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SUPPLEMENT ARTICLE

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Abstract

Acquired bleeding disorders can accompany hematological, neoplastic, autoimmune, cardiovascular or liver diseases, but can sometimes also arise spontaneously. They can manifest as single factor deficiencies or as complex hemostatic abnormalities. This review addresses (a) acquired hemophilia A, an autoimmune disorder characterized by inhibitory autoantibodies against coagulation factor VIII; (b) acquired von Willebrand syndrome in patients with cardiovascular disorders, where shear stress abnormalities result in destruction of von Willebrand factor; and (c) liver function disorders that comprise complex changes in pro- and anti-hemostatic factors, whose clinical implications are often difficult to predict. The article provides an overview on the pathophysiology, diagnostic tests and state-of-the-art treatment strategies.

KEYWORDS

Coagulation Protein Disorders, Hemophilia A, Liver disease, Von Willebrand Disease

1 | INTRODUCTION

Patients with acquired bleeding disorders are often not seen first by haematologists or experts in bleeding disorders but rather by general physicians, emergency or intensive care unit specialists, surgeons or any other specialty related to the site of first bleeding.

For these physicians, it is often difficult to recognize a bleed as a first symptom of what truly is a bleeding disorder. Firstly, because the bleed as such may not seem unusual. Laboratory tests would probably be done only if bleeds occurred without identifiable cause, were difficult to control, or frequently recurring. Secondly, if laboratory tests have been ordered, their interpretation can be challenging because abnormalities may sometimes indicate a haemostasis disorder, but more often result from underlying disorders, medications, the bleed itself or poor sample quality.

Even more confusing for non-experts, laboratory abnormalities such as a prolonged activated partial thromboplastin time (APTT) may indicate a bleeding disorder (eg deficiency in factor VIII, IX or XI), a thrombogenic state (eg lupus anticoagulant [LA]) or neither of the two (eg deficiency in factor XII, prekallikrein [PKK] or high molecular weight kininogen [HMWK]). Patients with liver disease, despite presenting with low platelet counts or a prolonged prothrombin time (PT) may eventually have a greater risk of thrombosis than a risk to bleed.

Whilst the inability of laboratory tests to predict bleeding has resulted in recommendations against routine testing in the general population, it is still important to raise awareness towards the most important acquired bleeding disorders and to guide physicians towards proper interpretation of laboratory results in different clinical scenarios. Here, we review acquired haemophilia A (AHA), the acquired von Willebrand syndrome (AVWS), and the haemostatic challenges in liver function disorders (LFD) with particular emphasis on the correct interpretation of laboratory abnormalities in these disorders.

2 | ACQUIRED HAEMOPHILIA A

2.1 | Epidemiology

Acquired haemophilia A is a rare disorder. The UK surveillance study estimated in 2007 an incidence of 1.4 cases per million inhabitants per year.[1] More recent estimates from Germany indicated an increase to up to 6 per million per year, possibly due to increased awareness of the disorder.[2]

Acquired haemophilia A affects men and women of all ages but is more frequent in the elderly. The mean age at diagnosis is approximately 70 years. About 30%-50% of patients have associated disorders, most often other autoimmune disorders or malignancy. About 5% of AHA cases occur in relation to pregnancy, usually postpartum.

Due to its rarity, the disorder occurs almost always unexpectedly and is often not recognized. In the European EACH2 registry, 10% of patients were diagnosed more than 1 month after the disorder had become symptomatic[3] A delay in diagnosis was the only predisposing factor for poor treatment response in this registry.[4]

2.2 | Pathophysiology

Acquired haemophilia A is due to neutralizing autoantibodies against factor VIII (FVIII). The residual FVIII activity is <1 IU/dL in 50% of patients (<5 IU/dL in 75%, <40 IU/dL in 100%).[5]

FVIII-binding antibodies are often of the IgG4 subclass (>90% of patients), but other IgG subclasses, IgM and IgA can occur in various combinations.[6] The differential impact of isotypes and subclasses to FVIII neutralization is not known. The anti-FVIII antibody response is usually polyclonal in nature, and different FVIII domains are involved.[7]

The role of associated disorders in the pathophysiology of the anti-FVIII immune response is unknown. A mystery is also the striking difference in bleeding phenotype between AHA and congenital haemophilia A (HA) or HA with inhibitors against FVIII (HA-I). Patients with AHA frequently suffer from cutaneous (Figure 1) and deep muscle bleeds, whereas joint bleeds are rarely seen.[1,3]

2.3 | Diagnosis

An isolated prolongation of the APTT (with normal PT) in a bleeding patient is the hallmark of AHA. Although APTT prolongation may result from many causes, it should never remain unexplained if observed in bleeding patients or before interventions with a high risk of bleeding.

In patients with AHA, FVIII activity will be found reduced, and the disorder is confirmed then by demonstrating the neutralizing capacity of the autoantibody in the Bethesda assay (Figure 2).[8]

If FVIII activity testing and the Bethesda assay are not immediately available, an APTT mixing study may help to demonstrate the presence of an inhibitor in the patient plasma, which is at least suggestive of AHA in a bleeding patient. The mix of patient and normal plasma is recommended to be tested both immediately (a prolongation here would be suggestive of heparin or the lupus anticoagulant) and after incubation at 37°C for 2 hours (a progressive prolongation would be suggestive of inhibitors in AHA).[9]

The differential diagnosis of an isolated APTT prolongation includes the following:

- low FVIII (AHA, HA, HA-I, von Willebrand disease (VWD) or AVWS)
- low factor IX (haemophilia B)
- low factor XI (historically also called haemophilia C)
- conditions *not* associated with bleeding (eg LA, low factor XII, PKK, HMWK)
- pharmacological anticoagulants (eg heparin, dabigatran).

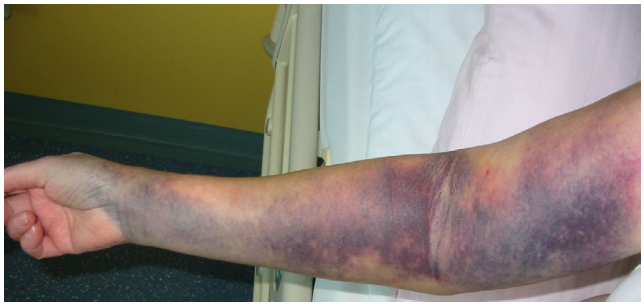

FIGURE 1 Subcutaneous haematoma after venipuncture in a patient with AHA. Subcutaneous bleeds are the most frequent symptom of AHA and occur in approximately 50% of patients.[3]

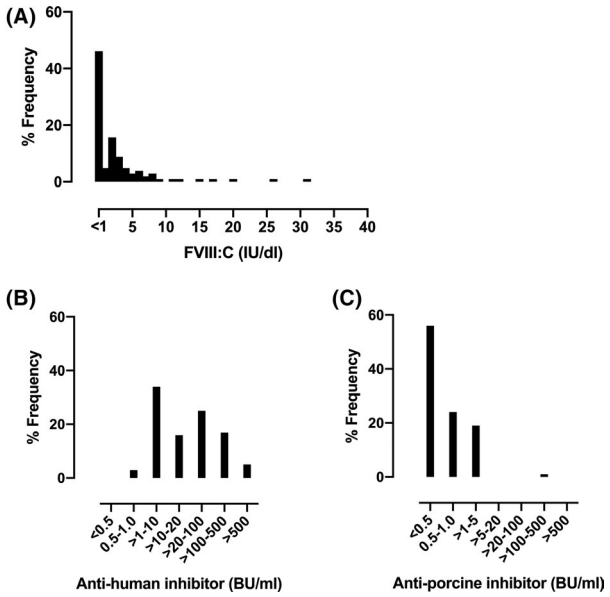

FIGURE 2 Laboratory data at presentation of AHA. Data show frequencies of (A) FVIII activity, (B) anti-human Bethesda inhibitor titre and (C) anti-porcine (susoctocog alfa) cross-reacting titre. Data were derived from the GTH-AH 01/2010 study.[5,7,11]

Acquired haemophilia A and LA are sometimes difficult to differentiate. Depending on its strength and the reagent used, LA can prolong the APTT to a variable degree and sometimes even interfere with APTT-based factor assays, including FVIII. AHA can be excluded in this situation by demonstrating normal FVIII activity in chromogenic substrate assay[10] or absence of FVIII-binding antibodies in immunoassays (Table 1).[11] Of note, AHA and LA are both autoimmune disorders and can occur simultaneously in patients.[12]

Acquired von Willebrand syndrome is usually straightforward to differentiate from AHA, because the APTT mixing study and the Bethesda assay will be negative. FVIII is usually only low in AVWS, if von Willebrand factor (VWF) antigen assays are also low.[13]

2.4 | Treatment

2.4.1 | Haemostatic therapy

Patients with AHA should be referred to expert centres. At least, expert advice should be sought if referral is not possible. Surgical interventions can be life-threatening in patients with AHA and should be strictly avoided until haemostasis is secured by adequate treatment.

The decision to treat bleeds, and also the monitoring of treatment success, is based on clinical decision-making.[14] Clinically relevant bleeds are treated with bypassing agents (recombinant factor VIIa [rFVIIa, eptacog alfa activated, NovoSeven], activated prothrombin complex concentrate [APCC]) or recombinant porcine factor VIII (rpFVIII, susoctocog alfa, Obizur). Human FVIII concentrates are only recommended if other options are not available because their efficacy is lower than that of the bypassing agents.[4] Tranexamic acid can be used as an adjunct agent, in particular for mucocutaneous bleeds, or as a single agent for minor bleeds.[14]

If rpFVIII is used, monitoring of the FVIII activity (by APTT-based one-stage assays) should be used to guide dosing. In particular, such monitoring may help to prevent unnecessary and potentially harmful overdosing and to recognize patients with cross-reacting antibodies. Such antibodies were found in 44% of patients (usually of low titre, compare Figure 2C)[7] and will require higher doses of rpFVIII.[15,16]

TABLE 1 Differential diagnosis between AHA and LA

	Acquired haemophilia A	Lupus anticoagulant
APTT	Prolonged	Prolonged
Anti-FVIII antibody (ELISA)	Present	Absent
APTT-based FVIII activity	Low	Sometimes artificially reduced
Chromogenic assay FVIII activity	Low	Normal

2.4.2 | Immunosuppressive therapy

Immunosuppression is recommended to eradicate autoantibodies and induce remission of AHA. Regimens include corticosteroids (eg prednisone or prednisolone 1 mg/kg body weight), rituximab (eg 375 mg/m^2 body surface area weekly for up to four doses) and/or cyclophosphamide (1-2 mg/kg body weight daily).[14] Caution should be exercised with old and fragile patients as registries show that mortality due to infection exceeds by far the risk of fatal bleeding. Prognostic factors have been determined in an observational registry and may be helpful to guide immunosuppressive therapy in the future.[5,6]

3 | ACQUIRED VON WILLEBRAND SYNDROME IN PATIENTS WITH CARDIOVASCULAR DISORDERS

Structural and functional alterations of the VWF can result in AVWS. A variety of conditions has been described that can cause AVWS, including.

- cardiovascular disorders with increased shear stress, including aortic valve stenosis, ventricular assist devices (VAD) and extracorporeal membrane oxygenation (ECMO);
- lymphoproliferative disorders including monoclonal gammopathy of unknown significance (MGUS);
- myeloproliferative neoplasms and thrombocytosis
- other cancers: and
- autoimmune disorders.

An overview on the management of AVWS has been published elsewhere.[17] Here, we focus on AVWS associated with cardiovascular disorders, in particular VAD and ECMO, that poses new and unique challenges to proper diagnosis and management.

3.1 | Epidemiology

The field of mechanical circulatory support (MCS) is constantly evolving leading to increased survival, less complications and improved quality of life of patients with advanced respiratory or heart failure. Nevertheless, patients with VAD and ECMO show an elevated risk for thromboembolic events and, in particular, for haemorrhage.

Extracorporeal membrane oxygenation patients present with bleeding from catheter insertion sites, mucous membranes, pulmonary bleeding and intracranial bleeding with significantly increased mortality.[18] VAD patients exhibit a high bleeding risk at multiple sites including pulmonary and intracranial bleeding, and an increased rate of gastrointestinal (GI) bleeds during long-term VAD support which may be caused by arteriovenous malformations.[19] Anticoagulation is necessary; however, non-surgical haemorrhage cannot be attributed to anticoagulation alone.[20]

Elevated shear stress due to pathological blood flow remains an issue in MCS, because these haemodynamic changes lead to AVWS in VAD and ECMO patients.[20,21] AVWS exacerbates bleeding symptoms due to the loss of high molecular weight (HMW) multimers of VWF resulting in impaired haemostatic activity.[22]

Severe AVWS develops in ECMO patients within one to six hours after implantation and persists as long as patients remain on support. Recovery from AVWS occurs rapidly within 3-24 hours after ECMO explantation.[21]

In VAD patients, AVWS develops rapidly within a few hours and recovers quickly after VAD explantation.[20] The type of VAD substantially influences severity and progression of AVWS. The older HeartMate II (HM II) has been a VAD with an axial continuous flow that has been superseded by the HeartMate III (HM III), a novel VAD featuring several modifications and potential improvements including a centrifugal-flow pump with wide blood-flow paths to improve haemodynamics, and an artificial pulse mode. A longitudinal large cohort study (N = 198) revealed that lower shear stress in the HM III results in less severe AVWS and less bleeding symptoms in HM III patients than in HM II patients.[20]

3.2 | Pathophysiology

In aetiological models, higher shear stress leads to unfolding of HMW multimers of VWF which enables cleavage of VWF at the A2 domain by ADAMTS13 (acronym for 'a disintegrin and metalloprotease with thrombospondin-1-like domains'). Resulting smaller VWF multimers exhibit impaired interaction with collagen and platelets.[23] Other models emphasize the mechanical destruction of VWF within the device, and shear-induced VWF binding to platelets.[24,25] Clinical bleeding symptoms associated with AVWS are caused by this consecutive loss of VWF HMW multimers.

Additionally VWF regulates angiogenesis and vessel maturation via control of vascular endothelial growth factor receptor-2 signalling and binding to αvβ3 integrin on vascular smooth muscle cells.[26] Long-term loss of VWF HMW multimers due to extended VAD therapy results in vessel malformations leading to increased mucosal and GI bleeding in VAD patients. There exists a balance between shear stress induced VWF degradation and endothelial release of new VWF which determines AVWS severity. Endothelial release is triggered by pulsatility. Hence, significantly lower GI bleeding incidence can be observed in newer VADs featuring artificial pulsatility compared to older models.[27]

3.3 | Diagnosis

Routine laboratory tests for VWF, including antigen and activity tests, are often normal in patients with AVWS due to cardiovascular disorders.[13] VWF activity tests are not performed under the shear stress conditions that occur in the human circulation, and so their sensitivity to detect functional consequences of a loss of HMW multimers is limited. Although the PFA-100 test is done at higher shear rates, it may not be useful in anaemic patients and has limited sensitivity.[13]

Loss of VWF HMW multimers can be directly determined via gel electrophoresis of VWF from patients' plasma on SDS-agarose low-resolution gels followed by membrane blotting and detection with appropriate primary and secondary antibodies. This method is the gold standard for detection of AVWS as it confers best sensitivity, but it is labour-intensive and is available only in specialized laboratories.

von Willebrand factor function tests on the market have variable sensitivity to the loss of HMW multimers. The ristocetin cofactor activity (VWF:RCo) is based on the binding of VWF to GPIb of fixed platelets. The von Willebrand factor activity tests (VWF:Ac) measure binding of VWF to immobilized recombinant GPIb, either using wild-type GPIb in the presence of ristocetin (VWF:GPIbR) or a gain-of-function variant without ristocetin (VWF:GPIbM).[28] The newer assays feature higher sensitivity for AVWS than VWF:RCo.[29] The highest sensitivity has been reported with collagen binding tests (VWF:CB). A commercialized chemiluminescent variant of the original assay was recently found to provide good agreement with the loss of HMW multimers in a comprehensive laboratory study.[30]

It should be noted that VWF function tests provide the best sensitivity to detect AVWS, when ratios of these parameters and the VWF antigen (VWF:Ag) are used. For example, VWF:CB/VWF:Ag and VWF:RCo/ VWF:Ag ratios were used with a cut-off <0.7.[13,29] However, in-house reference values are preferred to improve the performance of this strategy.

Sufficient sensitivity is crucial when screening for AVWS routinely. For instance, varying results were published on the longitudinal impact of HM II vs. HM III on AVWS.[20,31] No significant differences regarding the vWF:Ac/vWF:Ag ratio were found by Bansal et al between the two devices up until 90 days after implantation. In contrast, Geisen et al observed less reduction of vWF:CB/vWF:Ag ratio in patients with HM III than in patients with HM II support accompanied by less clinical bleeding symptoms. These different results may be caused by varying sensitivity of the employed functional assays in these studies.[29,32]

3.4 | Treatment

Increased risk for thrombosis as well as for haemorrhage calls for refined antithrombotic strategies in patients with VAD and ECMO. If indicated, early weaning from the device may be the best therapeutic option to prevent bleeding as well as thrombosis.

Thrombosis is a feared complication due to additional risks by pump occlusion requiring reoperation. Antithrombotic regimens should consider presence of AVWS causing additional bleeding risk. Despite the risk of thrombosis, a modest use of anticoagulants seems to be beneficial in these patients. Heparin is used concomitantly with antiplatelet therapy after surgery, to bridge to vitamin K antagonists.

Krueger et al reduced anticoagulation in 60 ECMO patients to 40 mg subcutaneous enoxaparin per day (the standard anticoagulation strategy for every critical care patient) and observed no fatal bleeding event and no intracranial haemorrhage, and patients required substantially less blood product transfusions.[33] Prophylactic administration of desmopressin and minimizing additional anticoagulation may be a feasibly strategy in ECMO patients. However, endothelial VWF depletion may limit the therapeutic value of desmopressin.

In some cases, recurrent GI bleeds may be stopped by transfusion of VWF concentrates,[34] although short half-life of VWF and ongoing mechanical destruction may hamper therapeutic efficacy. Refractory bleeding can be treated with tranexamic acid which, however, may prove inadequate with large wounds and should be used cautiously due to an increased risk of thrombosis.17 Specific parameters for acquired coagulation disorders could provide better indicators for therapeutic management of these patients in the future. Identification of acquired bleeding disorders and target-directed replacement therapy could also minimize the risk of severe bleeding, including intracranial haemorrhage as observed for ECMO patients.[35]

4 | LIVER FUNCTION DISORDERS

4.1 | Epidemiology

Historically, patients with LFD were thought to have a haemostasis-related bleeding tendency. This dogma was evidenced by clinical bleeding, notably variceal bleeding and massive blood loss during liver transplant surgery, combined with notable alterations in routine diagnostic tests of haemostasis, notably the PT, APTT, platelet count and fibrinogen levels. Although we will argue in this section that the dogma of LFD being associated with haemostasis-related bleeding is fully obsolete, clinical bleeding is still common and may result in significant clinical challenges.

The most frequent bleeding complication of patients with advanced LFD (ie cirrhosis) is variceal bleeding. However, variceal bleeding is unrelated to haemostatic failure, but rather a consequence of portal hypertension and local vascular abnormalities.[36] The risk of development of a variceal bleeding is not elevated when patients with cirrhosis use anticoagulant drugs, nor is severity or outcome of bleeding worse when patients are on anticoagulants at the time of the bleed.[37,38] This reinforces the notion that variceal bleeding is not a haemostatic bleed. Spontaneous bleeding in patients with cirrhosis is uncommon, and when it occurs, bleeds are minor (bruising, nose and gum bleeds, menorrhagia) and generally require no interventions.

Historically, bleeding complications during liver transplantation were severe and massive transfusion was common.[39] Development in surgical and anaesthesiologic management, and a better understanding of the haemostatic status of these patients have led to a remarkable decline in transfusion requirement in most centres.[40] In many centres, part of the patients are nowadays transplanted without the requirement of any transfusion, despite preoperative laboratory abnormalities and a long and invasive procedure.[41] These observations argue against liver diseases being associated with an overt bleeding disorder. In addition, the bleeding risk of other, more commonly performed invasive procedures is low in current clinical practice (<5% for most commonly performed procedures including liver biopsy, paracentesis, thoracentesis and cardiac catheterization), although the clinical perception is that interventions in patients with cirrhosis carry a much higher bleeding risk.[42] This perception is likely driven by the abnormalities in routine diagnostic haemostasis tests. Finally, patients with acute liver failure (ALF), for example due to acetaminophen overdose, have severe haemostatic alterations and were historically categorized as severe bleeders. In current experience, however, bleeding in ALF is rare, and likely unrelated to haemostatic failure.[43]

Historically, patients with liver disease were considered to be 'auto-anticoagulated', as evidenced by their abnormal diagnostic haemostasis tests, and the clinical perception of lack of thrombotic events. Large epidemiological studies, however, have demonstrated that liver diseases are associated with an increased risk for thrombotic events, notably venous thrombosis and portal vein thrombosis.[44,45]

4.2 | Pathophysiology

Although patients with liver disease frequently have abnormalities in routine diagnostic haemostasis tests that suggest a bleeding tendency (prolonged PT and APTT, thrombocytopenia, low fibrinogen), the interpretation of these tests in this particular patient population is not straightforward.[46]

Patients with advancing LFD acquire complex alterations in their haemostatic system. These changes include thrombocytopenia, low plasma levels of coagulation factors, inhibitors of coagulation and fibrinolytic proteins, and elevated levels of haemostatic proteins that are not synthesized by hepatocytes but are rather derived from endothelial cells. The reasons for the haemostatic changes are multifactorial and include defective hepatic synthesis, consumption by intrahepatic or systemic activation of coagulation, endothelial activation and splenomegaly (Figure 3). Although routine diagnostic tests are suggestive of haemostatic failure, these tests fail to capture the complex balance between pro- and antihaemostatic factors, which are all affected in patients with LFD. Laboratory studies using more advanced (mostly research-type) tests have demonstrated that defects in prohaemostatic pathways are compensated for by simultaneous changes in antihaemostatic pathways.[47] For example, thrombocytopenia is compensated for by highly elevated levels of VWF and low levels of ADAMTS13 as demonstrated by experiments examining platelet adhesion and aggregation under flow.[48] Defects in procoagulant pathways are compensated for by decreases in anticoagulant proteins. In fact, thrombin-generating capacity of patients with cirrhosis is higher than that of healthy individuals as

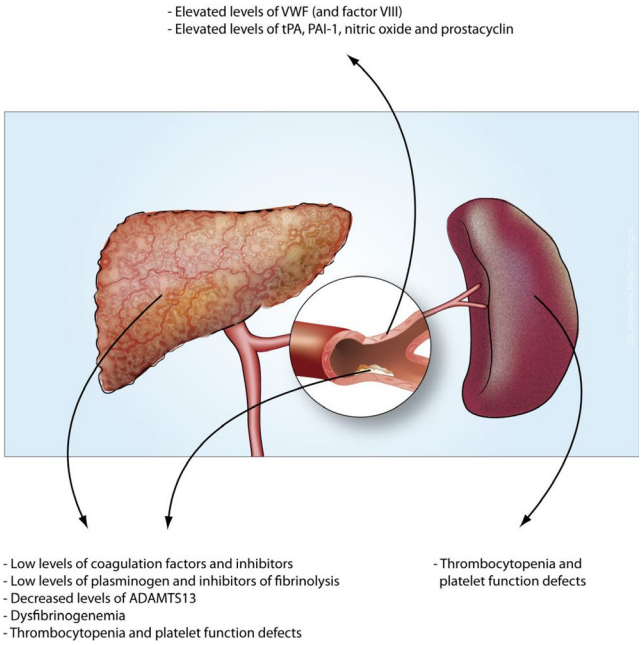

FIGURE 3 Causes of the haemostatic changes in patients with liver disease. The multiple changes that either reduce or promote haemostasis can be attributed to four mechanisms. (1) A reduced synthetic capacity of the liver results in decreased levels of many proteins involved in haemostasis. Moreover, decreased hepatic synthesis of thrombopoietin contributes to thrombocytopenia. (2) Systemic intravascular coagulation results in consumption of platelets and haemostatic factors. (3) Systemic activation of endothelial cells results in increased release or production of haemostatic factors. (4) Increased platelet pooling in the enlarged spleen may contribute to thrombocytopenia. Reprinted with permission from Blood (2010) 116 (6): 878-885

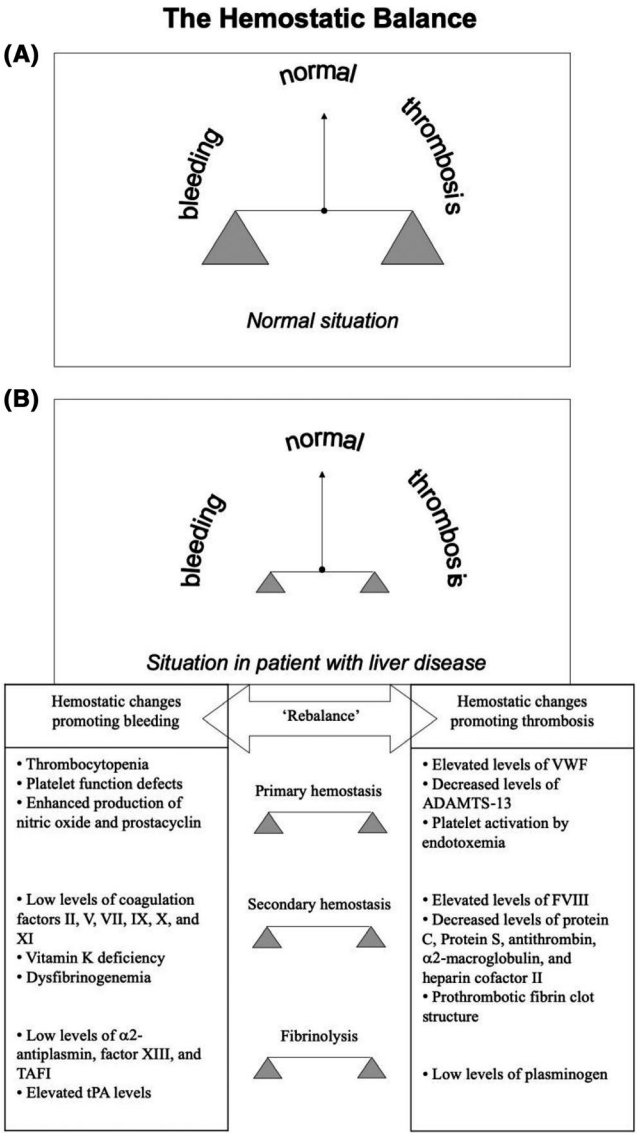

FIGURE 4 The concept of rebalanced haemostasis in patients with liver disease. (A) In healthy individuals, haemostasis is in a solid balance. (B) In patients with liver disease, concomitant changes in pro- and antihaemostatic pathways result in a 'rebalance' in the haemostatic system. Rebalance in the haemostatic system occurs at the level of primary and secondary haemostasis, and in the fibrinolytic system. This new balance, however, presumably is less stable compared with the balance in healthy volunteers and may thus more easily tip towards either bleeding or thrombosis. Reprinted with permission from Curr Opin Organ Transplant. 2008 Jun;13(3):298-303

tested by thrombomodulin-modified thrombin generation testing.[49] Fibrinogen deficiency is compensated for by posttranslational changes in the fibrinogen molecule that appear to make the clot more thrombogenic.[50] Finally, fibrinolytic status is maintained by simultaneous changes in pro- and antifibrinolytic proteins, except in patients with very advanced disease who present with both hyper- and hypofibrinolytic features.[51]

In summary, patients with liver diseases appear to remain in haemostatic balance due to a proportional decline in both pro- and antihaemostatic drivers (Figure 4).[52] This balance may be less stable than the haemostatic balance in healthy individuals, which explains the occurrence of both bleeding and thrombosis. Alternatively, it may be that distinct hypo- or hypercoagulable features drive bleeding or thrombosis risk in individual patients.

4.3 | Diagnosis

Routine tests of haemostasis do not accurately reflect haemostatic status in patients with liver diseases, and importantly they largely do not predict bleeding risk. There are strong indications that the PT is unrelated to bleeding risk. Some, but not all, studies have suggested the platelet count and fibrinogen levels to predict bleeding.[53,54] However, it is likely that thrombocytopenia and hypofibrinogenaemia in patients with cirrhosis signal severity of disease and severity of portal hypertension rather than haemostatic failure. Indeed, many of the bleeds identified in studies linking platelets and fibrinogen to bleeding risk are in fact portal hypertensive bleeds.

Increasingly, viscoelastic tests are used to assess haemostatic status in patients with liver disease. Although these tests have limitations (important disadvantages are the insensitivity for VWF and

the protein C system, which are thought to be important compensatory factors in patients with liver disease), they may better reflect haemostatic status. In patients with abnormal PT or platelet counts, viscoelastic tests are frequently normal, and the use of these tests may decrease unnecessary blood component transfusions in these patients.[55]

4.4 | Treatment

4.4.1 | Bleeding

Since patients with liver disease do not have an overt haemostasis-related bleeding tendency and are in haemostatic balance, even with significant thrombocytopenia and PT prolongation, prophylactic transfusion of blood products with the aim to prevent spontaneous or procedure-related bleeding is generally not indicated.[46] Experience from liver transplant surgery has shown that lengthy, major invasive procedures can be performed in patients with significant 'coagulopathy' without transfusion of any blood products.[41] Confusingly, it is still common practice in many centres to treat abnormal laboratory values prior to more minor procedures, without any evidence of benefit, but strong suggestion that this could do harm. Prophylactic infusion of blood products can even increase bleeding risk, because infusion of large volumes of blood products increase portal pressure in patients that frequently already have portal hypertension and are prone to bleed for that reason. When bleeding does occur, prohaemostatic management may be indicated, and the combination of factor concentrates (prothrombin complex concentrates and fibrinogen concentrate) may be preferred over blood products because of the difference in volume, but clinical studies guiding best practice are lacking.

4.4.2 | Thrombosis

Since patients with liver disease are at risk for development of venous thrombosis, thromboprophylaxis should not be withheld in patients at risk, even in those with abnormal laboratory tests. Venous thrombotic events obviously necessitate treatment, but the role of anticoagulation to treat (often asymptomatic) portal vein thrombosis has not been clearly established.[44]

Anticoagulant management of patients with cirrhosis is challenging.[56] Vitamin K antagonists are difficult to dose in patients who already have a substantially liver disease-associated INR prolongation at baseline. Heparins appear safe in patients with cirrhosis, but their mode of administration hampers long-term use. Direct oral anticoagulants (DOAC) have theoretical advantages over traditional

TABLE 2 Treatment strategies for bleeding and thrombosis in LFD

Clinical scenario	Potential interventions	Remarks
Preprocedural bleeding prophylaxis in patient with prolonged PT and/or thrombocytopenia	• Fresh-frozen plasma not indicated • Platelet concentrates often used, but efficacy unclear • Thrombopoietin receptor agonists increase platelet count, but unclear whether this reduces bleeding risk • Fibrinogen concentrate and prothrombin complex concentrates have been used, but unclear whether these reduce bleeding risk • Wait-and-see may be the best strategy as evidenced by experience from liver transplant surgery	• Procedural bleeding often unrelated to haemostasis (but to portal hypertension or puncture of vessels) • FFP and platelet concentrate increase portal pressure and therefore may increase bleeding risk. Factor concentrates lack this volume overload effect • Thrombocytopenia and hypofibrinogenaemia may be associated with increased bleeding risk, but this association may not be causal (but rather reflect severity of disease) • Procedural bleeding risk lower than generally anticipated
Actively bleeding patient	• FFP, platelet concentrate, fibrinogen concentrate, prothrombin complex concentrate, antifibrinolytic drugs (eg tranexamic acid) • May be guided by viscoelastic tests	• Low volume products have theoretical advantages over FFP and platelet concentrate • Prothrombin complex concentrates may require conservative dosing • Interventions likely not helpful when the bleeding is induced by portal hypertension or by mechanical causes, volume overload by blood products may exacerbate rather than stop the bleed (eg in variceal bleeding) • DDAVP and recombinant factor VIIa likely not helpful
Thromboprophylaxis	• Low molecular weight heparin (LMWH) • Unfractionated heparin (UFH) in patients with renal failure • Direct oral anticoagulants (DOACs)?	• LMWH has a good safety profile in patients with cirrhosis • Careful risk/benefit analysis required • anti-Xa monitoring of LMWH is unreliable, as is anti-Xa or APTT monitoring of UFH • DOACs may require dose-adjustments
Treatment of DVT or PVT	• Low molecular weight heparin • Unfractionated heparin in patients with renal failure • Direct oral anticoagulants?	• Vitamin K antagonists are difficult to dose due to INR elevations as a consequence of liver disease • Accumulation of DOACs is a potential concern as these drugs are cleared by liver and kidneys • Benefit of treating asymptomatic PVT is unclear

anticoagulants, but patients with LFD have been excluded from all randomized clinical studies on DOAC. Since the anticoagulant potency and clearance of anticoagulant drugs may be altered, there is very little clinical evidence to guide treatment, and carefully designed clinical studies are urgently required.

A summary of treatment strategies is provided in Table 2.

5 | CONCLUSION

Acquired bleeding disorders can be part of the pathophysiology of many diseases, including cardiovascular, hepatic, autoimmune and malignant disorders. Recognition of symptoms and laboratory signs is key to identification and proper management. The field is rapidly moving and, therefore, close cooperation is required among all specialties involved in patient management, including experts in haemostasis and thrombosis.

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AUTHOR CONTRIBUTION

AT wrote the introduction and the section on AHA. BZ wrote the section on AVWS. TL wrote the section on LFD. All authors critically revised the entire manuscript and approved of its final version.

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