Editorial

Periprocedural management of hemostatic alterations in patients with cirrhosis and vascular liver disorders: a step forward of the American Association for the Study of Liver Diseases

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"*Time flies over us, but leaves its shadow behind*" (Nathaniel Hawthorne, 1860, The Marble Faun). The shadow that separates the latest guidance on vascular liver disorders of the American Association for the Study of Liver Diseases (AASLD) from its former counterpart is 12 years long (1,2). Along the course, several guidelines from different societies have been published on this topic (3-7). As acknowledged in the preamble, the lack of high-quality evidence in the field led the AASLD to commission a guidance from an expert panel based on formal review and analysis of the literature. It thus differs from other guidelines that perform systematic reviews with explicit methods of searching, selection, and rating the quality of evidence and, if appropriate, meta-analysis on certain clinical questions (2).

The most distinguished feature of this new guidance is probably the incorporation of statements regarding the periprocedural management of hemostatic alterations in patients with cirrhosis. This disease has long been perceived as an acquired bleeding disorder resulting from thrombocytopenia and abnormal routine coagulation tests. However, unlike hereditary coagulopathies, cirrhosis affects the whole spectrum of the coagulation cascade (i.e., procoagulant/anticoagulant factors, and antifibrinolytics/profibrinolytics proteins) and is associated with both platelet hyperactivity and increased levels of von Willebrand factor, all of which results in a "rebalanced hemostasis". This new equilibrium is fragile and can easily be tipped towards either a prohemorrhagic or a prothrombotic phenotype. During the last 6 years several important scientific societies, some of them outside the field of Hepatology, have provided recommendations regarding the periprocedural management of hemostatic alterations in this setting (2,5,8-13) (*Table 1*). The common ground is an increasingly restrictive policy on transfusion of blood products. Indeed, all of them do not recommend implementing measures to reduce the international normalized ratio (INR) regardless of the bleeding risk, while the discussion on correcting or not the platelet count and fibrinogen levels is limited to high-risk procedures. The AASLD document is one of the most restrictive, as it does not recommend the routine preprocedural correction of either of them in both low- and high-risk procedures. Of note, this risk dichotomy is in

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Table 1 Recommendations of guidelines for minimum threshold values of common hemostatic parameters prior to high-risk procedures in patients with cirrhosis

Guideline & year	Prothrombin time/INR	Platelets ($\times 10^9$/L)	Fibrinogen (mg/dL)	Viscoelastic tests	Clarifications or additional notes
EASL 2022, (13)	No routine correction	No routine correction	No routine correction	Not validated	An individualized approach to patients with extreme changes in the hemostatic system and in high-risk procedures in whom local haemostasis is not possible and platelets <50×10^9/L
					TPO-RA are considered a valid alternative to platelet transfusion
ILTS 2022, (12)	No routine correction	>50	>130	–	Viscoelastic tests are not mentioned beyond the liver transplant setting
					TPO-RA are considered a valid alternative to platelet transfusion
AASLD 2021, (2)	No routine correction	No routine correction	No routine correction	Not validated	An individualized approach to patients with severe thrombocytopenia and fibrinogen levels <100 mg/dL
AGA 2021, (11)	No routine correction	No routine correction	Not mentioned	Not validated	An individualized approach to patients with extreme changes in the hemostatic system. TPO-RA may be used in patients with great concern about the bleeding risk
ISTH 2022, (10)	No routine correction	Very high risk: >50	No routine correction	Not validated	Examples of very high-risk surgery: neurosurgery and intraocular surgery
					TPO-RA are considered a valid alternative to platelet transfusion
ACG 2020, (5)	No routine correction	>50	No recommendation	May be useful	In elective procedures, TPO-RA are recommended over platelet transfusions
SIR 2019, (9)	INR >2.5	>30	>100	Not validated	If INR >2.5, it is recommended to give vitamin K (10 mg iv), not FFP
					No specific recommendation on TPO-RA use
AISF 2016, (8)	No routine correction	>50	Not mentioned	Not validated	Do not recommend TPO-RA. At that time, the only TPO-RA available was eltrombopag

INR, international normalized ratio; EASL, European Association for the Study of the Liver; TPO-RA, thrombopoietin receptor agonists; ILTS, International Liver Transplantation Society; AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; ISTH, International Society on Thrombosis and Haemostasis; ACG, American College of Gastroenterology; SIR, Society of Interventional Radiology; FFP, fresh frozen plasma; AISF, Italian Association of the Study of the Liver.

line with previous guidelines and is based on the estimated risk of major bleeding (greater or less than 1.5%), the feasibility of local bleeding control, and the consequences of bleeding regardless of its amount (e.g., central nervous system hemorrhage). Despite some discrepancies in certain procedures (i.e., liver biopsy, percutaneous ablation of liver cancer, endoscopic variceal ligation or dental extraction), most of them share the same risk stratification across guidelines (2,10,11,13).

This restrictive policy is based on cumulative data showing that traditional coagulation tests and platelet count do not adequately assess the risk of bleeding secondary to invasive procedures, nor is there high-quality evidence that their correction reduces this risk. There is more data on the poor predictive value of the INR and, thus, the universal agreement among guidelines. Discrepancies regarding the need to treat the platelet count is explained by the lack of randomized controlled trials, *in vitro* data suggesting that platelet levels >55,000/μL ensure normal primary hemostasis and by conflicting data from observational studies on the predictive value of platelet count in procedural bleeding. However, the majority of the guidelines published in the last 2 years recommend not to routinely correct the platelet level due to the limited evidence available, ability to use effective interventions if bleeding occurs and potential risks of platelet transfusion (2,10,11,13). In this last regard, thrombopoietin receptor agonists (TPO-RA) (i.e., lusutrombopag and avatrombopag) are considered as a valid alternative to platelet transfusion in scheduled procedures by some guidelines (5,12). Others, including the AASLD

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document, do not support their use since no reduction in bleeding complications has been shown so far (2). Of note, around 20–25% of the patients treated with TPO-RA do not reach the hypothetical safe threshold of >50,000/μL. A similar controversy exists regarding the correction of low fibrinogen levels (<100–150 mg/dL). Scarce data suggest that they might be associated with increased bleeding risk in critically ill patients with cirrhosis. These patients may also be a higher risk of procedural bleeding and, therefore, even the most restrictive guidelines acknowledge that deviations from the formal recommendations may be justified in patients with extreme changes in the hemostatic system (13). Accordingly, the AASLD guidance recommends an individualized approach to patients with severe thrombocytopenia and fibrinogen levels <100 mg/dL (2). More consensus exists regarding global tests of hemostasis. Although these tests better capture the general hemostatic status of a patient with cirrhosis and can reduce the need of preprocedural intervention and guide treatment should a bleeding occur, all guidelines agree that further studies are needed to confirm their reliability in identifying patients at risk for procedural bleeding (2,5,8-11,13). A final remark on the real-world management. Recent surveys from Spain and Italy have shown a lack of compliance with guidelines (14,15) and this highlights not only the need for high-quality studies (unlikely to be performed in the foreseeable future given the large sample required due to the low incidence of bleeding) (13), but also for multidisciplinary intra-hospital protocols to implement the current recommendations regardless of its more or less restrictive nature.

The rest of the guidance deals with vascular liver disorders and the main recommendations are depicted in *Table 2*. As far as portal vein thrombosis (PVT) is concerned, the AASLD proposed the establishment of a standardized terminology to allow comparison and external validation of future studies since terminology and classification systems of PVT vary extensively in the literature. The proposal was backed up by the Baveno VII consensus and includes a systematic documentation of initial site, extent/degree of luminal obstruction, and chronicity of PVT (2,7). Other important statements include not performing an extensive evaluation for thrombophilic conditions in patients with cirrhosis and PVT, unless family history or routine laboratory testing raises other concerns, and the incorporation of direct oral anticoagulants (DOACs) and of new radiological techniques in the treatment of PVT. Regarding the former, data is conflicting and comes from a limited number of studies, mostly case-control studies with small sample sizes and different designs. Therefore, recommendations from guidelines vary from consider testing on an individual basis (3,4) to limiting it to certain cases (2,5). This in opposition to PVT in the absence of cirrhosis where a full investigation for myeloproliferative disorders or another thrombophilic condition is universally supported. Regarding anticoagulation, and in contrast to other guidelines (6,7), the AASLD document makes no strong recommendation on the use of DOACs in patients with PVT with and without cirrhosis due to the limited evidence on their safety and efficacy, and states that the choice of anticoagulant agent should be individualize. As better specified in Baveno VII, if prescribed, DOACs should be limited to Child-Pugh A patients, used with caution in Child-Pugh B patients and not used in Child-Pugh C patients outside study protocols (7). In the setting of portal cavernoma, there is no established benefit of anticoagulation and treatment should be targeted at management of portal hypertension complications. In this regard, and in line with other guidelines (5,7), the AASLD document supports the percutaneous recanalization of the portal vein (PVR) followed by transjugular intrahepatic portosystemic shunt (TIPS) in patients with refractory complications and in liver transplant candidates with chronic PVT that hinders a physiological anastomosis between the graft and recipient portal vein (2). It must be noted that some centers do not systematically add a TIPS after PVR in the absence of parenchymal disease [e.g., cirrhosis or portosinusoidal vascular disorder (PSVD)].

The term PSVD has been recently proposed, and endorsed by Baveno VII, to define a broad clinico-pathological entity encompassing a heterogeneous group of vascular liver diseases including idiopathic noncirrhotic portal hypertension (INCPH). In contrast to the latter, diagnosis of PSVD can be made in the absence of signs of portal hypertension, provided there are specific histological lesions and no cirrhosis (7). Despite mentioning this new proposal, the AASLD still favors the term and definition of INCPH and does not recommend screening for PVT as suggested by the Baveno VII consensus (2). PVT is a frequent event in these patients, but its impact on the natural history is uncertain, explaining these different recommendations. The guidance also performed an update on Budd-Chiari syndrome, sinusoidal obstruction syndrome, hereditary hemorrhagic telangiectasia, hepatic/splenic artery aneurisms and congenital disorders. Beyond some new recommendations, the AASLD document highlights that patients with these disorders should be

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Table 2 Main recommendations on vascular liver disorders of the latest guideline of the American Association for the Study of Liver Diseases

Vascular liver disorder	Main recommendations
Portal vein thrombosis	New classification: recent *vs.* chronic (>6 months); completely, partially (>50% of lumen) or minimally occlusive; progressive, regressive and stable (thrombus increases, decreases or stays stable). Cavernoma: gross portoportal collaterals without original portal vein seen
	Anticoagulation in cirrhosis if: (I) recent completely or partially occlusive thrombosis of the main PV or SMV; (II) ischemic symptoms
	In patients without cirrhosis and with recent PVT, directed antithrombotic therapy should be considered
Budd-Chiari syndrome	A progressive "step-up" therapeutic strategy according to the clinical response from less to more invasive therapies is recommended
	All patients, even in the absence of a recognized prothrombotic disorder, should receive therapeutic anticoagulation
Sinusoidal obstruction syndrome	Ursodeoxycholic acid is recommended as prophylactic therapy in all patients undergoing allogeneic HSCT
	Defibrotide is recommended for treatment of moderate-to-severe SOS. The benefit in prophylaxis in high-risk cases is not established.
	TIPS is unproven in SOS and cannot be recommended
Hereditary hemorrhagic telangiectasia	Asymptomatic liver vascular malformations do not warrant therapy or imaging surveillance
	In symptomatic cases, standard therapy for specific complications (e.g., heart failure and portal hypertension) should be applied
	The use of bevacizumab and/or liver transplantation is warranted in non-responders to standard therapy
Idiopathic noncirrhotic portal hypertension	INCPH should be considered in any patient with evidence of portal hypertension but without cirrhosis or other known causes of noncirrhotic portal hypertension
	Underlying risk factors for venous thrombosis, immune disorders, and inherited disorders associated with INCPH should be routinely considered
Hepatic and splenic artery aneurysms	For recently diagnosed HAAs or SAAs of <2 cm in size, early follow-up imaging (e.g., 3 and 12 months) should be performed. Any significant growth of an aneurysm on serial imaging should prompt consideration of intervention
	In patients with pregnancy plans or LT candidates, elective interventions in patients with HAAs or SAAs should be considered
EHVPO and congenital disorders	In children with EHPVO, evaluation for early intervention in the presymptomatic stage is recommended
	Glutathione expression may occur in as many as 30–50% of cases of infantile hemangiomata, and the use of beta-blockers such as propranolol is recommended in these patients

PV, portal vein; SMV, superior mesenteric vein; PVT, portal vein thrombosis; HSCT, hematopoietic stem cell transplantation; SOS, sinusoidal obstruction syndrome; TIPS, transjugular intrahepatic portosystemic shunt; INCPH, Idiopathic noncirrhotic portal hypertension; HAA, Hepatic artery aneurysm; SAA, splenic artery aneurysm; LT, liver transplant; EHPVO, Extrahepatic portal vein obstruction.

referred to tertiary care centers with expertise in their management.

In conclusion, the AASLD guidance offers significant updates for best practice but is hampered by a paucity of robust evidence. Indeed, the research agenda is wide and due to the rarity of vascular disorders and preprocedural bleeding, multicenter collaboration is key to foster advances in the field. Hopefully, and regardless of the length of the shadow, the next AASLD document will shed some light on many of the current gaps of knowledge.

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