. 2021;5:280-300; 2. Rodeghiero F, et al. J Thromb Haemost. 2010;8:2063-5; 3. Dougall A, et al. Res Pract Thromb Haemost. 2020;4 suppl 1:PB1595. (ISTH 2020 poster presentation)

1 Use a validated screening tool
ISTH-SSC BAT

The ISTH-SSC subcommittees have developed a tool to **assess patients with a suspected inherited bleeding disorder.**

The questionnaire is to be collected by an adequately trained healthcare professional, who will **score symptoms and related treatments** before or at diagnosis (or both).

An **abnormal score** indicates that further testing is required:

- ≥3 in children
- ≥4 in adult males
- ≥6 in adult females

The ISTH-SSC bleeding assessment tool scores the following symptoms

1. Epistaxis
2. Cutaneous bruising
3. Bleeding from minor wounds
4. Oral cavity bleeding
5. Gastrointestinal bleeding
6. Haematuria
7. Dental extraction bleeds
8. Surgical bleeding
9. Heavy menstrual bleeding
10. Post-partum haemorrhage
11. Muscle haematomas
12. Haemarthrosis
13. Central-nervous system bleeding
14. Other bleeding problems

An online version of the ISTH bleeding assessment tool is available at **https://bleedingscore.certe.nl**

BAT, bleeding assessment tool; ISTH, International Society on Thrombosis and Haemostasis; SSC, Scientific and Standardization Committee

Elbatarny M, et al. Haemophilia. 2014;20:831-5; Rodeghiero F, et al. J Thromb Haemost. 2010;8:2063-5.

2 Laboratory assessment
Tests you can perform yourself

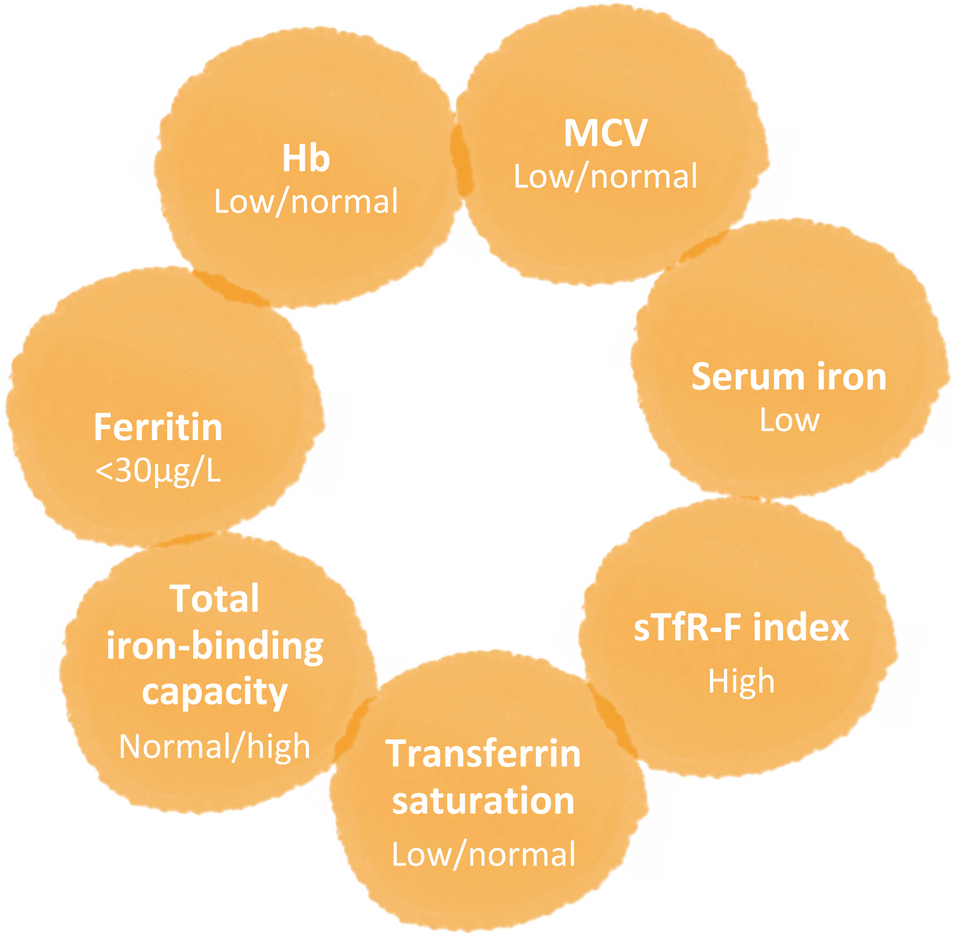
Full Blood Count

Iron and ferritin status

Assessment of iron status, haemoglobin, and red blood cell count is **not specific to von Willebrand disease,** but findings provide **important information for clinical management.**

Iron deficiency with or without anaemia is common in patients with bleeding symptoms and can **easily be diagnosed and treated.**

- Even without anaemia, iron deficiency can be symptomatic and impact quality of life, causing e.g., fatigue, muscular weakness, or hair and skin issues
- **Iron deficiency anaemia** may precede clinically significant bleeding, so bleeding disorder evaluation is required



Hb, haemoglobin; MCV, mean corpuscular volume, sTfR-F, soluble transferrin receptor/ferritin
O'Brien SH. Blood. 2018;132:2134-42; VanderMeulen H, et al. Transfus Apher Sci. 2018;57:735-8

2 Laboratory assessment
Tests you can perform yourself

Coagulation Screening

Routine coagulation screening can be performed, but these tests are **abnormal in only a minority of patients** with von Willebrand disease.

Even if the coagulation screening is **normal,** patients with bleeding symptoms and/or an abnormal BAT score should **still be referred to a haematologist.**

Normal PT and aPTT do not exclude von Willebrand disease

PT and aPTT

Evaluate the intrinsic (aPTT) and extrinsic (PT) coagulation pathway

- INR is not used in bleeding disorders[a]

Common causes of prolonged aPTT and/or PT

- Medication
- Reduced nutritional intake or malabsorption
- Systemic disease
- Consumptive coagulopathy
- Severe clotting factor deficiencies

Fibrinogen activity

Evaluates the level and function of fibrinogen (factor I)

[a] INR reflects PT in the management of warfarin and in hepatology

aPTT, activated partial thromboplastin time; BAT, bleeding assessment tool; INR, international normalised ratio; PT, prothrombin time

Green D. Blood Coagul Fibrinolysis. 2010;21 Suppl 1:S3-6; Hayward CPM. Int J Lab Hematol. 2018;40 Suppl 1:6-14; Kamal AH, et al. Mayo Clin Proc. 2007;82:864-73; Simon D, et al. Haemophilia. 2008;14:1240-9; O'Brien S. Blood. 2018;132:2134-42; Federici AB. Semin Thromb Hemost. 2006;32:555-65

2 Laboratory assessment
Tests where haematology support is required

There are **many pitfalls** in the interpretation of diagnostic laboratory tests, so refer to a haematologist or make sure you have **haematology support available for interpretation.**

VWF is an acute phase reactant; there are **many factors impacting VWF levels.**

- Repeat VWF testing is needed to establish a true baseline

Platelet function analysis is also performed by the haematologist.

- A normal platelet count is not an indication of good platelet function
- Platelet function tests expose platelets to specific triggers to check responses (e.g. PFA-100)

VWF Tests focusses on:

How VWF is present

Quantitative
VWF antigen (VWF:Ag) testing

Impacted by stress, infection, illness, exercise, high-dose hormonal therapy, pregnancy, trauma and blood group (lower in blood group O)

How VWF functions

Qualitative
VWF activity assays

Examine the platelet binding function of VWF (VWF:RCo)

Additional second-line VWF tests

Additional second-line VWF testing can be performed by a coagulation haematologist in a Haemophilia Treatment Centre, including assessment of VWF multimers, specialised VWF activity testing (platelet binding [VWF:GPIb assays], collagen binding [VWF:CB], ability to carry factor VIII [factor VIII activity]) and genetic testing

! Expert interpretation of results of these tests and patient history are essential for diagnosis of von Willebrand disease

Ag, antigen; CB, collagen binding; GPIbM, glycoprotein Ib mutation; PFA, Platelet Function Analyzer; RCo, ristocetin cofactor; VWF, von Willebrand factor

Leebeek FWG, et al. N Engl J Med. 2016;375:2067-80; Ng C, et al. Blood. 2015;125:2029-37; Favaloro EJ, et al. Haemophilia. 2004;10 Suppl 4:164-8

3 Management of von Willebrand disease
A multidisciplinary approach

Symptomatic treatment can be started in first line, even in absence of a definite diagnosis

- **Iron replacement therapy** for iron deficiency with or without anaemia
- **Antifibrinolytics** (tranexamic acid or aminocaproic acid) for bleeding symptoms (e.g., nosebleeds, excessive bleeding from minor wounds, heavy menstrual bleeding, prolonged bleeding after dental extraction)
  - Note: gum bleeding should not be treated with tranexamic acid but needs intervention from a dental care professional
- **Hormonal therapy** for heavy menstrual bleeding

For specific treatment, patients need to be referred to specialists

- **Haematologist** for haemostatic treatment (antifibrinolytics, DDAVP and/or VWF replacement therapy)
- **Gynaecologist** for heavy menstrual bleeding and planning of pregnancy and delivery
- **Dental care professional** for tailored oral health education and dental hygiene programmes alongside preventive dental care to treat gingivitis and periodontal disease
- **MSK experts** (i.e., physiotherapist, orthopaedic surgeon, physiatrist) in case of suspected joint bleeds
- **Anaesthesiologist** before planning surgery

For more details on the management of von Willebrand disease, please refer to Module 3 of this programme

DDAVP, desmopressin; MSK, musculoskeletal; VWF, von Willebrand factor

Connell NT, et al. Blood Adv. 2021;5:301-25; Peyrin-Biroulet L, et al. Am J Clin Nutr. 2015;102:1585-94

Next steps
when suspecting von Willebrand disease

Von Willebrand disease may be difficult to diagnose, **refer patients in whom you suspect von Willebrand disease to a haematologist** for diagnostic laboratory assessment and treatment.

Symptomatic treatment may be started in first line.

Please refer to the **other modules of this micro e-learning programme** for more information on:

- **Module 1:** Pathophysiology and symptoms
- **Module 3:** A multidisciplinary approach: impact of von Willebrand disease on the provision of general care

Summary

1. When you suspect von Willebrand disease, take a **thorough bleeding history**, including a detailed family history, using a validated BAT

2. Perform **laboratory testing;** general tests can be performed in first line, whereas expert interpretation is required for diagnostic testing

3. The **management** of von Willebrand disease requires a **multidisciplinary approach**

Next steps

Please now proceed to the **assessment quiz** in the e-learning to test your knowledge

Visit **Module 1** of this micro e-learning programme to learn more about:

- the potential existence of von Willebrand disease among your patient population
- the signs and symptoms of von Willebrand disease

Visit **Module 3** of this micro e-learning programme to learn more about:

- the impact of von Willebrand disease on provision of general care
- the key aspects of von Willebrand disease affecting your clinical practice
- the importance of a multidisciplinary approach

Note: you will be able to claim your CME credit after passing at least 2 of the 3 modules

CME credit available
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