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ISTH SSC COMMUNICATION

The management of liver disease in people with congenital bleeding disorders: guidance from European Association for Haemophilia and Allied Disorders, European Haemophilia Consortium, ISTH, and World Federation of Hemophilia

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Abstract

People with bleeding disorders (PWBD) have been exposed to the risk of developing chronic viral hepatitis and cirrhosis after replacement therapy. Today, the advent of new pharmacologic strategies for the control of hemostasis and the efficacious antiviral therapies against hepatitis C virus and hepatitis B virus have significantly reduced this risk. However, the definitive success for liver health in this clinical setting is also influenced by other factors, such as the severity of liver disease at the time of hepatitis B virus/hepatitis C virus antiviral therapy and the exposure to highly prevalent factors

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of chronic liver damage (eg, metabolic dysfunction and/or alcohol) that can cause a residual risk of complications such as hepatocellular carcinoma, portal hypertension, and liver insufficiency. With this background, a group of experts selected among hepatologists, hematologists, PWBD treaters, and patient representatives produced this practical multisociety guidance for the protection of liver health and the prevention and management of liver complications in PWBD based on the most updated protocols of care.

KEYWORDS
cirrhosis, fibrosis, gene therapy, HCC, hemophilia, hepatitis

1 | INTRODUCTION

Congenital bleeding disorders are a heterogeneous group of rare inherited defects of hemostasis, leading to an increased risk of bleeding [1]. In 2022, the World Federation of Hemophilia has estimated that 427 685 people worldwide suffer from bleeding disorders: 86% afflicted by hemophilia A or B or von Willebrand disease and 16% having inherited deficiencies of fibrinogen, factor (F)II, FV, FV + FVIII combined, FVII, FX, FXI, and FXIII [2]. People with bleeding disorders (PWBD) have a high prevalence of chronic liver disease, mainly due to transmission of the hepatitis B virus (HBV) and hepatitis C virus (HCV) after replacement therapy with nonviral inactivated plasma-derived coagulation factors [3,4]. This risk of infection was firstly eliminated by the viral inactivation of clotting factors concentrates along with the implementation of vaccination campaigns against HBV and, finally, by the development of recombinant coagulation factors [5]. In parallel, the introduction of efficacious nucleoside analogs able to suppress HBV replication and direct antiviral agents (DAAs) warranting HCV clearance have overcome the adverse effects and the lower antiviral success rate of interferon-based therapies by ultimately changing the risk of liver-related complications in infected patients [6,7]. Notwithstanding, concerns remain about how to monitor patients with pharmacologically suppressed chronic HBV and HCV infection eradicated with either interferon or DAAs. Indeed, studies of large cohorts of patients with successfully treated HBV and HCV infection have demonstrated a life-long persistence of the risk of developing primary liver cancer, mainly hepatocellular carcinoma (HCC) [8,9], often seen in relation to advanced liver fibrosis and comorbidities like obesity, diabetes, and excess alcohol intake [10–13]. Noteworthy, after HCV clearance, this residual risk of neoplastic transformation of the liver seems to be associated also with a risk of complications related to portal hypertension (eg, ascites, acute variceal bleeding, and hepatic encephalopathy), particularly in subjects who eradicated the virus while at an advanced stage of the disease [9,14–16]. Recently, these observations have been reproduced in the setting of PWBD. In a large cohort of 309 PWBD from the Netherlands, the prevalence of advanced liver fibrosis and cirrhosis was 21% and 42%, respectively, after a median follow-up of 44 years (IQR, 34-50 years) [17]. In this study, 223 of 309 HCV-positive persons (72%) had a history of at least 1 attempt of HCV eradication, and 199 of 223 (89%) reached a sustained virologic response. The overall risk of liver-related complications was 4%, with HCC being the dominant adverse event. The incidence of liver-related complications was 0.2 per 100 person-years in those exposed to interferon compared with 1.0 per 100 person-years in those who were cured with DAAs and who had more advanced hepatitis, demonstrating a residual risk of liver-related complications despite HCV clearance. Similar data were observed in Italy among 119 subjects with hemophilia who were prospectively screened after HCV clearance for any incidental or prevalent risk factor of chronic liver damage on top of the previous infection, presence of advanced fibrosis/cirrhosis, and any liver-related complication despite HCV clearance [18]. In this study, 96 subjects (81%) presented at least 1 potential risk factor of chronic liver damage, mainly due to metabolic issues, 21 (18%) had an advanced stage of fibrosis/cirrhosis, and 4 (3%) had HCC needing liver transplantation. This is noteworthy since risk factors of chronic liver damage such as obesity, diabetes, and excess intake of alcohol are frequently observed in PWBD [19–22].

2 | AIM AND METHODS

Owing to the complexity of liver problems that may potentially affect PWBD and the existence of specific recommendations for their management that were crafted by international liver societies, the European Association for Haemophilia and Allied Disorders and the European Haemophilia Consortium in collaboration with the International Society on Thrombosis and Haemostasis (ISTH) convened a group of experts selected among hepatologists, PWBD treaters, and patient representatives with the aim of producing a multisociety guidance for protecting liver health of PWBD and optimizing the prevention and management of liver complications.

The World Federation of Hemophilia was invited to join since many of its constituent countries have endemic rates of hepatitis that impact PWBD who use plasma collected in the country (Annual Global Survey 2022) [2].

TABLE Hepatological topics covered by the guidance.

Hepatological topics	References
Testing for hepatitis virus infection in all individuals exposed to blood-derived products	[23–25]
Testing for occult HBV infection	[26]
Management of viral hepatitis other than HCV, HBV, and HDV	[27]
HAV and HBV vaccination	[28]
Investigating persons with abnormal liver test results and/or risk factors for noncommunicable liver diseases	[29–39]
Referral and treatment of PWBD and virus-related chronic hepatitis	[23–25]
Referral and treatment of PWBD after successful HBV/HCV therapy	[40,41]
Investigation for the presence of advanced fibrosis/cirrhosis in patients with known liver disease	[40-42]
Surveillance and management of hepatocellular carcinoma and cholangiocarcinoma	[35,43]
Monitoring portal hypertension in patients with cirrhosis	[41,44]
Eligibility for liver transplantation	[41,43,44]
Investigation of liver health before AAV gene therapy in hemophilia	[45–47]
Surveillance of liver health post-AAV gene therapy in hemophilia	[46,47]

The reader can find the original guidelines the statements of this guidance are based on.

AAV, adeno-associated virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; PWBD, people with bleeding disorders.

In this document, the word "recommendation" was used when a strong guidance statement was available based on previous documents from other scientific societies, whereas the word "suggestion" was used when the statement was based on a weaker guidance statement based on expert opinion from the panel. In more detail, any recommendation/suggestion was made by adopting and adapting the most updated practice guidelines or guidance from the European Association for the Study of the Liver, the American Association for the Study of Liver Diseases, and Baveno VII recommendations on portal hypertension, which are consensus documents for the management of liver disease. The source of these statements is reported in the Table [23–47] to enable the reader to dive into the details of the hepatological aspects summarized in this guidance. Those statements not fully covered by already published guidelines in the field of hepatology and specific for congenital bleeding disorders (eg, gene therapy in hemophilia) were based on expert experience from the panel or on documents already published by PWBD treaters.

2.1 | Testing for hepatitis virus infection in all individuals exposed to blood-derived products

The Global Hepatitis Report 2024 from the World Health Organization has pointed out that HBV (with/without hepatitis delta virus [HDV]) and HCV infections account for communicable diseases at an increasing rate of death, particularly in low- and middle-income countries [48]. Although most PWBD have been tested already [28], those epidemiological data support the full adoption of the clinical practice guidelines for preventing, testing, and treating chronic viral hepatitis [23–25], especially in PWBD from those geographical areas.

2.1.1 | Recommendations

- All individuals who have been exposed to clotting factor concentrates or blood products should be tested for current (serum positivity for hepatitis B surface antigen [HBsAg]) or resolved (serum positivity for hepatitis B surface antibody [HBsAb]/hepatitis B core antibody [HBcAb]) HBV infection and for current/resolved HCV infection (serum positivity to HCV antibody) at least once in their lifetime (minimum 6 months after any exposure to evaluate for chronic viral hepatitis).
- In HBsAg-seropositive individuals, the level of HBV replication, which has pragmatic implications for therapeutic strategies, should be determined with a sensitive polymerase chain reaction (PCR) assay for serum HBV DNA.
- All HBsAg-seropositive individuals should be tested for past exposure or ongoing infection with HDV by means of a total serum anti-HDV antibody assay, which is present in all immunocompetent patients with infection.
- Anti-HDV–positive individuals should be tested for an active infection (serum HDV RNA positivity by PCR assay).
- Anti–HCV-seropositive individuals should be investigated for the presence and the level of HCV replication by means of a sensitive PCR assay for serum HCV RNA and to identify the infecting HCV genotype.

2.2 | Testing for occult HBV infection

Recipients of nonviral inactivated plasma-derived coagulation factors may have occult HBV infection (OBI), a condition in which replication-competent HBV DNA is present in the liver (ie, episomal HBV covalently closed circular DNA) and/or in the blood despite testing negative for serum HBsAg using currently available assays [49]. The definition of seropositive OBI includes positive HBcAb and/or positive HBsAb. For seronegative OBI (comprising between 1% and 20% of individuals with OBI), the HBcAb and HBsAb are negative [26]. OBI has important

clinical implications in subjects subsequently exposed to immunosuppressant therapy. Ideally, the diagnosis of OBI is based on the detection of HBV DNA in liver biopsies; however, from a practical point of view, the detection of HBV DNA in the blood is the most frequently used diagnostic tool, particularly in seropositive OBI subjects [50].

2.2.1 | Suggestion

- PWBD who are candidates to receive immunosuppressant therapy, particularly if they are HBcAb-positive, should be evaluated by a hepatologist to rule out OBI and decide on pre-emptive therapy to manage the risk of HBV reactivation.

2.3 | Management of viral hepatitis other than HCV, HBV, and HDV

Alteration of liver tests can be caused by viral hepatitis other than HCV, HBV, and HDV, and most frequently, hepatitis A virus (HAV), hepatitis E virus (HEV), Epstein–Barr virus (EBV), or cytomegalovirus (CMV). Typically, these infections may be acquired by the fecal-oral route (HAV and HEV) or contact with bodily fluids (eg, saliva, urine, and genital secretions) from infected individuals (CMV and EBV). Generally, these infections cause acute hepatitis, named acute liver injury, which is time-limited and does not require specific hepatological treatment, and the risk of developing acute fulminant hepatitis is low in immunocompetent individuals [27].

2.3.1 | Suggestion

- In cases of acute hepatitis caused by HAV, HEV, EBV, CMV, or any other virus, PWBD should be referred to a hepatologist to avoid overtreatment and decide on follow-up and monitoring.

2.4 | HAV and HBV vaccination

Currently, safe and effective vaccines to prevent HAV and HBV transmission are available and incorporated into the models of care for PWBD [28].

2.4.1 | Recommendations

- HBV vaccination is part of the obligatory vaccination policy in higher-income countries and should be universally recommended among newborns with congenital bleeding disorders.
- HAV is generally prevented by good personal and environmental hygiene and proper sanitation, which should be recommended among PWBD.
- HAV vaccination is recommended for PWBD who are included in the high-risk population identified by the World Health Organization: international travelers, males who have sex with males, people who use or inject drugs (all those who use illegal drugs), people with occupational risk for exposure, people who anticipate close personal contact with an international adoptee, and people experiencing homelessness.

2.5 | Investigating persons with abnormal liver test results and/or risk factors for noncommunicable liver diseases

PWBD harbor the risk of noncommunicable liver diseases like the rest of the population not suffering from congenital bleeding disorders. These include steatotic liver disease (SLD), mainly associated with metabolic dysfunction (metabolic dysfunction-associated SLD [MASLD]), excessive alcohol intake (alcohol-related liver disease), or both [51]. A quarter of the population worldwide has an SLD due to metabolic syndrome, MASLD, a condition driven by the epidemic of obesity and diabetes and is associated with metabolic conditions and excess dietary intake of calories coupled with sedentary lifestyle. MASLD, previously known as nonalcoholic fatty liver disease, has been reported in people with hemophilia at a rate that mimics the epidemiology of the population worldwide [19]. A similar trend could be expected for PWBD, whatever the hereditary disorder. The clinical importance of SLD lies in the propensity to cause severe and progressive liver disorders such as steatohepatitis, which may be more commonly seen in genetically susceptible individuals [52]. SLD may also be the consequence of excess alcohol intake [29]. In susceptible individuals, alcohol intake over the threshold of 2 standard drinks/d for women or 3 standard drinks/d for men (1 standard drink is equal to 10 g of alcohol/d) [29] is a well-recognized risk factor of chronic liver damage beyond steatosis and might cause accelerated onset of significant liver morbidity in conjunction with the presence of such comorbidities as MASLD and viral hepatitis [51]. Owing to all these observations, the models of care for PWBD should adhere to the international recommendations on MASLD [30].

Although the prevalence of PWBD is not known, other noncommunicable diseases of the liver are represented by (idiosyncratic) drug-induced liver injury, also including exposure to herbal and dietary supplements [31,32,53], immune-mediated diseases of the liver (eg, autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis [PSC]) [33,34], vascular liver diseases [36], and potentially rare genetic disorders, such as hemochromatosis, Wilson disease, and alfa-1 antitrypsin deficiency, which fall in the expertise

domain of the hepatologists [37,38]. Coeliac disease may also account for unexplained liver enzyme fluctuation [39].

2.5.1 | Recommendation

- PWBD and unexplained alteration of liver tests should be screened for SLD due to metabolic syndrome and/or alcohol, which are common risk factors for chronic liver damage.

2.5.2 | Suggestion

- PWBD with unexplained elevation of serum aminotransferase and/or cholestatic enzymes could suffer from liver disease including SLD, an immune-mediated disease of the liver (autoimmune hepatitis, primary biliary cholangitis, or PSC), a hereditary metabolic disorder (hemochromatosis, Wilson disease, and alfa-1 antitrypsin deficiency), coeliac disease, and vascular liver diseases and should be referred to a hepatologist for diagnosis, staging assessment, and decision on management.

2.6 | Referral and treatment of PWBD with virus-related chronic hepatitis

2.6.1 | Suggestions

- PWBD with active HBV ± HDV or HCV infection (HCV RNA positive or HBsAg positive ± total HDV antibody) should be managed by a hepatologist or an infectious disease expert in viral hepatitis for their management and antiviral treatment.

2.7 | Referral and treatment of PWBD after successful HBV/HCV therapy

As pointed out in the Introduction, PWBD are at risk of developing HCC and portal hypertension-related complications despite successful antiviral therapy [17–18]. These observations are similar to the experience accumulated outside the setting of congenital bleeding disorders and point out the importance for PWBD treaters to consider the international recommendations on the management of patients with advanced chronic liver disease [40–42,54] and summarized in the Figure.

2.7.1 | Recommendation

- All PWBD found to be HCV antibody–positive and HCV RNA–negative, HBsAg-negative and HBcAb-positive ± HBsAb should be screened for additional factors of chronic liver damage and evaluated for the presence of signs of an advanced chronic liver disease even if asymptomatic and/or with normal liver test results.
- The screening should rule out the most common risk factors of chronic liver damage (eg, alcohol exposure and metabolic syndrome), evaluate active hepatocellular and/or cholestatic liver damage (eg, aminotransferase and cholestatic enzymes rise), and detect clinical or imaging signs of advanced chronic liver disease (eg, history of liver-related complications, irregular surface of the liver, liver caudate lobe hypertrophy, and indirect signs of portal hypertension).
- Patients with previous diagnosis of advanced fibrosis/cirrhosis should continue with hepatological follow-up despite successful antiviral therapy, decrease of noninvasive tests of fibrosis, and/or liver stiffness measurement (LSM).

2.8 | Investigation for the presence of advanced fibrosis/cirrhosis in patients with known liver disease

The identification of advanced fibrosis/cirrhosis has relied traditionally on liver biopsy; however, noninvasive tests have emerged as an alternative approach that combines several clinical and biochemical data and LSM to accurately assess the severity of liver fibrosis/cirrhosis [54]. Evaluation of liver stiffness is recommended as a second-line approach after stratification by inexpensive routine tests like Fibrosis-4 (FIB-4), which combines age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count (see Supplementary Figure S1), or the AST-to-platelet ratio index [42]. Among all the techniques to measure liver stiffness, transient elastography (TE) measurement by FibroScan (Echosens) is preferred because it is the most validated and the most widely available in liver clinics [40]. FibroScan has also been recommended to rule out (value, <10 kPA) patients with compensated advanced chronic liver disease (cACLD) [41]. This nomenclature better covers, in asymptomatic patients, the continuum spectrum of severe fibrosis and cirrhosis and identifies patients at risk of developing liver-related complications. A FibroScan value of ≥15 kPa is highly suggestive of cACLD, whereas a value between 10 and 15 belongs to the gray zone where platelets can help. Indeed, a FibroScan value of <15 kPa together with platelet count of >150 000 can help rule out cACLD [40].

2.8.1 | Recommendations

- PWBD with active HCV/HBV infection and after successful antiviral therapy or spontaneous clearance of HCV/HBV should be evaluated for the presence of advanced fibrosis/cirrhosis based on clinical information and biochemical and radiological tests. They should also be screened for other potential risk factors of chronic liver damage such as alcohol and metabolic disease and other less common liver diseases based on indexes of hepatocellular injury (aminotransferase) and/or cholestasis (gamma-glutamyl transferase and alkaline phosphatase).

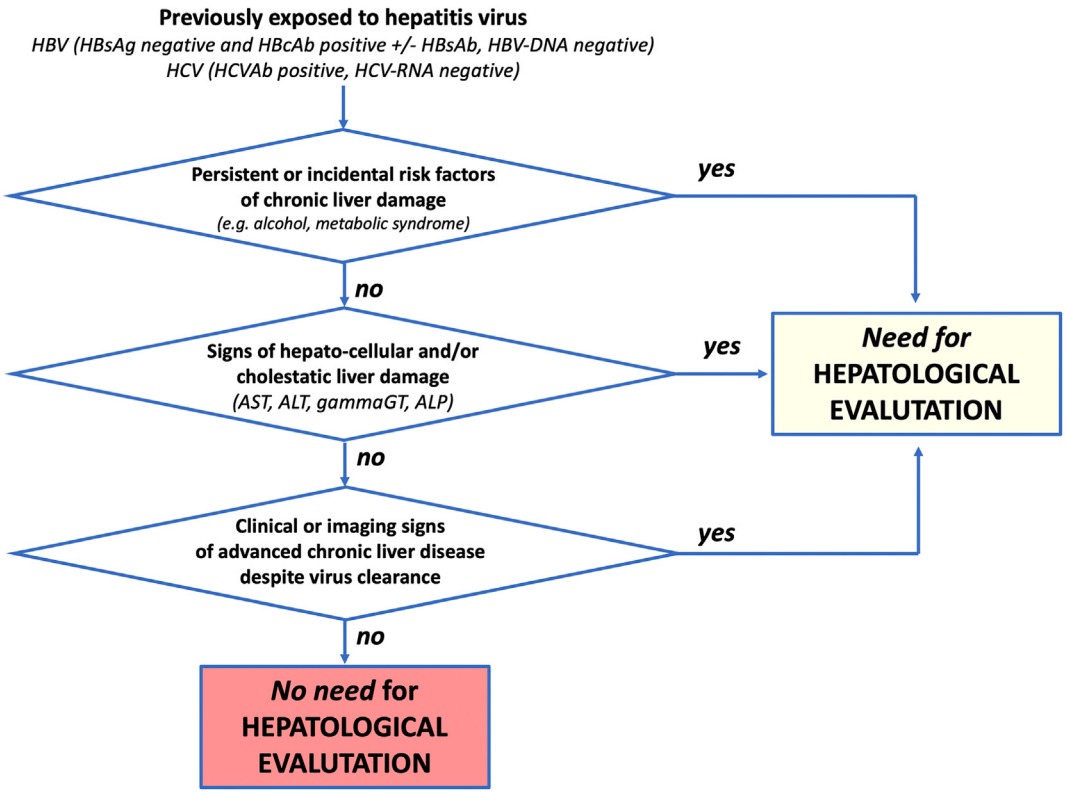

FIGURE Algorithm recommended for the referral to a hepatological evaluation of people with bleeding disorders after successful hepatitis B virus (HBV)/hepatitis C virus (HCV) therapy. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; gammaGT, gamma-glutamyl transferase; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.

- If chronic liver disease is diagnosed, the patient should be referred to a hepatologist as it becomes mandatory to stage the liver disease with noninvasive procedures that assess liver fibrosis and, finally, the presence of cACLD.
- In patients with metabolic risk factors of chronic liver disease (eg, diabetes, obesity, dyslipidemia, and arterial hypertension) never exposed to HBV/HCV, noninvasive tests of liver fibrosis can be used to screen for the presence of advanced fibrosis/cirrhosis. The European Association for the Study of the Liver guidelines recommend the use of a FIB-4 (age, AST, ALT, and platelet) of ≥1.30 as the first diagnostic tool to identify patients who may further benefit from LSM measurement (see FIB-4 formula in Supplementary Figure S1). Patients with FIB-4 and LSM by TE of ≥8 kPa should be referred to a hepatologist to conclude the diagnostic workup.
- PWBD with previous liver-related complication due to portal hypertension (eg, ascites, esophageal varices, upper gastrointestinal bleeding, and encephalopathy) and/or HCC, even after successful etiologic therapy and improvement of liver function, should continue HCC screening and monitoring by a hepatologist.

2.8.2 | Suggestion

- Liver biopsy is not contraindicated in PWBD but, if necessary for diagnostic and therapeutic purposes, should be carried out in an experienced center. Management of coagulation test alterations should be in agreement with the hematologist. The final decision to perform a liver biopsy should be jointly taken at least by the hepatologist and the congenital bleeding disorder treater in agreement with the patient's preference for shared decision making. A valid option to minimize the risk of bleeding could be the transjugular route in expert hands [55].

2.9 | Surveillance and management of HCC and cholangiocarcinoma

Primary liver cancers, HCC, and cholangiocarcinoma (CCA) represent the sixth most commonly diagnosed cancers and the third most common cause of cancer-related death [43,56]. HCC accounts for 90% of primary liver cancers; the incidence is increasing, thereby standing as a global health problem. CCA, which could be intrahepatic, perihilar, or distal, is the second most common cause of primary liver cancers. Despite being less frequent than HCC, its incidence is increasing worldwide together with an alarming mortality rate due to the typical asymptomatic course, late diagnosis, aggressive biology, and resistance to treatments. The pillar intervention to reduce mortality from these cancers is the detection of subjects at risk of primary liver cancers to address them to surveillance for prompt cure and better survival [35,43,56,57].

2.9.1 | Recommendations

- Individuals with advanced liver fibrosis or cirrhosis should undergo a liver ultrasound examination ± estimation of serum alpha-fetoprotein every 6 months to detect focal liver lesions suspected of HCC.
- Secondary prevention (surveillance) of CCA is recommended in PWBD with PSC, any etiology cirrhosis, choledochal cyst, choledocholithiasis, cholelithiasis, cholecystolithiasis, and Caroli disease.

2.9.2 | Suggestions

- The diagnostic workup of any focal liver lesions should be conducted by a hepatologist in the frame of a multidisciplinary team that includes radiologists and surgeons dedicated to the management of patients with advanced chronic liver disease. Any invasive procedure should be discussed with the PWBD treater to reduce the risk of periprocedural bleeding.
- PWBD who suffer from HCC or CCA should be treated similarly to people without hereditary hemorrhagic disease. The risk-benefit ratio of invasive treatments and/or systemic therapies should be jointly weighed by the hepatologist, hematologist, and patient's preference.

2.10 | Monitoring portal hypertension in patients with cirrhosis

The early stages of advanced fibrosis/cirrhosis are usually asymptomatic and, in the absence of any history of decompensation, are named cACLD [41]. Patients with cACLD are at risk of developing a first episode of decompensation like ascites, acute variceal bleeding, hepatic encephalopathy, jaundice, and, consequently, the onset of symptomatic illness [44]. The risk of first decompensation is strongly associated with the development of clinically significant portal hypertension (CSPH) [58]. Traditionally, upper gastrointestinal endoscopy has been the most widely used approach for diagnosing CSPH, though its diagnostic accuracy is suboptimal. CSPH may develop in up to one-third of patients lacking esophageal varices, a fact that in part accounts for the first episode of decompensation being more frequently initiated by ascites than by variceal bleeding [58]. The early identification of patients with CSPH is the premise to manage the risk of complications due to portal hypertension even in the era of successful etiologic therapies [15,16,59]. CSPH is defined by a hepatic venous pressure gradient of ≥10 mmHg, but recent data have shown that it can accurately be detected with noninvasive tests such as LSM by TE and platelet count [41]. A promising tool is also represented by spleen stiffness measurement, which can implement the LSM-based algorithms to detect CSPH varices at risk non-invasively [60].

2.10.1 | Recommendation

- All PWBD with a diagnosis of cACLD should be screened by a hepatologist for the presence of CSPH (portal hypertension at risk of complications).

2.10.2 | Suggestions

- PWBD and decompensated cirrhosis should be sent for hepatological evaluation for the best management of the complications due to portal hypertension.
- Portal hypertension decompensations (ie, variceal bleeding and ascites) should be managed similarly to the general population. The hematological support to promote hemostasis should be discussed with any specialist experienced in the support of hemostasis in PWBD.

2.11 | Eligibility for liver transplantation

As liver decompensation occurs, PWBD should be evaluated by a team of hepatologists in tertiary care centers equipped with a program of liver transplantation that could offer the only effective therapeutic option to selected patients with end-stage liver disease due to acute or chronic liver failure, recurrent/refractory ascites, and refractory variceal bleeding [41,44,61]. Liver-restricted HCC is an indication for liver transplantation in selected patients with both compensated and decompensated liver disease [56]. In people with hemophilia, liver transplant confers the additional therapeutic advantage of curing the underlying congenital bleeding disorder.

2.11.1 | Suggestions

- PWBD and decompensated liver disease should be referred for liver transplantation with the same criteria as any patient with chronic liver disease. The management of the hemorrhagic and thrombotic risk of this subgroup of patients should be carefully evaluated in a multidisciplinary team including the PWBD treater.

2.12 | Investigation of liver health before adeno-associated virus (AAV) gene therapy in hemophilia

Hepatocytes are the biological target of gene transfer for approved AAV5-based gene therapies for hemophilia A and B [62]. While these therapies have the potential to provide long-term benefits with sustained factor activity levels after a single administration, transduced hepatocytes may be the target of innate and adaptive immunological responses that may cause hepatotoxicity. In addition, the high amounts of intracellular viral capsid and high protein production within the cell may contribute to toxicity, thus giving rise to concerns for liver health and transgene expression. More toxicity has been seen in the phase 3

FVIII AAV gene therapy trial than in the FIX AAV gene therapy trial, possibly due to the greater challenge in producing FVIII in hepatocytes [63]. Lastly, there are still concerns about the potential risk of genotoxicity that could cause liver tumorigenesis. A recent study based on liver biopsies from hemophilia A dogs more than a decade after portal vein delivery of AAV-canine FVIII demonstrated a predominance of nonintegrated episomal form of vector persistence in the liver [64]. In this study, the integration was seen at low frequencies but not associated with oncogene upregulation or histopathologic evidence of tumorigenesis. This notwithstanding, a cautionary note was launched because 1 single patient, 1 year after AAV gene therapy for hemophilia B, developed HCC [65]. This single case was thoroughly studied for molecular and vector integration analysis, and no relationship to gene therapy administration was found.

The short- and long-term risk of hepatotoxicities observed in the clinical trials of AAV gene therapy in hemophilia have been only partially clarified [66–68]. The ALT increase in 80% of hemophilia A patients and 20% of hemophilia B patients in the AAV gene therapy trials requires further investigation. Hemophilia gene therapy requires the exclusion of subjects with active chronic viral hepatitis or advanced fibrosis/cirrhosis to lessen the risk of short- and long-term hepatic adverse events following AAV gene therapy [45–47,68]. Furthermore, due to the high proportion of subjects with MASLD among people with hemophilia, it is noteworthy that HCC may also be detected in noncirrhotic patients with MASLD [43].

2.12.1 | Recommendation

- People with hemophilia and evidence of previous HBV/HDV, HCV infection, or other common risk factors of chronic liver disease (eg, obesity, diabetes mellitus, dyslipidemia, arterial hypertension, and alcohol intake of over 2 alcoholic units/d) should undergo detailed hepatic investigations before AAV gene therapy to rule out chronic active hepatitis and advanced fibrosis/cirrhosis and to motivate individuals to control additional risk factors of chronic liver damage.
- Candidates for AAV gene therapy should be screened for intake of medication and herbal products at risk of liver damage.

2.13 | Surveillance of liver health after AAV gene therapy in hemophilia

2.13.1 | Recommendations

- After liver-directed AAV gene therapy, periodic evaluation of liver tests is mandatory. The frequency of this periodic evaluation may differ in hemophilia A and B patients.
- In case of flares of aminotransferase and/or markers of cholestasis, patients should be referred to a hepatologist to start a complete etiologic workup, define the severity of the acute impairment of liver tests, and discuss the best strategy of treatment with the hemophilia specialist.
- Recipients of liver-directed AAV gene therapy should be followed up very closely for the risk of aminotransferase flares requiring anti-inflammatory steroids. Of note, any hepatologist assessing patients in this setting should be aware of the potential association of aminotransferase flares with the loss of vector expression. Clinical or research biopsies could be useful in elucidating the extent of hepatocyte toxicities [69].
- Ultrasound examination of the liver should be carried out every 6 months in agreement with the schedule to avoid delayed detection of HCC in population at risk of this malignancy.

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AUTHOR CONTRIBUTIONS

V.L.M. and F.P. planned and organized the guidance work. V.L.M. led the literature search, and V.L.M. and M.C. created the recommendations/suggestions. All authors contributed to the composition of the manuscript, analyzed the most important critical contents of any recommendation/suggestion, and finally approved the submission.

DECLARATION OF COMPETING INTERESTS

V.L.M.: advisory board – BioMarin, CSL Behring, and Pfizer; speaker – Gore and Alfasigma; travel grant – Sanofi and Takeda. M.C.: advisory board – Galapagos, Agios, and Target HCC. G.R.F.: speaker, consultancy, and safety panel – Gilead, GSK, BioMarin, CSL Behring, and Pfizer. P.A.: advisory board – BioMarin; speaker invitation – Kedrion and Grifols; advisory board and patent – BioVie; speaker invitation and travel grant – Bhering. W.M.: research support – Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, and Takeda/Shire; travel support – Bayer, BioMarin, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Takeda/Shire, and uniQure; speaker bureau – Bayer, BioMarin, Biotest, CSL Behring, Chugai, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, and Takeda/Shire; scientific advisory board for Bayer, BioMarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Regeneron, Roche, Sanofi, Takeda/Shire, and uniQure. R.K.: advisory board and/or speaker – Bayer, BioMarin, Biotest, Chugai, CSL Behring, Grifols, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, and Takeda. G.F.P.: advisory committee – BioMarin, Frontera Therapeutics, Metagenomi, Novo Nordisk, and Roche; consultant fees – Generation Bio, hC Bio, Regeneron, Spark

Therapeutics, St Jude, and Third Rock Ventures. B.O.M.: advisory board – BioMarin, CSL Behring, and Roche; speaker – Sobi. M.Y.L.: advisory boards – Sanofi, Takeda, and BioMarin. V.H.-G.: speaker – Gore and Cook; advisory board – Cook. M.M.: speaker – Novo Nordisk, Sanofi, and Takeda; grant application scoring – Grifols. F.P.: advisory board – Sobi, Sanofi, Roche, CSL Behring, and BioMarin; speaker – Takeda and Spark.

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SUPPLEMENTARY MATERIAL

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