Thrombosis Research 130S2 (2012) S2–S6

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Original Article

Diagnosis and treatment of acquired von Willebrand syndrome

Andreas Tiede *

Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany

ARTICLE INFO

Keywords:
Acquired von Willebrand syndrome
Epidemiology
Diagnosis
Treatment
Haemate® P
Humate-P®

ABSTRACT

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that is characterized by structural or functional alterations in von Willebrand factor (VWF) caused by a range of lymphoproliferative, myeloproliferative, cardiovascular, autoimmune, and other disorders. The pathogenic mechanisms responsible for the VWF abnormalities depend on the underlying condition, but include clearance due to binding of paraproteins, inhibition of VWF, adsorption to the surface of platelets, increased fluid shear stress, and resultant proteolysis or, more rarely, decreased synthesis. The diagnosis and treatment of AVWS are complicated by the need for multiple laboratory tests and the management of bleeding risk in a typically elderly population with serious underlying conditions that predispose towards thrombosis. Recently developed diagnostic algorithms, based on standard laboratory assays, may assist clinicians with the diagnostic workup and help differentiate between AVWS and von Willebrand disease (VWD) types 1 and 2. AVWS should be considered in all patients with new-onset bleeding whenever laboratory findings suggest VWD, particularly in the presence of an AVWS-associated disorder. AVWS testing is also recommended prior to surgery or an intervention with a high risk of bleeding in any individual with an AVWS-associated disorder. Treatment of the underlying condition using immunosuppressants, surgery, or chemotherapy, can lead to remission of AVWS in some individuals and should always be considered. Strategies to prevent and/or treat bleeding episodes should also be in place, including the use of VWF-containing factor VIII concentrates, desmopressin and tranexamic acid. Treatment success will depend largely on the underlying pathogenesis of the disorder.

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that can be defined as any structural or functional alteration in von Willebrand factor (VWF) that is not inherited and causes bleeding. The diagnosis and treatment of AVWS are complicated by the need for many different laboratory tests to help differentiate between AVWS and some subtypes of congenital von Willebrand disease (VWD), with management of bleeding risk often confounded by the presence of serious underlying conditions in populations at increased risk of thrombosis.

The prevalence of AVWS remains poorly defined, since less than 700 cases have been reported in the world literature (Table 1) [1–3]. Federici et al. were the first to review the literature (1968–1999), identifying 266 cases of AVWS characterized by reduced plasma levels of VWF [1]. An additional 186 patients were detected via the establishment of an international registry by the International Society on Thrombosis and Haemostasis (ISTH) [1].

Table 1
Overview of studies assessing the epidemiology of acquired von Willebrand syndrome (AVWS) [1–3].

Source	Cases	Denominator	Reference
Literature survey (1968–1999)	266	?	[1]
ISTH Registry (2000)	186	?	[1]
German reference laboratory (2000, over 2 years)	187	5,014 samples	[2]
Hannover cohort (2008, over 10 years)	35	1,500 patients	[3]

ISTH, International Society on Thrombosis and Haemostasis.

In subsequent years, a further 187 cases of AVWS were found by a reference laboratory in Germany amongst 5,014 plasma samples from patients with symptoms of defective primary hemostasis [2], with 35 new patients from a sample of 1,500 individuals with acquired bleeding described in 2008 [3]. Although these studies do not allow us to estimate the true prevalence of AVWS, they confirm that, although rare, a rate of one case of AVWS in every 30–40 samples from patients with bleeding disorders [2,3] suggests the condition is certainly one to consider in daily hematologic practice.

Risk factors for AVWS

What these landmark epidemiologic studies did help to establish was the type of patient most likely to be at risk of developing

Abbreviations: AVWS, acquired von Willebrand syndrome; FVIII, factor VIII; HMW, high molecular weight; IgG, immunoglobulin G; ISTH, International Society on Thrombosis and Haemostasis; MGUS, monoclonal gammopathy of undetermined significance; rFVIIa, recombinant activated factor VII; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:CB, VWF collagen binding; VWF:RCo, VWF:risocetin cofactor.

* Correspondence: Andreas Tiede, MD, PhD, Hannover Medical School, Haematology, Haemostasis, Oncology and Stem Cell Transplantation, Feodor Lynen St. 5, 30625 Hannover, Germany. Tel.: +49 511 532 8377; fax: +49 511 532 8351.
E-mail address: tiede.andreas@mh-hannover.de (A. Tiede).

0049-3848/$ – see front matter

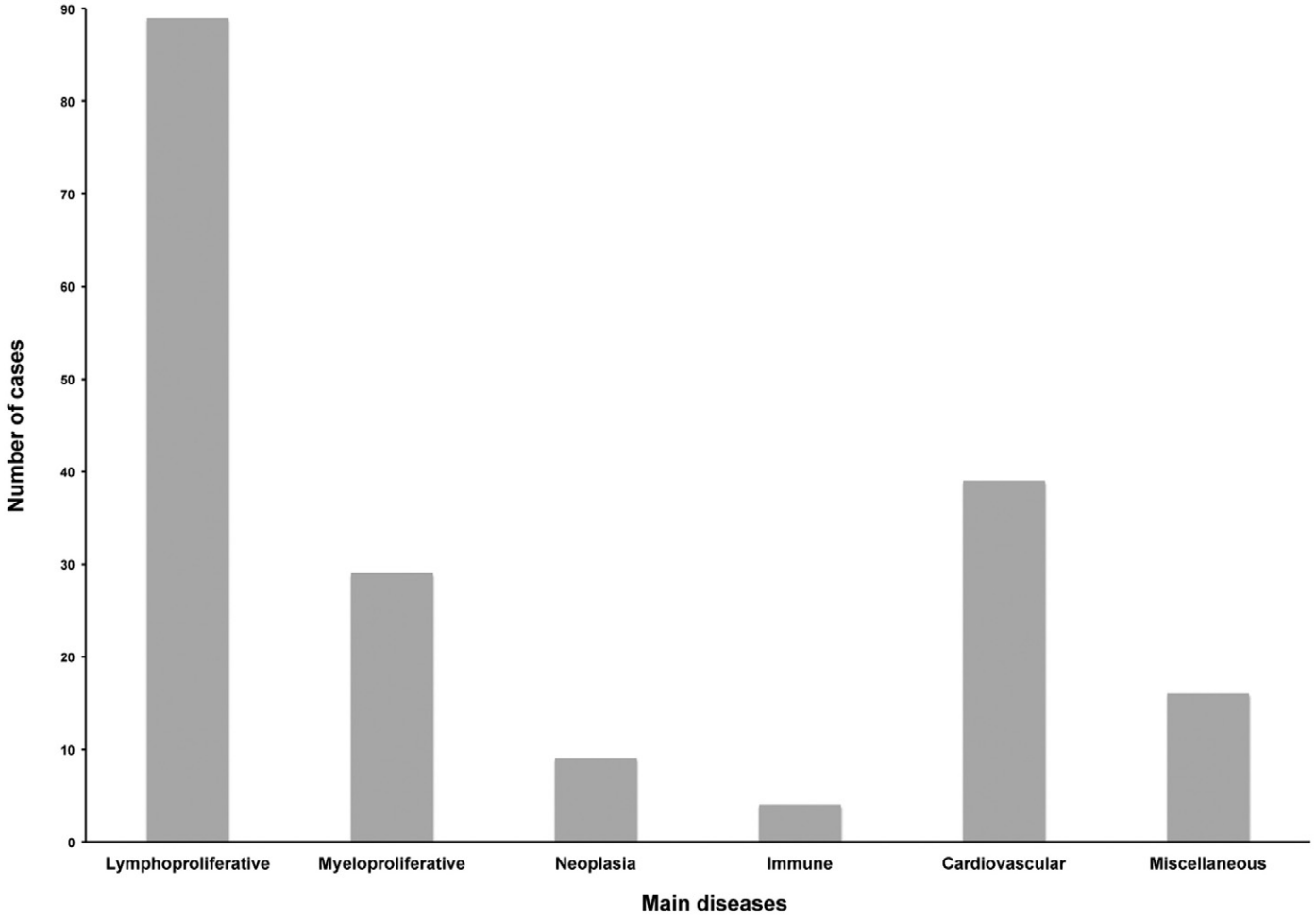

Fig. 1. Frequency of underlying conditions associated with acquired von Willebrand syndrome in 186 patients identified in an ISTH registry [1]. Miscellaneous conditions include infectious diseases, other systemic diseases, drug-induced and idiopathic diseases. ISTH, International Society on Thrombosis and Haemostasis.

AVWS. The ISTH registry [1] found the highest frequency of AVWS in elderly patients, reporting a median age at diagnosis of 62 years (range 2–96 years). The registry also identified that the highest rate of AVWS was in patients with lymphoproliferative disorders (affecting 48% of patients in the registry) – most notably monoclonal gammopathy of undetermined significance (MGUS) (affecting 23% of registered patients) (Fig. 1). Congenital and acquired cardiovascular defects, including atrial septal defects and aortic stenosis, were reported in 21% of patients in the registry. Other reported underlying conditions included myeloproliferative disorders (e.g. essential thrombocythemia) and neoplasia. Autoimmune disease, hypothyroidism, and uremia were also found to be risk factors in a small percentage of patients.

Later reports suggested an increase in the contribution made by cardiovascular disorders to the incidence of AVWS, rising from 21% of patients in the ISTH registry, to 40% of patients in the study by Budde et al. [2], and to 45% of patients in our Hannover cohort (reported in 2008) [3]. This apparent increase in frequency may be due to differences in the inclusion criteria used in each study or to increasing awareness of AVWS amongst cardiologists. It may also be due to an increased use of left ventricular assist devices, which are being used more frequently to sustain heart failure patients awaiting heart transplantation, and which are now known to be associated with a high risk of developing AVWS [4–6].

Pathogenesis of AVWS

The defects in VWF structure or function associated with AVWS depend primarily on the underlying cause of the condition (Table 2). In lymphoproliferative disorders such as MGUS and in some cancers, autoimmune clearance due to binding of paraproteins or inhibition of VWF results in very low circulating concentrations of the protein [7–14]. AVWS associated with myeloproliferative disorders is most likely due to increased binding of VWF to

Table 2
Pathogenic mechanisms responsible for structural or functional disturbances of von Willebrand factor (VWF) in different acquired von Willebrand syndrome-associated conditions.

Reduced VWF synthesis	Inhibition/clearance by paraproteins or autoimmune inhibitors	Adsorption of VWF high-molecular weight multimers	Increased shear stress and proteolysis
• Severe hypothyroidism • Drugs (e.g. valproic acid)	• B cell lymphomas • Monoclonal gammopathy of unknown significance • Multiple myeloma • Autoimmune disorders	• Myeloproliferative neoplasias (essential thrombocythemia, polycythemia vera) • Thrombocytosis (non-malignant) • Other malignant disorders	• Aortic valve stenosis • Artificial heart valves • Left ventricular assist devices • Other (mostly congenital) heart defects with disturbed flow

cell surfaces, particularly platelets and myeloma cells, which can consume large VWF multimers [15–18]. Cardiovascular conditions such as ventricular septal defects and aortic stenosis can lead to pathologic increases in fluid shear stress resulting in increased proteolysis of VWF by ADAMTS13 and depletion of high-molecular-weight (HMW) VWF multimers [19–21]. In some of the rarer causes of AVWS, including hypothyroidism, a decrease in the synthesis of VWF has been proposed [22].

Laboratory tests used in the diagnosis of AVWS

The most accurate diagnostic tests for AVWS rely on detecting abnormally low levels of VWF activity in comparison with VWF antigen levels, and on the demonstration of a selective deficiency of HMW VWF multimers. The routine tests recommended are essentially the same as those used to diagnose VWD: VWF antigen assays (VWF:Ag), activity assays [VWF activity (VWF:Act), or ristocetin cofactor assay (VWF:RCo)], collagen binding capacity (VWF:CB), and multimer analysis using electrophoretic separation and immunostaining [23].

Under normal circumstances, the VWF:RCo correlates with VWF:Ag and the VWF:RCo/Ag ratio is approximately 1.0. In AVWS, a reduced VWF:RCo/Ag ratio of <0.6–0.7 (actual threshold to be established by each laboratory) indicates inhibitory antibodies or a selective loss or decrease in HMW multimers [3]. A decrease in VWF:CB/Ag ratio may also indicate a loss or decrease in HMW VWF multimers [3]. VWF multimer analysis is considered the gold standard for the detection of structural abnormalities in VWF that may indicate AVWS, since a decrease in HMW multimers may be the only way of detecting AVWS in the significant number of patients with cardiovascular disorders and/or lymphoproliferative disorders who have normal VWF:RCo, VWF:CB, and even normal VWF:RCo/Ag and VWF:CB/Ag ratios [3,6].

A number of special laboratory tests have been described in the literature that may assist in the diagnosis of AVWS; however, none have entered routine clinical practice and none are 100% sensitive for AVWS. Inhibitory antibodies in AVWS can sometimes be detected using neutralization assays of VWF:RCo, VWF:Ag, VWF:CB, or ristocetin-induced platelet aggregation; however, these assays are technically demanding and will fail to detect relevant non-neutralizing antibodies [3]. Enzyme-linked immunosorbent assays are capable of detecting a broader spectrum of VWF-binding antibodies and these may provide useful information in some patients, where available. An increased VWF propeptide/VWF:Ag ratio may also indicate the presence of AVWS; however, this test does not always discriminate between AVWS and VWD and is not recommended for routine use at the present time [23].

Diagnostic algorithms for AVWS

We have recently proposed two diagnostic algorithms for AVWS: one for patients with new-onset bleeding undergoing testing for VWD (Fig. 2A) and one for patients with an AVWS-associated disorder scheduled for surgery or an intervention with a high risk of bleeding (Fig. 2B) [23]. We recognize that differentiating between AVWS and VWD types 1 and 2 can be especially challenging, and

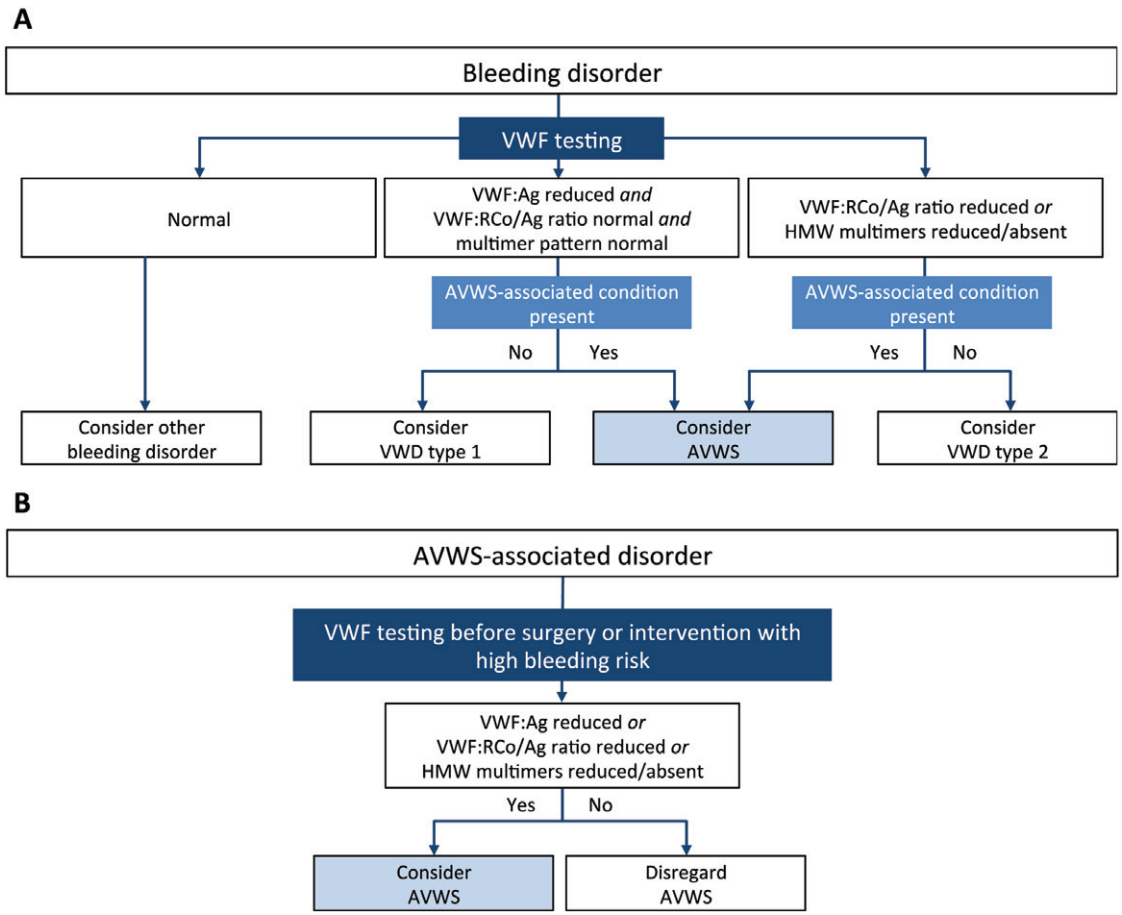

Fig. 2. Suggested diagnostic algorithms for acquired von Willebrand syndrome (AVWS) in patients with a bleeding disorder undergoing von Willebrand factor (VWF) testing (A) and in patients with an AVWS-associated disorder prior to surgery or intervention with high bleeding risk (B) [23]. Reproduced with permission from Tiede A, et al. How I treat the acquired von Willebrand syndrome. Blood 2011;117:6777–85 © 2011 by the American Society of Hematology. HWM, high molecular weight; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor.

we have attempted to guide physicians towards achieving a correct diagnosis using the routine laboratory tests outlined above.

In brief, we suggest that AVWS should always be considered whenever laboratory findings suggest VWD, particularly in the presence of an AVWS-associated disorder. Late-onset bleeding and a negative family history should always prompt suspicion of AVWS, bearing in mind that mild VWD can remain asymptomatic for decades. Using the standard laboratory tests described above, we recommend that AVWS should be considered in all bleeding patients with reduced VWF:Ag, reduced VWF:RCo/Ag ratio, or disturbed multimer pattern [23]. We do not recommend routine testing in all patients with an AVWS-associated disorder because of their high prevalence of this type of disorder in the general population; however, we do suggest offering testing to patients with AVWS-associated disorders before major surgery or high-risk interventions [23].

Treating the underlying disorder

Once a diagnosis of AVWS has been confirmed, the first priority should be to treat the underlying disorder as this can sometimes lead to resolution of the bleeding tendency. If an underlying condition would not require treatment on its own (i.e. otherwise asymptomatic low-grade lymphoma, asymptomatic non-severe aortic valve stenosis), the goal of improving AVWS may still be a reason to consider treatment, depending on the severity of the bleeding tendency. In individuals with B-cell lymphomas or multiple myeloma treated with chemotherapy (with or without rituximab), remission of AVWS can be achieved in up to 70% of patients [23]. Correction of any underlying cardiac defect, such as aortic valve stenosis, usually results in an improvement in AVWS in most patients [24]; use of thyroxin in patients with hypothyroidism [25] and discontinuation of treatment in drug-induced cases [26,27] have also been reported to resolve the condition.

Preventing and treating bleeds

For patients with AVWS who continue to show a bleeding tendency despite attempts to correct the underlying pathology, strategies to prevent and/or treat bleeds must be in place (Table 3) [1,3,28]. A variety of therapeutic approaches have been used to treat such patients, including VWF-containing factor VIII (FVIII) concentrates, desmopressin, tranexamic acid and recombinant factor VIIa (rFVIIa) [23]. VWF-containing concentrates are effective in most patients with AVWS [3], and we recommend initiating treatment at a dose of 30–100 VWF:RCo units/kg, depending on the patient's residual activity, severity of bleeding, and inhibitor status [23]. As the half-life of VWF can be short in patients with MGUS or inhibitors, close monitoring is recommended [23].

Desmopressin has been used in patients with AVWS to control bleeding, although the reported efficacy is lower (10–75%) than that of VWF-containing FVIII concentrates [1]. Success with desmopressin treatment appears to depend on the underlying disorder; relatively low rates of success have been reported in patients with cardiovascular and myeloproliferative disorders [1]. Desmopressin must be used with caution in the elderly and patients with cardiovascular conditions; and fluid overload and hyponatremia are well-known side effects of the treatment.

In autoimmune and lymphoproliferative disorders, intravenous administration of high-dose immunoglobulin G at a dose of 0.5–1.0 g/kg for 2–4 days can correct VWF activity for 2–3 weeks [28,29]. Plasmapheresis has also been used successfully to deplete autoantibodies and paraproteins in such patients [30].

Tranexamic acid (20–25 mg/kg every 8–12 hours) is usually administered as an adjunctive treatment to desmopressin or VWF-containing FVIII concentrates for surgery and bleeding, particularly in the gastrointestinal tract [23]. A few reports on the successful use of rFVIIa have been published; however, the treatment is not licensed for use in AVWS, and caution should be exercised in the elderly and those at risk of thromboembolism [23].

Summary and conclusions

The possibility of AVWS should always be considered in patients with an acquired bleeding disorder and those with an initial diagnosis of VWD. New diagnostic algorithms have been developed based on routine laboratory assays to assist with the diagnostic workup. Initial treatment should target the underlying cause of the condition, with additional treatment options available for patients who continue to bleed despite attempts to correct the underlying pathology. VWF-containing FVIII concentrates and desmopressin are important options for the treatment and prevention of bleeds in AVWS patients and will remain so for the foreseeable future. As with all very rare conditions, it is vital that clinicians share their patient information with international registries in order for us to gain a deeper understanding of these enigmatic conditions. Physicians who diagnose and treat patients with AVWS are therefore encouraged to contribute to an important new international registry (http://www.IntReAVWS.com) that will form the basis of future studies into this rare and often challenging bleeding disorder.

Acknowledgements

The author is grateful to August Federici (Milan, Italy), Jacob Rand (New York, NY, USA), and Ulrich Budde (Hamburg, Germany) for many fruitful discussions. Swiss Medical Press GmbH (Hochwald, Switzerland) is acknowledged for editorial support in the preparation of this manuscript.

Conflict of interest

The author or his institution have received research grant, lecture fees and honoraria for consultation from the following pharmaceutical companies: Bayer, Baxter, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer.

Role of the funding source

CSL Behring paid for editorial support in the preparation for this manuscript.

Table 3
Options for the prevention or treatment of bleeding in patients with acquired von Willebrand syndrome (AVWS) [1,3,28].

VWF-containing concentrates	Desmopressin	Intravenous immunoglobulin	Other options
• Appear effective in most cases • Half-life can be short (monitor if parameter available) • Humate-P® (30–100 FVIII IU/kg) was effective in 80% of cases [3]	• Lower reported efficacy rates (10–75%) [1] • Consider potential side effects in patients at risk	• Very effective in AVWS due to IgG antibody or IgG paraprotein [28] • 0.5–1.0 g/kg for 2 days • VWF:Ag increases after 3 to 4 days, lasting approximately 3 weeks	• Tranexamic acid • Recombinant FVIIa (off-label; very few case reports)

FVIIa, activated factor VII; FVIII, factor VIII; IgG, immunoglobulin G; VWF, von Willebrand factor; VWF:Ag, VWF antigen.

References

[1] Federici AB, Rand JH, Bucciarelli P, Budde U, van Genderen PJ, Mohri H, et al. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost 2000;84:345–9.

[2] Budde U, Bergmann F, Michiels JJ. Acquired von Willebrand syndrome: experience from 2 years in a single laboratory compared with data from the literature and an international registry. Semin Thromb Hemost 2002;28:227–38.

[3] Tiede A, Priesack J, Werwitzke S, Bohlmann K, Oortwijn B, Lenting P, et al. Diagnostic workup of patients with acquired von Willebrand syndrome: a retrospective single-centre cohort study. J Thromb Haemost 2008;6:569–76.

[4] Geisen U, Heilmann C, Beyersdorf F, Benk C, Berchtold-Herz M, Schlensak C, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. Eur J Cardiothorac Surg 2008;33:679–84.

[5] Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol 2010;56:1207–13.

[6] Meyer AL, Malehsa D, Bara C, Budde U, Slaughter MS, Haverich A, et al. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail 2010;3:675–81.

[7] Fricke WA, Brinkhous KM, Garris JB, Roberts HR. Comparison of inhibitory and binding characteristics of an antibody causing acquired von Willebrand syndrome: an assay for von Willebrand factor binding by antibody. Blood 1985;66:562–9.

[8] Lazarchick J, Pappas AA, Kizer J, Hall SA. Acquired von Willebrand syndrome due to an inhibitor specific for von Willebrand factor antigens. Am J Hematol 1986;21:305–14.

[9] Mohri H, Ohkubo T. Acquired von Willebrand's syndrome due to an inhibitor of IgG specific for von Willebrand's factor in polycythemia rubra vera. Acta Haematol 1987;78:258–64.

[10] Goudemand J, Samor B, Caron C, Jude B, Gosset D, Mazurier C. Acquired type II von Willebrand's disease: demonstration of a complexed inhibitor of the von Willebrand factor–platelet interaction and response to treatment. Br J Haematol 1988;68:227–33.

[11] van Genderen PJ, Vink T, Michiels JJ, van 't Veer MB, Sixma JJ, van Vliet HH. Acquired von Willebrand disease caused by an autoantibody selectively inhibiting the binding of von Willebrand factor to collagen. Blood 1994;84:3378–84.

[12] Coleman R, Favaloro EJ, Soltani S, Keng TB. Acquired von Willebrand disease: potential contribution of the VWF:CB to the identification of functionally inhibiting auto-antibodies to von Willebrand factor. J Thromb Haemost 2006;4:2085–8.

[13] Guerin V, Ryman A, Velez F. Acquired von Willebrand disease: potential contribution of the von Willebrand factor collagen-binding to the identification of functionally inhibiting auto-antibodies to von Willebrand factor: a rebuttal. J Thromb Haemost 2008;6:1051–2.

[14] Mannucci PM, Lombardi R, Bader R, Horellou MH, Finazzi G, Besana C, et al. Studies of the pathophysiology of acquired von Willebrand's disease in seven patients with lymphoproliferative disorders or benign monoclonal gammopathies. Blood 1984;64:614–21.

[15] Richard C, Cuadrado MA, Prieto M, Batlle J, López Fernández MF, Rodriguez Salazar ML, et al. Acquired von Willebrand disease in multiple myeloma secondary to absorption of von Willebrand factor by plasma cells. Am J Hematol 1990;35:114–7.

[16] Budde U, Schaefer G, Mueller N, Egli H, Dent J, Ruggeri Z, et al. Acquired von Willebrand's disease in the myeloproliferative syndrome. Blood 1984;64:981–5.

[17] Budde U, Scharf RE, Franke P, Hartmann-Budde K, Dent J, Ruggeri ZM. Elevated platelet count as a cause of abnormal von Willebrand factor multimer distribution in plasma. Blood 1993;82:1749–57.

[18] Budde U, van Genderen PJ. Acquired von Willebrand disease in patients with high platelet counts. Semin Thromb Hemost 1997;23:425–31.

[19] Tsai HM, Sussman II, Nagel RL. Shear stress enhances the proteolysis of von Willebrand factor in normal plasma. Blood 1994;83:2171–9.

[20] Wu T, Lin J, Cruz MA, Dong JF, Zhu C. Force-induced cleavage of single VWFA1A2A3 tridomains by ADAMTS-13. Blood 2010;115:370–8.

[21] Yoshida K, Tobe S, Kawata M, Yamaguchi M. Acquired and reversible von Willebrand disease with high shear stress aortic valve stenosis. Ann Thorac Surg 2006;81:490–4.

[22] Michiels JJ, Schroyens W, Berneman Z, van der Planken M. Acquired von Willebrand syndrome type 1 in hypothyroidism: reversal after treatment with thyroxine. Clin Appl Thromb Hemost 2001;7:113–5.

[23] Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. Blood 2011;117:6777–85.

[24] Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343–9.

[25] Bruggers CS, McElligott K, Rallison ML. Acquired von Willebrand disease in twins with autoimmune hypothyroidism: response to desmopressin and L-thyroxine therapy. J Pediatr 1994;125:911–3.

[26] Castaman G, Rodeghiero F. Acquired transitory von Willebrand syndrome with ciprofloxacin. Lancet 1994;343:492.

[27] Conrad ME, Latour LF. Acquired von Willebrand's disease, IgE polyclonal gammopathy and griseofulvin therapy. Am J Hematol 1992;41:143.

[28] Federici AB, Stabile F, Castaman G, Canciani MT, Mannucci PM. Treatment of acquired von Willebrand syndrome in patients with monoclonal gammopathy of uncertain significance: comparison of three different therapeutic approaches. Blood 1998;92:2707–11.

[29] Mohri H. Acquired von Willebrand syndrome: features and management. Am J Hematol 2006;81:616–23.

[30] Federici AB. Therapeutic approaches to acquired von Willebrand syndrome. Expert Opin Investig Drugs 2000;9:347–54.