REVIEW

Practical clinical approach to the evaluation of hepatobiliary disorders in inflammatory bowel disease

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ABSTRACT

Hepatobiliary disorders are frequent extraintestinal manifestations in inflammatory bowel disease (IBD) and may appear at any time point during the natural course of the disease. Conceptually, these manifestations can be categorised as: (1) disorders that have an association with IBD; (2) diseases directly and structurally related to intestinal inflammation; (3) diseases related to the adverse effects of IBD treatment; and (4) disorders stemming from the metabolic derangements caused by IBD. The clinical presentations of these disorders range from a mild transient elevation of liver enzymes to liver failure and death. Given this wide differential diagnosis and spectrum of severity, it is understandable that the evaluation of patients with IBD with a hepatobiliary abnormality is often challenging. In this review, we present a concise summary of the common hepatic manifestations seen in patients with IBD and focus on the relevant practical issues encountered by gastroenterologists caring for patients with IBD. A practical clinical approach to the evaluation of liver enzyme abnormalities in patients with IBD is provided based on the predominant enzyme elevation pattern (hepatocellular vs cholestatic), before presenting a working scheme for the prevention of hepatitis B virus (HBV) reactivation in patients with IBD receiving immunosuppressive medications. Finally, we specify several laboratory alterations seen in patients with IBD that can potentially interfere with the interpretation of liver function tests, before defining the specific circumstances when a referral for a hepatological consultation is required for further assessment.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, recurrent and debilitating gastrointestinal condition of unclear aetiology, with the principal forms being Crohn's disease (CD) and ulcerative colitis (UC). Multisystemic involvement is a chief feature of both CD and UC, and several organ systems may be involved throughout the course of the disease. Hepatobiliary disorders (HDs) are common manifestations of IBD, and 5% of patients with IBD will go on to develop the chronic liver disease.[1 2] The prevalence of HDs in IBD is variably reported, probably due to the wide spectrum of HDs and the various definitions employed across different studies. In fact, when a transient elevation in liver function tests is also considered, then the prevalence rises to 50%.[3] The pathogenesis of liver injury in IBD is poorly understood, but immunological, genetic and environmental factors may contribute to the development of HDs.[4] Clinically, the presentation of HDs may range from an incidental finding of an abnormal liver function test in an asymptomatic patient to severe, life-threatening liver failure. These manifestations may be linked to IBD in several ways[1]: disorders that have a proven association with IBD and possibly a common pathophysiology, including primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH) and IgG4-related cholangitis[2]; diseases directly and structurally related to intestinal inflammation, including portal vein thrombosis (PVT), liver abscesses and granulomatous hepatitis[3]; diseases related to adverse effects of IBD treatment, including drug-induced liver injury (DILI) and hepatitis B reactivation due to immunosuppressants; and[4] disorders linked to the metabolic consequences of IBD, including cholelithiasis, non-alcoholic fatty liver disease (NAFLD) and amyloidosis. Importantly, multiple HDs may coexist in the same patient. This is true especially with the rising incidence of NAFLD as this disorder may coexist with AIH/DILI, underscoring the importance

of liver biopsy in these cases. Clinical presentations, hallmark laboratory findings and the diagnosis of the disorders mentioned above are briefly summarised in table 1, while common drugs used to treat IBD and their liver-related adverse events are summarised in table 2.

A full description of HDs in IBD is beyond the scope of this review, and they have been detailed in several reviews published in recent years.[5–10] The main purpose of this current paper is to provide the clinician with practical guidance on the approach and evaluation of abnormal liver enzymes and suspected hepatobiliary involvement in a patient with IBD.

APPROACH TO ELEVATED LIVER ENZYMES IN PATIENTS WITH IBD

As HDs are common in patients with IBD, every gastroenterologist should possess a basic toolbox for the evaluation of liver test abnormalities in this specific patient population. Liver enzyme levels are routinely obtained for patients with IBD and should be specifically requested for those who complain of pruritus, abdominal pain, jaundice or malaise. Abnormal liver enzyme tests only rarely represent a medical emergency; however, it is important that every gastroenterologist is able to recognise clues and signs of such emergencies in a timely manner in order to refer these cases to emergency care as soon as possible. Medical emergencies presenting with abnormal liver enzymes include[1]: acute liver failure[11 12] (eg, secondary to DILI/viral infection)[2]; ascending cholangitis, especially in patients with PSC[3 13] a liver abscess[14]; and[4] pregnancy-related emergencies,[15] which include haemolysis with elevated liver enzymes and low platelets, and the acute fatty liver of pregnancy. Thus, indications that necessitate a referral to emergency care include: encephalopathy and/or asterixis, sepsis, right upper quadrant tenderness/mass with fever, and pregnancy with jaundice, thrombocytopaenia or haemolysis.

After excluding the above-mentioned rare emergencies, a reasonable next step is to repeat the blood liver enzyme panel in order to confirm a persistent abnormality, as the elevation of liver enzymes is often transient. For a thorough hepatic evaluation, a basic panel of laboratory tests should include levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK-P), gamma glutamyl transferase (GGT), and bilirubin, together with tests of synthetic function, including albumin and the prothrombin time (PT)/international normalised ratio (INR). Initially, the most intuitive and logical approach to persistently abnormal liver enzymes is to differentiate between a hepatocellular (ALT/AST) and cholestatic (ALK-P/GGT) pattern of abnormality, as these point towards a different set of differential diagnoses (table 3).

HEPATOCELLULAR ENZYME ELEVATION WORKUP

As DILI is a common reason for hepatocellular enzyme abnormality,[16 17] it is fundamental to obtain a thorough medication history, including the exact time when each medication was commenced. In addition to regular medications, enquiries concerning intermittent medication use (eg, analgesics and antibiotics) and herbal/complementary medicine ingestion are of major importance. As there are no specific tests to confirm DILI, this diagnosis relies on the exclusion of other HDs and the resolution of enzyme elevation after the withdrawal of a suspected drug. Exclusion of viral hepatitis is also important and can be achieved by virus serology testing for antibodies against the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) and when there is a compatible clinical scenario also hepatitis A virus (HAV), hepatitis E virus (HEV)/HEV-RNA and cytomegalovirus/Epstein-Barr. An upper abdominal ultrasound should be ordered early and examined for liver parenchymal abnormalities (eg, abscess and steatosis), vascular lesions (PVT) or biliary disorders (eg, choledocholithiasis). Subsequently, and after excluding the disorders listed above, a further evaluation for less common aetiologies is warranted. This would include serology for autoimmune hepatitis, such as antinuclear antibody (ANA), antismooth muscle antibody (ASMA), antiliver kidney microsomal antigen (LKM), antisoluble liver antigen (SLA) and immunoglobulin G (IgG) levels, including IgG4. As coeliac disease is more prevalent in patients with IBD,[18] a serological evaluation including antitissue transglutaminase and antiendomysium antibodies should be ordered. Assessment for rare metabolic diseases, such as Wilson's disease, hereditary fe (HFE) haemochromatosis and alpha-1 antitrypsin deficiency, is also reasonable. If this evaluation is negative or there is a need to confirm a diagnosis of AIH/NASH, then the next step is to perform a liver biopsy. A summary of this stepwise approach for the evaluation of hepatocellular enzyme elevation in patients with IBD is depicted in figure 1.

CHOLESTATIC ENZYME ELEVATION WORKUP

When approaching persistent cholestatic enzyme elevation in patients with IBD, it is worthwhile to start by obtaining a thorough medication history as stated above. Thiopurines are the main class of drugs prescribed in IBD which can potentially cause cholestasis.[19] Moving on, the main focus should be on a formal assessment of the biliary tree searching for PSC. This is usually accomplished using magnetic resonance cholangiography (MRC), which enables a non-invasive high-quality visualisation of the biliary tree including potential pathologies such as strictures and dilations characteristic of PSC, stones, dominant strictures and so on. Given the availability and widespread use of MRC, the role of endoscopic retrograde cholangiography (ERC) has diminished and this procedure is currently reserved for interventional purposes,

Table 1 Hepatobiliary disorders in IBD

Disease	Clinical presentation	Diagnosis	Prevalence (CD vs UC)	Management	Complications
Primary sclerosing cholangitis	Asymptomatic Pruritus Fatigue Weight loss Hepatomegaly Splenomegaly Jaundice Cholangitis	Biochemical markers of cholestasis MRCP/ERCP Liver biopsy (concentric fibrosis, onion-skin)	UC>CD	Symptomatic relief Treat complications Liver transplantation	Cirrhosis Liver failure Portal hypertension Cholangitis Cholangiocarcinoma Colorectal cancer Gallbladder stones and malignancy
Autoimmune hepatitis	Asymptomatic to acute liver failure Fatigue Weight loss Fever Hepatomegaly Abdominal pain Splenomegaly Jaundice	Increased hepatocellular enzymes High IgG Autoantibodies (ANA, ASMA, anti-LKM, anti-SLA) Liver biopsy (interface hepatitis)	N/A	Immunosuppressants (steroids, azathioprine)	Cirrhosis Liver failure Portal hypertension Hepatocellular carcinoma
IgG4-related cholangitis	Cholangitis Pruritus Jaundice Abdominal pain	High serum IgG4 level Liver biopsy (IgG4-positive plasma cells)	N/A	Steroids Immunomodulators	Cirrhosis Liver failure Portal hypertension
Granulomatous hepatitis	Asymptomatic Fever Abdominal pain Hepatomegaly Splenomegaly	Biochemical markers of cholestasis Liver biopsy (granuloma formation)	CD~UC	Treat underlying cause Glucocorticoids	Liver failure (rare)
Hepatic amyloidosis	Asymptomatic Abdominal pain Hepatomegaly	Elevated ALK-P levels Liver biopsy (positive congo red stain)	CD>UC	Treat underlying cause Colchicine	Rare
Cholelithiasis	Asymptomatic Cholecystitis Cholangitis	Elevated cholestatic liver enzymes Ultrasound (thickened bladder wall, dilated bile ducts)	CD>UC	Cholecyctectomy (in case of complications)	Cholecystitis Cholangitis Pancreatitis
Non-alcoholic fatty liver disease	Asymptomatic Hepatomegaly	Elevated hepatocellular enzymes Ultrasound (echogenic liver) Liver biopsy	N/A	Treat metabolic syndrome Withdraw steroids and MTX	Cirrhosis Liver failure Portal hypertension Hepatocellular carcinoma
Pyogenic liver abscess	Fever Abdominal pain Constitutional symptoms	US/CT Elevated cholestatic enzymes	CD>UC	Antibiotics Drainage	Rupture and sepsis
Portal vein thrombosis	Asymptomatic Abdominal pain Fever	US Doppler CT	CD~UC	Portal hypertension Variceal bleeding	Anticoagulation

ALK-P, alkaline phosphatase; ANA, antinuclear antibody; ASMA, antismooth muscle antibody; CD, Crohn's disease; LKM, liver kidney microsomal antibody; MTX, methotrexate; SLA, soluble liver antigen; UC, ulcerative coliti; US, ultrasound.

Table 2 Drugs used in IBD ant their hepatic complications

Hepatic injury	Drug
Drug-induced hepatitis	Azathiopirine/6-MP Methotrexate 5-Amino salyclic acid Cyclosporine Anti-TNF Anti-integrins
Drug-induced cholestasis	Azathioprine/6-MP Anti-TNF
Fibrosis/cirrhosis	Methotrexate
Reactivation of HBV	Anti TNF therapy Steroids
Granuloma formation	Sulfasalazine
SOS	Azathiopirine/6-MP
NRH	Azathiopirine/6-MP
Peliosis hepatis	Azathiopirine/6-MP
Steatohepatitis	Methotrexate Steroids Parenteral nutrition

IBD, inflammatory bowel disease; 6-MP, 6-mercaptopurine; NRH, nodular regenerative hyperplasia; SOS, sinusoidal obstruction syndrome; TNF, tumour necrosis factor.

such as stone extraction or stricture dilation.[20] There is also a role for endoscopic retrograde cholangiopancreatography (ERCP) in cases of a suspected cholangiocarcinoma, where brushing for cytology may aid in the diagnosis. When no biliary tree abnormalities are found on MRC, a liver biopsy should be performed to exclude a small-duct PSC variant, as well as other cholestatic diseases, such as PBC, amyloidosis or granulomatous hepatitis. A summary of this stepwise approach for the evaluation of cholestatic enzyme elevation in patients with IBD is depicted in figure 1.

CAUTIONS ON BLOOD TEST INTERPRETATION

The PT represents an important parameter of the liver synthetic function and is prolonged in cases of severe liver disease due to the reduced synthesis of coagulation factors. However, in CD there may be other reasons for PT prolongation, with perhaps the most important being a vitamin K deficiency due to reduced absorption in the diseased small bowel.[21–23] A simple and practical means to differentiate between PT prolongation due to liver dysfunction and due to vitamin K deficiency is via an intravenous vitamin K trial, as correction of the PT would point to a vitamin K deficiency.

Table 3 Common causes of liver enzyme abnormality in IBD

Hepatocellular enzyme abnormality	Cholestatic enzyme abnormality
DILI	PSC
Steatosis/NASH	DILI
Viral hepatitis	Primary biliary cholangitis
Auto immune hepatitis	Granulomatous hepatitis
TPN	Choledocholithiasis
Celiac disease	Amyloidosis
	TPN
	AIH/PSC overlap

DILI, drug-induced liver injury; IBD, inflammatory bowel disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; TPN, total parenteral nutrition.

The interpretation of low albumin levels should also be approached with caution, since reduced albumin levels in patients with IBD may be due alternative aetiologies other than a reduced liver synthetic reserve. Marked systemic inflammation, protein malnutrition and protein-losing enteropathy[24] may all account for extreme hypoalbuminaemia in the absence of a significant liver disease.

Occasionally ALK-P, usually a marker of cholestasis, may be elevated in patients with IBD due to increased levels of the bone isoenzyme and not due to cholestasis. This may occur in patients with significant bone disease and healing fractures due to increased osteoblast activity.[25–28] A differentiation between ALK-P elevation due to cholestasis and due to bone disease can be made by measuring GGT levels which are elevated in cholestasis, or on rare occasions, by measuring the different levels of ALK-P isoenzymes.

PREVENTING HEPATITIS B VIRUS REACTIVATION IN IBD

It has been well established that immune suppression may cause hepatitis B virus (HBV) reactivation, potentially leading to acute liver failure and death. Such reactivation has been mostly reported in patients receiving oncological treatments, but recent retrospective cohort studies have assessed the risk of reactivation specifically in the IBD population,[29–32] reporting that the risk of reactivation is related to several factors[1]: HBV infection status, including HBV-DNA levels[2]; number of immunosuppressants used; and[3] duration of immunosuppression. The administration of prophylactic antiviral therapy to patients at risk of reactivation has been widely advocated by the leading societies.[33 34]

According to the European Crohn's and Colitis Organisation (ECCO), serology for HBV should be determined immediately after a diagnosis of IBD,[35] including levels of HBsAg, total hepatitis B core (HBc) and hepatitis B surface (HBs) antibodies. Any patient with a negative serology should receive an HBV vaccination, taking into account that high dose vaccines may be needed in order to achieve an anti-HBs response in these immunocompromised patients. All patients positive for HbsAg who are candidates for immune suppression should be started on antiviral treatment with a nucleos(t)ide analogue (NA) and referred to a hepatologist for further assessment.[36] NAs are best started 2 weeks prior to the introduction of immunomodulators and should be continued for 12 months after their

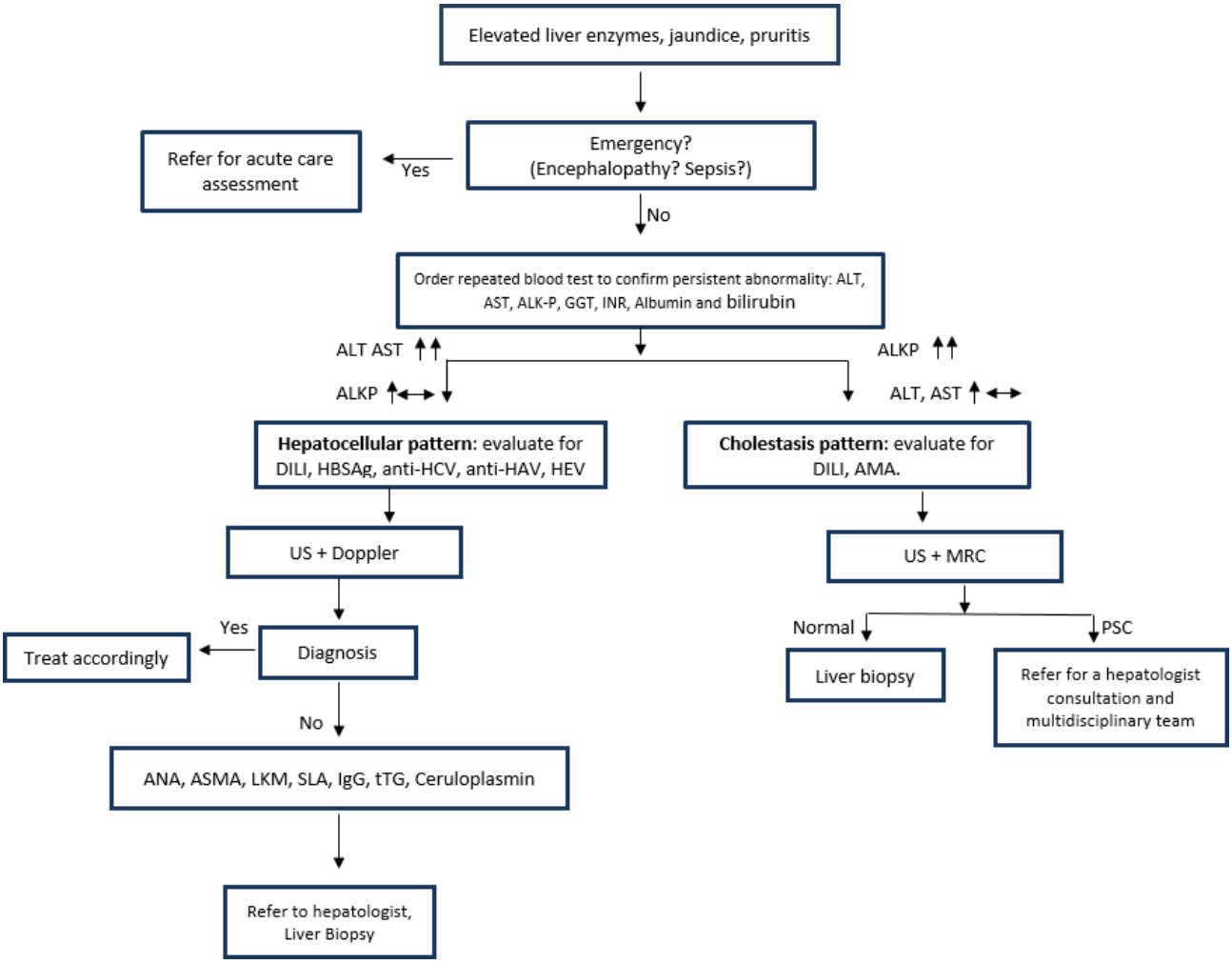

Figure 1 A stepwise approach for the evaluation of liver enzyme abnormality in patients with IBD. ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, antismooth muscle antibody; AST, aspartate aminotransferase; DILI, drug-induced liver injury; GGT, gamma glutamyl transferase; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; IBD, inflammatory bowel disease; IgG, immunoglobulin G; INR, international normalised ratio; LKM, liver kidney microsomal antibody; MRC, magnetic resonance cholangiography; PSC, primary sclerosing cholangitis; SLA, soluble liver antigen; US, ultrasound.

withdrawal. Patients who are HbsAg negative and anti-HBc positive are generally at a lower risk for reactivation, and therefore a pre-emptive rather than prophylactic strategy is usually implemented. This strategy includes monitoring of HBsAg and HBV DNA every 1–3 months during and after immunosuppression and commencing NA treatment when HBV DNA is detectable or there is HBsAg seroconversion.[37 38] A practical approach to the prevention of HBV reactivation in IBD is illustrated in figure 2.

WHEN TO REFER TO THE HEPATOLOGY CLINIC

Whenever a caring gastroenterologist encounters evidence of advanced liver disease, a referral to an expert hepatologist is essential, this includes[1]: clinical signs of cirrhosis on physical examination[2]; laboratory markers of advanced synthetic dysfunction (prolonged INR, hypoalbuminaemia and elevated bilirubin levels)[3]; signs of portal hypertension (thrombocytopaenia, ascites, splenomegaly and oesophageal/gastric varices); and[4] evidence or suspicion of PSC on imaging. Moreover, whenever there is evidence of persistent liver enzyme abnormality of unclear aetiology, a referral for a hepatologist consultation is reasonable for further evaluation, including the possibility of performing a liver biopsy (box 1). In all cases of a significant HD in a patient with IBD and especially in the case of PSC, a multidisciplinary approach, including a gastroenterologist, hepatologist and invasive endoscopist and radiologist, should be implemented.

CONCLUSIONS

The topic of hepatobiliary manifestations in patients with IBD has been extensively reviewed elsewhere, and consequently, we aimed to provide clinicians

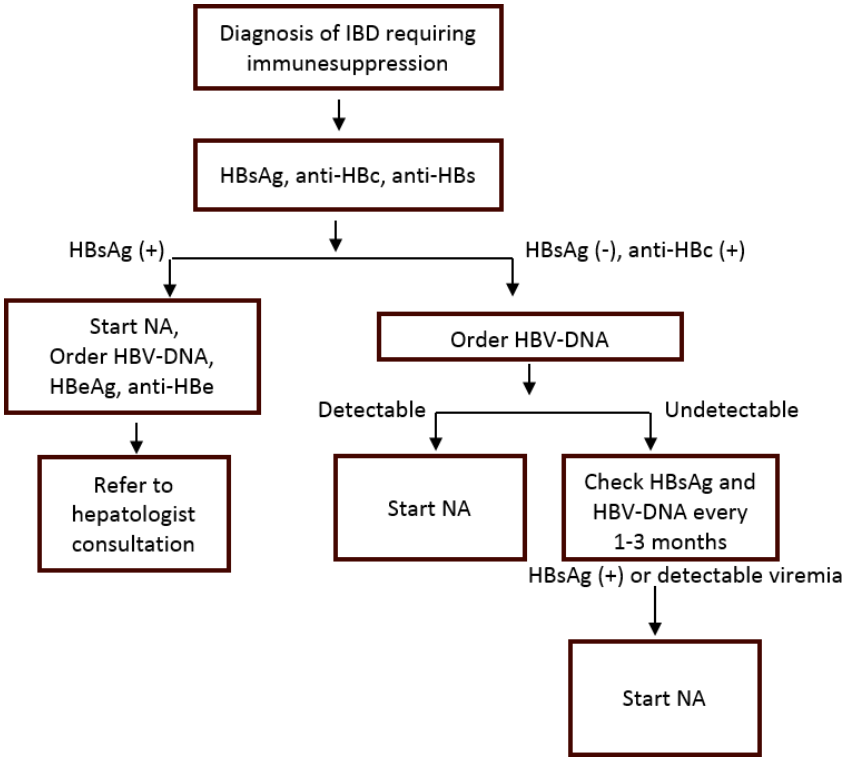

Figure 2 Prevention of HBV reactivation in IBD. HBc, hepatitis B core; HBe, hepatitis B envelope; HBeAg, hepatitis B envelope antigen; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IBD, inflammatory bowel disease; NA, nucleoside/nucleotide analogue.

treating patients with IBD and the commonly encountered abnormal liver function tests with a practical, clinically oriented approach that may aid in daily practice and decision-making. Specifically, we have emphasised certain checkpoints during the workup when patients should be referred for emergency care or expert hepatological evaluation. Moreover, we have provided a practical working scheme for the prevention of HBV reactivation in patients with IBD receiving immunosuppressive treatment. Given the abundance of scientifically oriented, exhaustive reviews on the topic of HDs in IBD, we believe that concise practical guidance as offered in this paper may have added value for the practising gastroenterologist.

Box 1 When to refer for a hepatologist consultation

- Clinical signs of cirrhosis
- Liver synthetic dysfunction/hyperbilirubinaemia
- Laboratory or radiologic sings of portal hypertension
- Confirmed/suspected PSC
- Persistent liver enzyme abnormality of unknown aetiology
- Positive serology for HBV

HBV, hepatitis B virus; PSC, primary sclerosing cholangitis.

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