Manejo del paciente con Enfermedad de Von Willebrand y Hemofilias Adquiridas

Management of patients with Acquired von Willebrand Syndrome and Acquired Haemophilia A

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Introduction

The acquired haemostatic inhibitors (AHI) are relatively rare forms of acquired haemostatic defects but they should be immediately diagnosed because of their severe bleeding tendency[1]. These AHI are circulating antibodies (mainly immunoglobulin) that specifically neutralize the activity of the various haemostatic proteins and result in a deficiency state; they may develop in the plasma of individuals whose haemostatic mechanisms were previously normal. In this scenario, the immunoglobulin (IG) is designated as auto-antibody inhibitor, in contrast to alloantibody inhibitors, which arise in individuals with congenital factor deficiencies as a consequence of replacement therapy[1]. The most well-characterized inhibitor is directed against factor VIII (FVIII) and occurs with a prevalence of 15-30% in patients with inherited hemophilia A (alloantibody); the clinical condition caused by the auto-antibodies is named Acquired Hemophilia A (AHA)[2]. The other acquired haemostatic defect involving the complex FVIII/von Willebrand factor (VWF) is known as Acquired von Willebrand Syndrome (AVWS) to be distinguished from the inherited defects of VWF defined as von Willebrand Disease (VWD)[2]. Besides AVWS and AHA other very rare AHI have been reported against Factor V, VII, IX, X, XI, XII and XIII[1]. The management of patients with AVWS, AHA and other AHI is difficult and costly: the attention of an experienced hematologist consultant is always required.

Definition and epidemiology of AVWS: The AVWS is an acquired bleeding disorder, first reported in 1968, with clinical and laboratory features similar to inherited von Willebrand disease[3]. This rare bleeding disorder occurs mainly in patients with

underlying lymphoproliferative, cardiovascular, myeloproliferative and immunologic disorders. However abnormalities about the levels, structure and function of circulating von Willebrand factor (VWF) can be found in many other clinical conditions[4, 5]. Among hematologic diseases Monoclonal gammopathies of uncertain significance (MGUS) and Essential Thrombocythemia (ET) are considered to be the relatively most frequent conditions associated with AVWS but other acquired VWF defects can be also found in many other chronic and acute Lympho- and Myeloproliferative disorders[6-8]. In most instances, AVWS is identified because of bleeding complications: in fact more than 80% of the patients with this syndrome are active bleeders. Recurrent bleeding episodes occur in about 20-33% of patients with AVWS, especially following major trauma and surgery[4]. Because of the heterogeneous mechanisms of AVWS, more than one therapeutic approach is often required to prevent or treat acute bleedings. Remission from some forms of AVWS can be obtained when the underlying disorders are treated. It has been challenging to collect data on AVWS as even large centres do not have sufficient number of patients with AVWS to comprehensively evaluate this rare bleeding disorder and there have been no large prospective studies of AVWS. Consequently, the actual prevalence of AVWS in the general population is somewhat uncertain. Between 1998 and 1999, a retrospective survey was conducted and published as an official communication of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH), which described information on cases in the ISTH-SSC registry[4]. Since then, a few additional reports on AVWS cases have been published by single institutions[9, 10]. The prevalence of AVWS is probably underestimated because a few physicians search for VWF abnormalities among patients with hematological, cardiovascular and immunologic disorders: a significant increase of cases associated with cardiovascular disorders has been observed[11].

Pathogenesis of AVWS: In contrast to inherited VWD, VWF is synthesized in normal or even increased quantity in most patients with AVWS. Low plasma levels of VWF can result from accelerated VWF removal from the plasma by three main pathogenic mechanisms: a) specific or non-specific auto-antibodies that form circulating immune complexes with, and inactivate, VWF (these complexes are cleared by cells bearing Fc-receptors that bind immunoglobulin G (IgG); b) adsorption of VWF by malignant cell clones; and c) loss of high-molecular-weight (HMW) VWF multimers under conditions of high shear stress. Compared with AHA (which is always caused by auto-antibodies against FVIII), AVWS has more heterogeneous pathogenic mechanisms. None of the proposed mechanisms appear to be disease-specific, and the same mechanism can be responsible for AVWS in different underlying disorders associated with the syndrome. Additionally, in some patients, the basic mechanism is unknown[4-10]. Another important mechanism sometimes forgotten of the acquired VWF defects is the increased VWF proteolysis by specific proteases which cleave the VWF HMW forms[12].

Diagnostic tests. The tests used to assess AVWS are the same as for VWD and the differential diagnosis between AVWS and VWD can be sometimes difficult. Bleeding time and activated partial thromboplastin time (APTT) are not very useful. FVIII:C, VWF:Ag, VWF:RCo and collagen-binding activity (VWF:CB) are sometimes decreased, most frequently in lymphoproliferative disorders (LPD). A reduced activity/antigen ratio (VWF:RCo/Ag or VWF:CB/Ag) can indicate structural or functional disorders, even if the VWF plasma concentrations are normal. A loss or decrease of HMW multimers can be quantified using densitometry. However, these methods are not available in many laboratories and have not yet been standardized. Moreover, pre-analytical variables can contribute to the losses of HMW multimers. A decrease of HMW multimers can sometimes be observed in patients with normal VWF:RCo and VWF:CB and even normal VWF:RCo/Ag and VWF:CB/Ag ratios[11]. The assessment of VWF propeptide (known previously as VWF:Ag II) has been suggested to improve diagnosis of AVWS because it represents a marker of VWF biosynthesis. An increased propeptide/VWF:Ag ratio reflects accelerated clearance of VWF from the plasma. However, the same has been found in a subset of patients with VWD type 1 indicating accelerated clearance of VWF as a reason for their condition[13]. Therefore, propeptide/VWF:Ag ratio may not always discriminate between AVWS and VWD and cannot be recommended for routine use at present time[10]. Autoantibodies play a role in the pathogenesis of some patients with AVWS, in particular those with LPD. The presence of auto-

antibodies appears to be associated with a more severe bleeding tendency[8]. In a minority of patients, inhibitory (neutralizing) antibodies can be detected in mixing studies of VWF:RCo or VWF:CB. In contrast to AHA, where FVIII inhibitors are virtually always detectable with standard laboratory assays, the frequency of inhibitor detection is low in AVWS[4]. In patients with AVWS, inhibitors are sometimes saturated in complexes with VWF, preventing detection unless the complex is dissociated by heating or other methods. Non-neutralizing VWF-binding antibodies can be detected by ELISA and have been reported to occur in patients with LPD but also other underlying disorders[14]; however, no standardized assays are available yet for detecting these. Plasma-derived VWF contains ABO blood group antigen and should not be used as an antigen for ELISA, since the presence of isoagglutinins may cause false-positive results. Recombinant human VWF expressed in cultured animal cells is currently under investigation as a reagent that may potentially resolve this issue[11].

General therapeutic approaches to AVWS: The treatment goals in AVWS are: to control acute bleeds, to prevent bleeding in high-risk situations, and to obtain long-term remission. The strategies utilized to obtain these goals depend on the underlying disease mechanisms (**Table 1**). Whenever possible, treatment should address the underlying disorder, which can treat the AVWS as well. However, it is not always possible to treat the underlying disorder. Efficacy and safety of the commonly used haemostatic treatments is summarized below by single therapeutic approach.

Table1: Therapeutic options in AVWS according to underlying disorder.

Underlying disorder	Causal treatment	Additional treatment options
Autoimmune disorders		IVIG (only IgG-MGUS or anti-VWF IgG), plasmapheresis or immunoadsorption, antifibrinolytics, VWF-containing concentrate, rFVIIa
Systemic lupus erythematosus	Steroids, cyclophosphamide	
Lymphoproliferative disorders		
MGUS	Usually untreated	
Lymphoma, multiple myeloma	Chemotherapy according to entity	
Cardiovascular		
Aortic valve stenosis and other anomalies with increased sheer stress	Corrective surgery	VWF-containing concentrate, antifibrinolytic
Dysfunctional heart valve prosthesis, LVAD	Corrective surgery if applicable	Reduce or withdraw anticoagulation, VWF-containing concentrate
Myeloproliferative neoplasia		Withdraw aspirin (if applicable), desmopressin, antifibrinolytics, VWF-containing concentrate
Essential Thrombocythemia	Cytoreductive therapy, chemotherapy or stem cell transplantation in case of progression	
Polycythemia vera	Phlebotomy, cytoreductive therapy chemotherapy or stem cell transplantation in case of progression	
Chronic myeloid leukemia	Tyrosine kinase inhibitors, stem cell transplantation	

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Desmopressin (DDAVP), a synthetic analogue of vasopressin, can be used to prevent and control bleeding in some patients with AVWS. DDAVP is usually administered in doses of 0.3 microgram (µg)/kilogram (kg) of body weight, given intravenously over 30 minutes, once or twice daily. In the only prospective clinical trial of DDAVP therapy, performed in 10 patients with monoclonal gammopathy of uncertain significance (MGUS), all subjects had improved VWF levels 30 minutes after treatment, whereas VWF levels were close to baseline by 4 hours after DDAVP treatment[4]. Therefore VWF:Ag and VWF:RCo, along with FVIIIC, should always be closely monitored when DDAVP is used for prophylaxis and treatment of bleeds. DDAVP must be used with caution in patients with cardiovascular disorders and in elderly: measures need to be taken to prevent fluid overload and hyponatremia, which are the most common adverse effects of DDAVP.

VWF/FVIII concentrates can be used for replacement therapy. In clinical practices, doses between 30 and 100 VWF:RCo units/kg are recommended, depending on the patient's residual VWF activity, severity of bleeding and presence of inhibitors. Similar to DDAVP, the half-life of infused VWF can be very short in AVWS, in particular in patients with AVWS associated with MGUS or inhibitors[4]. Close monitoring of the clinical response, with measurements of VWF activities, are needed for tailoring doses and dose intervals.

Intravenous gammaglobulin (IVIG) for AVWS were assessed in an open-label cross-over study in patients with AVWS associated with MGUS of the IgG class (IgG-MGUS): doses of 1 gram/kg body weight per day were used for 2 days. An increase of VWF and FVIII, and shortening of the bleeding time, were observed the day after the second infusion, with levels reaching their maximum after 4 days and slowly returning to baseline within 21 days[6]. IVIG was not effective in AVWS patients with MGUS of the immunoglobulin M (IgM-MGUS) class. Repeated doses of IVIG every 3 weeks are effective to induce long remission from AVWS but lower doses (0.5-0.75 mg/Kg) are not sufficient to correct these VWF defects[6].

Activated recombinant factor VII (rFVIIa) as a hemostatic agent has been also used in patients with AVWS and VWD type 3, particularly for those who have significant bleeding manifestations and alloantibodies against VWF. rFVIIa is usually administered at a dose of 90 µg/kg body weight (range 40 to150 µg/kg), for a median of 3 doses (range 1-54). Treatment is usually effective, with responses reported in 96% of patients. Thromboembolic complications are rare among hemophilia patients receiving rFVIIa, but it is unclear if this is also true for patients receiving this therapy for AVWS or VWD. Caution should be exerted, particularly when treating elderly patients and others at increased risk for thromboembolism[11].

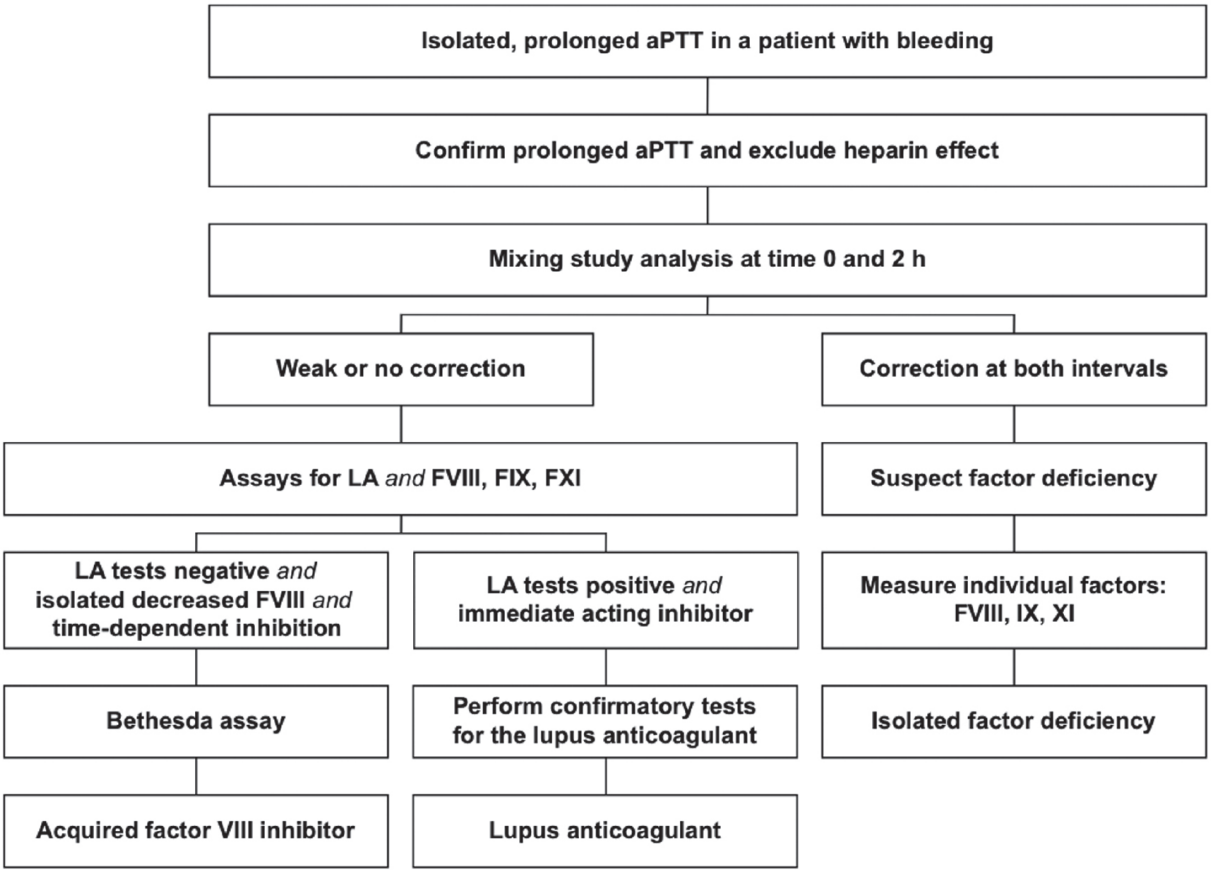
Plasmapheresis can be used to reduce the levels of autoantibodies and paraproteins of any immunoglobulin class although the treatment is more effective in reducing the levels of IgM antibodies. Plasmapheresis has been reported as therapy for patients with AVWS due to IgM-MGUS. When this treatment is given, fresh frozen plasma replacement should be used, instead of albumin, to prevent depletion of fibrinogen and other coagulation factors. The restoration of VWF levels can be accelerated by concurrent treatment with VWF-containing concentrate or DDAVP[11].

Definition, epidemiology and clinical features of Acquired Hemophilia A. The acquired hemophilia A (AHA) is a potentially life-threatening bleeding disorder occurring in patients without a previous personal or family history of bleeding caused by the immune-mediated development of acquired FVIII auto-antibodies[2]. The demographic, the clinical presentations, the management of bleeding episodes as well as the eradication of auto-antibodies with immune therapies have been extensively investigated in the European Acquired Hemophilia (EACH2) Registry[15-17]. The incidence of AHA has been reported to be between 1.3 and 1.5/million/year and has a biphasic age distribution: a small peak occurs in 20- to 40-year old patients with a female predominance due to the high prevalence of the post-partum period and a large peak in patients aged over 65 year with an incidence of 14.7/million/year in people aged over 85. Clinical presentation of patients with AHA is quite different from that of inherited HA. Patients usually present with subcutaneous bleeds, which are often extensive. Soft tissue bleeds such as muscle hematoma, retroperitoneal bleeds and intracranial haemorrhage are also common, whereas joint bleeds are seen less commonly than in congenital HA. The muscle hematomas can be very important with rapid and significant reduction of HB levels. Gastrointestinal bleeding can be life-threatening and haematuria may occur. Some patients are diagnosed with bleeding at the time of invasive procedures while postpartum haemorrhage and bleeding following

Caesarian section is the usual presentation of AHA associated with pregnancy. Bleeding episodes are unpredictable and may be very severe: about 8% of AHA patients have fatal bleedings. In contrast, about 25% of these patients have a relatively mild bleeding and do not usually require haemostatic therapy. A general approach to the management of AHA has been recently published[18].

Diagnostic approach to patients with AHA The diagnosis of AHA is often delayed but it should be suggested by the recent onset of typical bleeding symptoms and the finding of a prolonged activated Partial Thromboplastin Time (PTT). AHA diagnosis is confirmed by the finding of a reduced FVIII activity level and the presence of a time- and temperature-dependent inhibitor. The kinetic of this anti-FVIII inhibitor (auto-antibody) is usually different (type 2 kinetic curve) from that of the alloantibody found in a patient with inherited HA (type 1 kinetic curve). After confirming the presence of a anti-FVIII inhibitor, the Bethesda assay with Nijmegen modification is used to evaluate inhibitor titre levels: it is very important to know the levels of anti-FVIII inhibitors because patients with low (<5) or high (>5) inhibitor titres must be managed with different therapeutic options. A lupus anticoagulant (LAC) can mimic an AHI, although typically the LAC should be differentiated from AHI in the laboratory by the absence of increasing neutralization of clotting factors activity after prolonged incubation in mixing studies: in fact, lupus-like inhibitors decrease all factor levels measured in the PTT system (i.e. FVIII, FIX, FXI as well as FXII) while a specific inhibitor predominantly decreases one single factor (FVIII in case of the AHA) for which it is specific. This is very important because specific inhibitors will often give false-positive LAC results in many commercial assays. Last but not least, the LAC is not associated with the same type of extreme bleeding symptoms which characterizes AHA. A practical flow chart for diagnostic approach is shown in **Figure 1**.

Figure 1: Suggested flow chart for the correct diagnosis of AHA



Therapies for acute bleeds and inhibitor eradication. Management of patients with AHA is complex and ideally should be always coordinated by an expert hematologist with the help of other specialists according to the specific clinical sites of bleedings. Treatment of AHA is directed at bleeding

control, inhibitor eradication to prevent subsequent bleeding events and treatment of any underlying causative disease. No randomized control clinical data is available to guide appropriate intervention and therefore selection of appropriate therapeutic approaches has been based primarily on expert opinion. Recent data from the European Acquired Hemophilia (EACH2) Registry have been used to prepare recommendations to guide selection of initial therapeutic intervention[15-18]. Optimal treatment involves protection of the patients against trauma; invasive procedure should not be undertaken unless unavoidable. Bleeds are usually treated acutely with FVIII bypassing agents such as activated Prothrombin Complex Concentrates (aPCC) or recombinant activated Factor VII (rFVIIa): the most widely used aPCC is FVIII Inhibitor Bypassing Agent (FEIBA) and the rFVIIa is NovoSeven. The safety and efficacy data of FEIBA and NovoSeven was derived from congenital HA with alloantibody but numerous case reports and retrospective analyses indicate that both FEIBA and rFVIIa are safe and effective in controlling bleeding episodes in AHA patients. However, these drugs are associated with potentially life-threatening side effects, such as myocardial infarction, disseminated intravascular coagulation, arterial and venous thrombosis, pulmonary embolisms and stroke. Recombinant or plasma derived FVIII concentrates are rarely efficacious. Porcine plasma-derived FVIII concentrate has been used in the past with some success but the data about efficacy and safety are scanty. Some patients with a low-tire autoantibody inhibitor and measurable baseline FVIII may respond to a DDAVP infusion: therefore this approach should be tested. The different therapies are summarized in **Table 2**.

The inhibitor eradication therapy is necessary in patients with AHA to reduce morbidity and mortality because the risk of recurrent bleeding events still persists until the anti-FVIII inhibitors are present. Eradication of the autoimmune inhibitor antibody with immunosuppression is indicated as soon as the diagnosis is confirmed and the bleeding problems have been contained. Steroids, alone or combined with citotoxic agents such as cyclophosphamide or azathioprine, induce remission in about 70% of patients. Current evidence does not support the use of intravenous immunoglobulin (IVIG) to suppress the AHA inhibitors except perhaps for low titer autoantibody (**Table 2**).

Table 2: Treatment strategies for acquired hemophilia A.

	Bleeding control	Inhibitor eradication
First-line treatment	aPCC or rFVIIa	Steroid ± cyclophosphamide
Second-line treatment	Bypassing agent: Alternate Sequential Parallel Immunoadsorption protocol	Rituximab ± Steroid Cyclophosphamide Ciclosporin Azathioprine CVP

rFVIIa, recombinant factor VIIa; aPCC, activated prothrombin complex concentrates; CVP, cyclophosphamide, vincristine, prednisone

Current perspectives on AVWS and AHA AVWS is a significant under-recognized bleeding disorder occurring in several different clinical situations. The diagnostic approach to AVWS remains a challenge to the practicing physician due to the variable clinical presentation and the many different tests that have to be obtained to prove or rule out the diagnosis. Management requires consideration of the underlying disorder and pathogenic mechanisms. Research in this area has been limited by a number of difficulties, including the prolonged follow up required, the many confounding factors and increasingly documented clinical and biological heterogeneity. Since prospective clinical studies are difficult to organize in this heterogeneous group of patients, we encourage physicians to report their experience in the updated version of the AVWS registry promoted by the ISTH (www.intreavws.com), available in 2016. As far as AHA, a lot of information has been collected by the European Registry. However, patients with AHA are still under- and misdiagnosed in hospitals where physicians are often not able to provide appropriate therapy during life-threatening bleedings. The

immediate consultation with haematologists expert in haemostasis is strongly recommended. More information about the correct eradication protocols especially for young women and old immune-compromised individuals is also required.

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