Liver Disease in Pediatric Inflammatory Bowel Disease

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Pamela L. Valentino and Binita M. Kamath

Introduction

Hepatic involvement in inflammatory bowel disease (IBD) is a spectrum that ranges from transient abnormalities in laboratory values to liver diseases that can require transplantation. There is no standard of care in the diagnostic approach to elevated liver biochemistry in IBD. While it is appropriate to minimize invasive investigations, this should not be at the expense of overlooking a diagnosis of chronic liver disease. The chronic hepatic diseases associated with IBD include primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and autoimmune sclerosing cholangitis (ASC, an overlap syndrome in which features of both PSC and AIH are detected on laboratory, histological, and cholangiographic investigations [1]). Medications used in IBD treatment can also cause significant hepatotoxicity, and thus require close monitoring during their administration. Other hepatobiliary manifestations reported in the IBD literature include cholangiocarcinoma, cholelithiasis, hepatic abscess, hepatic or portal vein thrombosis, fatty liver, and amyloidosis (all of these have been described in children except the last). In this chapter, we will explore hepatic involvement in pediatric IBD in further detail.

Abnormal Liver Chemistry

Abnormal liver biochemistry, in patients with IBD, is a common finding. In adults with ulcerative colitis (UC), 40% of patients can present with abnormal liver enzymes [2]. In one study of 200 adult UC patients, where the outcomes of elevated liver biochemistry were assessed, the investigators identified nonspecific transient increases in 63% of patients, fatty liver disease in 11.2%, PSC in 6.3%, drug toxicity in 6%, and other diagnoses in 13.5%, such as autoimmune hepatitis, chronic hepatitis C infection, and total parenteral nutrition-associated cholestasis. The patients with transient abnormalities in hepatic enzymes all had mild elevations at less than three times the upper limit of normal; however, time to resolution was not reported [2]. In another cohort of 786 adult patients with IBD, 15% developed elevated liver enzymes, of which 2.5% developed PSC, 42.3% had hepatotoxicity from azathioprine (AZA) or 6-mercaptopurine (6MP) use, 40.8% had fatty liver disease, and 28% had no known associated liver disease [3].

There has only been one study to date investigating the prevalence of abnormal liver biochemistry in pediatric IBD patients. Nemeth et al. retrospectively assessed 46 children with IBD and identified 24 patients (52%) who developed elevated liver enzymes at some point over a mean follow-up of 5.2 years [4]. Of the 9 patients with "severe liver involvement," defined as liver enzymes greater than three times the upper limit of normal, eight had biopsies with histologic findings that included bile duct proliferation, portal fibrosis, and/or portal inflammation. Four of the eight patients had changes consistent with a diagnosis of small duct PSC. Of those with "severe liver involvement," more patients were observed to have pancolonic UC as compared to those with distal UC or Crohn disease (CD). Unfortunately, the small number of patients, lack of radiological reporting, and the inability to show statistical differences among the IBD groups were major limitations in this study.

In general, there is a paucity of data regarding the prevalence and natural history of abnormal liver biochemistry in pediatric IBD. The data that exist suggests that up to half of patients with IBD will have abnormal liver enzymes during their disease course, and in the majority, these are transient changes. The limited literature also seems to indicate that if transaminases are less than two times the upper limit of normal for a short period of time (such as less than 4 weeks),

P.L. Valentino, MDCM, FRCP(C)
B.M. Kamath, MBBChir, MRCP, MTR (✉)
Department of Paediatric Gastroenterology, Hepatology, and Nutrition, University of Toronto, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, Canada M5G 1X8
e-mail: pamela.valentino@sickkids.ca; binita.kamath@sickkids.ca

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then observation alone may be appropriate without resorting to invasive investigations.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is an autoimmune cholestatic liver disease characterized by intrahepatic or extrahepatic pericholangitis with progression to multifocal biliary strictures, liver fibrosis, cirrhosis, and complications of portal hypertension [1]. A Canadian study of 49 cases of PSC described an incidence rate of 0.23 cases per 100,000 person-years in children and 1.11 cases per 100,000 person-years in adults [5]. The first reported association between PSC and IBD was by Warren et al. in 1966; they described 42 cases of PSC, 12 of which had concurrent UC [6]. The prevalence of PSC in pediatric IBD has most recently been reported as 1.5% in a study of 1,009 children with IBD across 19 North American centers [7], and as 2.6% in a study of 786 adult patients with IBD in Spain [3]. Pediatric PSC has an equal sex distribution, instead of the male overrepresentation seen in adults [8].

The presentation of PSC can be quite variable: in 47 children with PSC, 40% presented with hepatomegaly, 36% had abdominal pain, 23% had splenomegaly, 19% had pruritus, 17% had jaundice, and 19% were asymptomatic [9]. The previously described Canadian incidence study of patients with PSC identified 73.4% of patients to also have IBD (CD: 19/49, UC: 17/49) [5]. This is consistent with a subsequent study, where the prevalence of IBD in PSC was 68.9% (20/29) [8, 10]. Despite the high prevalence of IBD in PSC patients, the overall frequency of PSC in patients with IBD is quite low. An American multicenter pediatric cohort study of IBD identified PSC in 1.5% of 1009 IBD patients (CD: 7/728, UC: 8/281) [7]. Typically, the IBD phenotype associated with PSC is primarily pancolonic UC with low-grade inflammation, rectal sparing, and backwash ileitis [1, 5, 8, 11]. Cases of Crohn disease (CD) occur as well, and the Canadian PSC incidence study described a variable phenotype: 57.9% (11/19) had enterocolitis, 36.8% (7/19) had isolated colitis, and 5.3% (1/19) had an ileitis without evidence of colonic inflammation [5]. In PSC/IBD patients undergoing proctocolectomy, there is an increased risk of peristomal varices at the ileostomy site, as well as an increased risk of pouchitis after ileal pouch anal anastomosis [1]. Meanwhile, patients with PSC who have underlying mild IBD may be asymptomatic from a GI standpoint. Thus, as stated in the 2010 American Association for the Study of Liver Diseases (AASLD) PSC practice guidelines, a complete screening endoscopy is warranted in all patients with apparently isolated PSC at diagnosis, due to implications for long-term management [1].

Diagnosis of Primary Sclerosing Cholangitis

There are no widely accepted and validated current diagnostic criteria for pediatric PSC; however, there are typical findings on laboratory investigations, cholangiography, and liver biopsy. This disease can be classified as "large duct" PSC, "small duct" PSC, and ASC. The first indication of PSC is often abnormal liver biochemistry. At the time of PSC diagnosis, in the Mount Sinai Medical Centre study, mean serum biochemical values were alanine-aminotransferase (ALT) 233 (±327), aspartate-aminotransferase (AST) 236 (±248), gamma-glutamyltranspeptidase (GGT) 553 (±676), alkaline phosphatase (ALP) 610 (±340), total bilirubin 1.3 mg/dL (±1.9), direct bilirubin level 0.7 mg/dL (±1), and albumin level 3.9 g/dL (±0.5) [9]. In children, serum GGT levels have been regarded as a better screening tool for biliary disease than ALP due to the elevated ALP levels seen with bone growth [1]. Serology can also be helpful in the diagnosis of PSC as these patients have an increased presence of perinuclear-antineutrophil cytoplasmic antibody (p-ANCA) positivity with 67–87% prevalence [12, 13]. In a study of 73 adult patients with PSC at the Mayo clinic, there was no significant difference in ANCA positivity between patients with IBD (81% positive) or without IBD (93% positive) [14]. When reviewing serology results, it appears that the atypical pattern of p-ANCA fluorescence is frequently found in PSC/IBD, with visualization of fluorescent staining at the periphery of the nucleus and multiple foci within the nucleus as well [12]. In the setting of a child with IBD and raised liver enzymes, ANCA testing may be positive; however, its absence is insufficiently robust for the exclusion of a diagnosis of PSC in patients with IBD.

Imaging investigations are crucial to the diagnosis of PSC. An abdominal ultrasound is usually the first-line investigation to assess the biliary tree, look for biliary dilatation or wall thickening, as well as peri-hilar lymph nodes, and screen for other conditions that could be associated with a raised GGT, such as cholelithiasis. The definitive radiological tests are cholangiographic studies, either magnetic resonance cholangiography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) (both of which have superseded the more invasive percutaneous cholangiography). Cholangiography can assess for both intrahepatic and extrahepatic "large duct" involvement, as well as determine if the disease is localized or diffuse (Fig. 11.1). The Majoie classification for cholangiography has been used in previous reports to categorize the extent and localization of disease (Table 11.1). Typical findings include biliary duct wall irregularities with stenosis and dilatation, as well as reduction of intraparenchymal arborization [15]. In a prospective pediatric study by Ferrara et al. in 2002, 21 patients aged 7–14 years, with

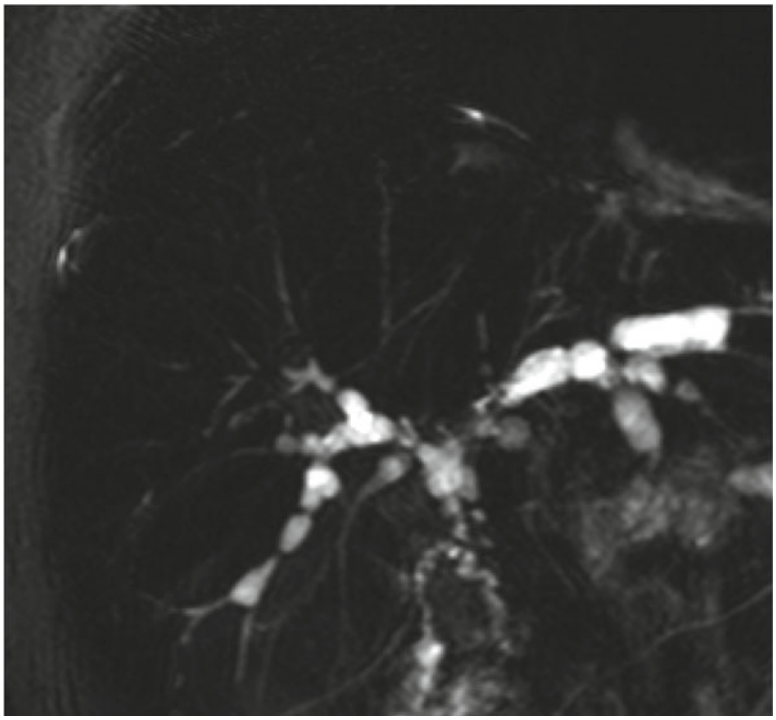

Fig. 11.1 MRCP of a 17-year-old patient with PSC. Note the intrahepatic and extrahepatic beading of the biliary tree with sequential strictures and saccular dilatations. The common bile duct wall is also thickened

Table 11.1 The Majoie classification of cholangiographic findings in primary sclerosing cholangitis [15]

Intrahepatic	Extrahepatic
Minimal strictures with normal diameter of biliary ducts or minimal dilatation	Duct contours have slight irregularities without stenosis
Multiple strictures with saccular dilatations and reduction of intraparenchymal arborization	Segmental stenosis of the biliary duct
Lack of visualization of one of the main hepatic ducts	Almost the entire biliary duct is stenotic
	Pseudo-diverticular out-pouching of the biliary ducts with irregular duct margins or diameter

suspicion of PSC, were all evaluated by ERCP, MRCP, and liver biopsy [16]. Three patients were noncooperative and could not complete the MRCP protocol. MRCP showed abnormalities consistent with PSC in 13/21 (62%) patients, while ERCP diagnosed PSC in 16/21 (76%) patients. In the five patients with normal MRCP imaging, no abnormalities were identified on ERCP. In this study, the specificity of MRCP for PSC was 100% with a sensitivity of 81%. However, the sensitivity was reduced by the inability for the children to complete the exam and not the intrinsic ability for the modality to identify abnormalities. While both MRCP and ERCP are of high quality, ERCP carries the risks of pancreatitis, cholangitis, hemorrhage, duodenal perforation, and death [17, 18]. Thus, MRCP, with sedation when appropriate, can be recommended as a reliable primary diagnostic imaging modality in PSC.

A liver biopsy is indicated in a child with IBD and persistently raised liver enzymes, particularly if the GGT is also elevated. The liver biopsy should be performed in this setting regardless of the radiological findings as PSC may involve the smallest biliary ducts and only be detected microscopically. A biopsy is also needed to identify any evidence of ASC, which requires a different therapeutic approach (see section "Autoimmune Sclerosing Cholangitis"). The histopathology in small duct PSC can reveal acute and/or chronic cholangitis, fibrosis, or cirrhosis (Table 11.2) [19]. A finding known as "onion skinning" is the most characteristic histopathologic lesion of PSC, which describes concentric periductal fibrosis (Fig. 11.2).

Table 11.2 Ludwig histopathological classification in PSC [89]

Portal tract fibrosis with cholangitis and portal hepatitis
Periportal fibrosis or hepatitis
Septal fibrosis and/or bridging fibrosis
Cirrhosis

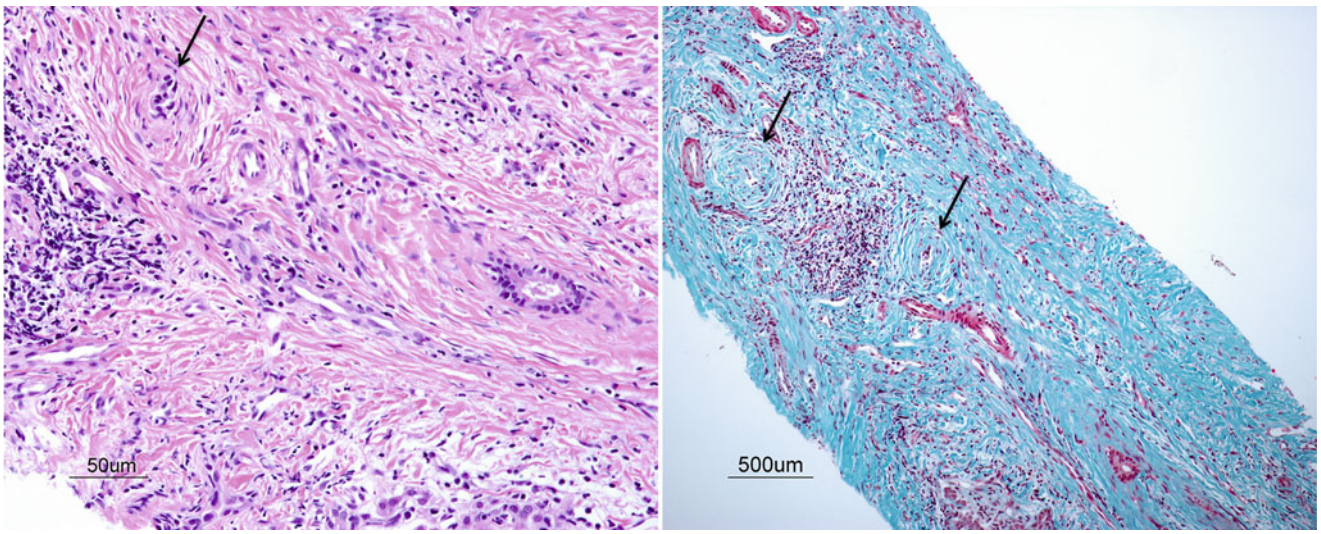

Fig. 11.2 Liver histopathology from a 15-year-old boy with PSC and UC. On H&E staining (**a**) and trichrome staining (**b**) there is evidence of periductal fibrosis ("onion skinning," arrow) with degeneration and atrophy of the ductal epithelium of some cholangioles. Also note the severe bridging fibrosis with fibrous septae linking portal tracts. (Images courtesy of Dr. Ernest Cutz, MD, FRCPC, Hospital for Sick Children, University of Toronto)

Treatment of Primary Sclerosing Cholangitis

Unfortunately, pharmacological treatments for PSC have been disappointing, as they have not shown a decrease in the rate of disease progression or a change in the rate of survival. Treatment with corticosteroids, penicillamine, and azathioprine have not shown long-term success in improving outcomes in PSC [20, 21]. Tacrolimus has been shown to cause a reduction in ALT and ALP but was poorly tolerated in adults [22]. Mycophenolate mofetil, methotrexate, budesonide, etanercept, pentoxifylline (an anti-TNF agent), and pirfenidone (an antifibrotic agent) have all not shown any short- or long-term benefit [22]. Ursodeoxycholic acid (UCDA), a dihydroxy bile acid, has been the mainstay of medical therapy for PSC, having been shown to decrease the hepatotoxicity of other bile salts, provide a hepato-protective effect, and improve the serum ALT [23, 24]. However, a recent trial of high dose ursodeoxycholic acid (28–30 mg/kg/day) vs. placebo in adults revealed an association with higher rates of liver transplantation and death, suggesting toxicity at these doses [22]. The AASLD guidelines recommend against the use of UCDA in adults with PSC; however, there is insufficient evidence to establish firm guidelines for or against the use of this therapy in children [1]. Many pediatric hepatologists continue to utilize ursodeoxycholic acid at lower doses (up to 20 mg/kg/day divided twice daily), as there may be potential benefit for improving outcomes. Oral vancomycin, at 50 mg/kg/day, has also been reported to improve liver biochemistry and reduce inflammation on liver biopsy in children with both UC and PSC [25]. Of note, those with liver cirrhosis on biopsy did not show a statistically significant degree of improvement. Furthermore, survival outcomes after long-term vancomycin use have not been reported. Minocycline and metronidazole have also been shown to reduce abnormal liver biochemistry in PSC [22]. These data suggest that antibiotics can decrease inflammation in the PSC liver, implicating bacteria in the pathogenesis of PSC. Overall, the management of PSC involves close cooperation with a hepatologist, limitation of exposure to hepatotoxic medications, as well as regular monitoring of liver biochemistry.

While MRCP is a noninvasive diagnostic tool, which is desirable in pediatrics, an ERCP has the advantage of providing therapeutic potential. In the setting of a localized large duct stricture, a biliary intervention via ERCP can ameliorate the course of disease. A bile duct stricture in PSC can lead to worsening liver function with progression to cirrhosis as well as increased risk of bacterial cholangitis [26]. With ERCP-mediated balloon dilatation ± stenting of a stenotic duct, there can be improvement of liver biochemistry, including bilirubin, decreased jaundice and pruritus (if present), and improved survival [27].

Outcomes in Primary Sclerosing Cholangitis

Primary sclerosing cholangitis causes liver fibrosis and can progress to liver cirrhosis, as well as hepatic failure. Angulo et al. in 2002 compared patients with small-duct PSC ($N=18$) vs. classic PSC ($N=36$), and found that survival with native liver was significantly higher in the group with small duct PSC ($p=0.04$), suggesting a better prognosis with this pattern

of disease [28]. A small group of patients (3/18) with small-duct disease were found to develop classic PSC during follow-up. It is unclear if the two patterns of disease are on a continuum or are distinct entities. In a single-centre study from Mount Sinai, 19% of children required liver transplantation [9]. A recent study from the SPLIT (Studies of Pediatric Liver Transplantation) database assessed the outcomes of children with PSC following liver transplantation [29]. The patient survival was 98.7% at 1 year and 86.6% at 5 years, compared to 94.3 and 88.2%, respectively, in the non-PSC group. Meanwhile, the graft survival was 93% at 1 year and 76.1% at 5 years, compared to 90 and 79.5%, respectively, in the non-PSC group. There were no significant differences in patient and graft survival between the two groups. However, with a univariate analysis, mortality was significantly higher in PSC patients with a diagnosis of IBD pretransplant. Of potential interest, a recurrence of PSC was diagnosed in 6 of 61 patients (9.8%) over a median follow-up time of 36.6 ± 32.7 months, and all who recurred had been diagnosed with concurrent IBD pretransplant. In a prospective comparison of adult PSC patients with a dominant stricture of the biliary duct, the transplant-free survival after 18 years of follow-up was poorer in the group of patients with concomitant UC (23 vs. 77.8%, respectively, $p = 0.045$) [30]. Proctocolectomy has not shown any difference in survival or decrease in the complications of portal hypertension, in adult patients with concomitant PSC/UC [31]. There is insufficient evidence to recommend colectomy in children with PSC/UC to prevent progression of PSC disease or liver transplantation.

Another important complication of PSC is an increased risk of cholangiocarcinoma. In a study of 1,274 adult patients with UC, the overall prevalence of this malignancy was 0.3%; however, in patients with concurrent PSC, the prevalence was 13% [32]. Furthermore, patients with PSC and a dominant bile duct stricture have a statistically significant increased risk of cholangiocarcinoma, as well as colorectal carcinoma, if they have concurrent IBD [30]. These cancers are rare in children, and the AASLD guidelines do not recommend increased surveillance in the pediatric population with PSC/IBD, while adult screening with colonoscopy is recommended every 1–2 years after diagnosis [1].

Other Autoimmune Liver Diseases

Autoimmune Hepatitis

AIH is an autoimmune disorder characterized by hepatic inflammation and it can be categorized according to the type of autoantibodies present. In AIH type 1, antinuclear antibodies and/or smooth muscle antibodies (ANA/SMA) are frequently positive, while in AIH type 2 antibodies to liver/kidney microsomal type 1 (LKM1) can be positive. Children can be seronegative, or have antibodies titers that are lower than in adults such that 1:20 for ANA or SMA, and 1:10 for anti-LKM1 are significant levels in children, while in adults 1:40 is clinically relevant, as per AASLD guidelines [33]. Both types of AIH favor a female predominance (75%), have elevated immunoglobulin G (IgG) titers, and in children, progress with a similar disease course. However, patients with type 2 disease frequently present at a younger age (median age: 7.4 vs. 10.5 years) [34]. The clinical presentation can include nonspecific symptoms such as fatigue, nausea, abdominal pain, and arthralgia, while others may present with jaundice, acute hepatitis, or even liver failure [33]. A liver biopsy is necessary to confirm the diagnosis as well as to rule out other causes of liver biochemistry derangement. Findings include portal tract inflammation, lobular hepatitis, interface hepatitis, and cirrhosis [34]. Plasma cell infiltration of the portal tracts are commonly associated with the periportal hepatitis; however, in some patients with AIH this may be absent [33]. Autoantibodies are integral to making a diagnosis of AIH as described earlier. However, ANCA can also be frequently positive in AIH type 1. In one study within adults, 65% of 46 patients with AIH type 1 were ANCA positive; however, none of the 19 patients with AIH type 2 were positive [35]. The International Autoimmune Hepatitis Group (IAIHG) developed and revised a scoring system for the diagnosis of AIH in 1999 that incorporates many of these parameters [36]. Some indices included in the score are liver biochemistry, autoantibodies, viral serology status, drug or alcohol use, and findings on liver histology. With a total AIH score above 15 points, the diagnosis of AIH is considered definite, while with a score between 10 and 15 points, AIH is probable. Ebbeson and Schreiber retrospectively evaluated this tool in 2004, in children with diagnoses of AIH ($N = 21$) and sclerosing cholangitis ($N = 7$) [37]. They found 85.7% (18/21) of patients clinically diagnosed with AIH to have "definite AIH" according to the IAIHG tool, while 14.3% (3/21) had "probable AIH." Of the patients with sclerosing cholangitis, all four with isolated cholangitis were found to have a score of <10 points, while the three patients with overlap disease (ASC) had scores consistent with definite AIH. This study evaluated a small group of patients; however, it suggests that patients with hepatic inflammation consistent with AIH may be reliably differentiated from isolated PSC with this tool. However, this tool is not specific enough to rule out ASC in patients who appear to have AIH.

Immunosuppressive therapy is the standard of care for AIH in children due to the increased disease severity at onset as well as the aggressive course with poorer long-term outcomes observed if treatment is delayed [33]. Prednisone (1–2 mg/kg/day) is used to induce remission and can be continued at a lower dose (2.5–5 mg/day) for long-term maintenance. Azathioprine is usually added for maintenance

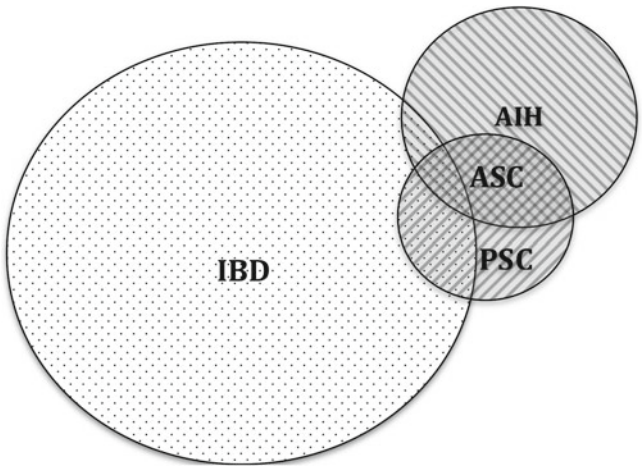

Fig. 11.3 Overlap between IBD and chronic liver diseases. This Venn diagram represents the relationship between IBD and chronic liver diseases, as well as the perceived prevalence (not drawn to scale)

treatment, as recommended in AASLD guidelines [33]. In children who fail to respond to these medications, additional options include MMF, cyclosporine, and tacrolimus, although the evidence for use of these agents is based on case series and not randomized trials comparing to standard treatment regimens [33]. After successful therapy for 2–3 years, with persistent normalization of liver biochemistry, immunosuppression discontinuation may be attempted after a liver biopsy has confirmed complete histologic remission of disease.

Other autoimmune diseases, such as hypothyroidism, occur in 20–22% of patients with AIH [34]. Of particular relevance here is the overlap with IBD. Within the IBD population, AIH is an uncommon finding: 0.9% of 1,009 children in a multicenter study with IBD, and 1.4% with UC had a "chronic active hepatitis." [7] However, within the pediatric AIH population, IBD is more frequently diagnosed with a prevalence of 12–20% of children with AIH in one study, advocating a low index of suspicion for IBD in this population [34] (Fig. 11.3).

Autoimmune Sclerosing Cholangitis

Autoimmune sclerosing cholangitis occurs almost exclusively in children and young adults [19, 38, 39]. It is diagnosed when features of both PSC and AIH are present on liver biopsy and imaging; however, as in PSC, there are no specific diagnostic criteria. These patients have an increased frequency of concomitant IBD (44%) compared with both PSC and AIH [34]. In one study at King's College in London, children referred with biochemical evidence of liver disease as well as positive autoantibodies were prospectively assessed [19]. Of the 76 patients referred between 1984 and 1997, 55 patients, who were investigated with both a liver biopsy as well as cholangiography, were included in the study. A diagnosis of ASC was attributed to patients who had histological evidence of AIH and cholangiographic evidence of intrahepatic or extrahepatic sclerosing cholangitis. Of note, this definition of ASC may have precluded a diagnosis of small duct sclerosing cholangitis, overlapping with AIH, which would only be diagnosed histologically. Nonetheless, 27/55 (49%) patients were diagnosed with ASC while 28/55 (51%) of patients were diagnosed with AIH. There were no significant differences in the median age at diagnosis (10.5 years ASC, 11.8 years AIH) or female preponderance (55% ASC, 79% AIH). Signs and symptoms were also similar at diagnosis with the majority presenting with jaundice, hepatomegaly, and splenomegaly, except for pruritus, which was significantly increased in AIH (25 vs. 7% in ASC). Laboratory investigations at baseline were mostly similar between ASC and AIH except for median AST (102 IU/L in ASC, 333 IU/L in AIH, $p=0.002$), median total bilirubin (1.2 mg/dL or 20 μmol/L in ASC, 2.0 mg/dL or 35 μmol/L in AIH, $p=0.04$), and ANCA positivity (74% in ASC, 36% in AIH, $p=0.009$). In children with ASC, ANA and SMA titers were positive in 20/27 (74%) of patients and LKM1 antibodies were present in 1/27 (4%) of patients. Autoimmune disorders in first-degree relatives were also significantly increased in AIH (71 vs. 37% in ASC). On histology, there was increased acute and/or chronic cholangitis in patients with ASC compared to AIH (35 vs. 12%, respectively, $p=0.049$) but decreased portal tract inflammation (58 vs. 92%, respectively, $p=0.004$).

Routine sigmoidoscopy with rectal biopsies was also performed in all patients within this cohort except for one who refused. IBD was diagnosed in 44% of patients with ASC. This was significantly different from the 18% of patients with AIH who were also diagnosed with IBD. There was potential for the underestimation of the prevalence of IBD in this population as the colitis associated with PSC frequently has rectal sparing and only rectal biopsies were taken in this cohort.

On treatment with immunosuppression, 100% of patients with AIH experienced normalization of liver biochemistry, while in ASC, 83% had normal AST levels, and 73% had normal bilirubin. Meanwhile, there was no significant difference in rate of relapse with 36% of AIH patients versus 33% of ASC patients experiencing at least one episode of relapse. Of those patients with ASC who had follow-up cholangiography, 8/17 had progression of intrahepatic and extrahepatic biliary disease. Upon follow-up, all patients were alive and no patients with AIH required liver transplantation in this cohort. Meanwhile, 4/27 (15%) of children with ASC required liver transplantation. This study suggests that children with AIH/IBD should be screened with cholangiographic imaging to assess for PSC, as this could have implications for a poorer prognosis [19]. This is clearly stated in the AASLD practice guideline in 2010 [33].

Conversely, children with cholangiographic evidence of PSC should undergo liver biopsy and autoantibody detection to screen for evidence of overlap, as ASC requires immunosuppressive treatment [1, 33]. According to AASLD guidelines, though based on limited evidence, treatment with corticosteroids (±azathioprine) may be attempted in PSC patients with elevated IgG, positive autoimmune antibodies, and interface hepatitis on liver biopsy.

Drug Hepatotoxicity

Methotrexate

Methotrexate, an anti-inflammatory that inhibits synthesis of purines and pyrimidines via inhibition of the folate metabolism, has been found to maintain remission in IBD [40]. Previous use in rheumatological diseases has identified a hepatotoxic effect of methotrexate, with reports of elevation of liver biochemistry and hepatic fibrosis (15% prevalence) [41]. The use of methotrexate in psoriasis came with the recommendation in 1996 to perform protocol liver biopsies after administration of a cumulative dose of 1,500 mg [42]. With further investigation, this practice was changed. Updated publications for psoriasis and juvenile idiopathic arthritis have included recommendations for biopsies in cases of refractory abnormal liver biochemistry despite decreased or held doses of methotrexate. A biopsy can also be considered with higher cumulative doses of methotrexate (3.5–4.0 g) [43, 44]. Subsequent studies in adults and children with IBD have also not supported protocol liver biopsies although the numbers of patients in each study were limited. The two adult retrospective studies that included the most number of liver biopsies after methotrexate administration (Fournier 2010: $N=17/87$ and Te 2000: $N=20/32$) demonstrated that an increased cumulative dose of methotrexate did not correlate with worse liver histopathology [45, 46]. In the pediatric IBD literature, retrospective studies of methotrexate use have described abnormal liver biochemistry requiring dose reductions or drug discontinuation (Turner 2007: $N=7/60$ and Uhlen 2006: $N=2/61$) [47, 48]. However, liver biopsies were not performed in these cases making it difficult to interpret the exact effect of methotrexate in children with IBD. Previous studies of methotrexate hepatotoxicity have also described hepatic steatosis on liver biopsy. These findings were significantly worse in psoriatic adult patients with obesity ± diabetes mellitus compared to psoriatic patients without these risk factors (and matched for cumulative methotrexate doses) [41, 49]. It is rare for patients to receive baseline liver biopsies prior to methotrexate use. Therefore, the contribution of methotrexate to the degree of steatosis is unclear. Nonetheless, patients with obesity or diabetes mellitus require close monitoring as methotrexate could further exacerbate underlying nonalcoholic fatty liver disease (NAFLD). From the available limited evidence, when starting methotrexate, liver biochemistry should be obtained at baseline and in follow-up: weekly after the initial dose or after changes in doses for the first month, and every 2–3 months thereafter. With development of persistently abnormal liver biochemistry, in consultation with a hepatologist, the dose of methotrexate can be adjusted, or temporarily held with mild to moderate abnormalities (e.g., up to 2–3× ULN, the upper limit of normal), or completely discontinued if highly abnormal (e.g., >5× ULN). Liver biopsies can be reserved for cases of persistently abnormal liver biochemistry or if discontinuation of the methotrexate would be deleterious for the IBD management. Caution should be exerted in prescribing methotrexate to patients with underlying liver disease and avoided in children with PSC unless under exceptional circumstances (Table 11.3).

Table 11.3 Drug hepatotoxicity reported in different IBD therapies

Drug	Liver outcome
Methotrexate	Hepatic fibrosis
	Hepatic steatosis
Azathioprine/6-Mercaptopurine	Hepatitis
	Peliosis hepatis
	Veno-occlusive disease
	Severe cholestasis
	Nodular regenerative hyperplasia
	Portal hypertension
5-aminosalicylic acid	Fever, rash, jaundice, hepatomegaly
	Acute liver failure
Anti-TNF, biologic agents	Hepatitis
	Hepatitis B reactivation
	Hepatosplenic T-cell lymphoma
Cyclosporine	Mild elevated liver biochemistry
	Biliary sludge

Azathioprine/6-Mercaptopurine

The thiopurine immunomodulators provide an anti-inflammatory effect, and maintenance of remission in IBD, by conversion to 6-thioguanine nucleotides, which insert into the DNA of rapidly dividing cells and suppress replication [50]. While, adverse effects can occur in 15–30% of patients with IBD on thiopurines, hepatotoxicity is rare [51]. Adult retrospective studies have shown frequencies of Azathioprine (AZA)/6-Mercaptopurine (6MP) hepatotoxicity ranging from 0 to 5.2% [52–57]. The majority of patients improved with dose reductions or drug discontinuation. One patient developed peliosis hepatis, blood-filled cavities on histopathology, which resolved with drug withdrawal. Other reports have identified isolated cases of veno-occlusive disease and severe cholestasis, of which both resolved upon drug

discontinuation [58, 59]. A case–control study of adults with IBD treated with azathioprine identified 37 cases of nodular regenerative hyperplasia and found a positive association with male gender and stricturing IBD disease. These cases were identified either due to abnormal liver biochemistry versus symptoms or abdominal imaging consistent with portal hypertension (PHT). Of these cases, 15 required treatment for PHT and 1 patient received a liver transplant [60]. Meanwhile, studies in children have assessed smaller cohorts of patients: Cuffari et al. in 1996 found 1 in 25 adolescents (4%) developed hepatitis, confirmed with liver biopsy [61]. Grossman et al. in 2008 assessed a cohort of 30 children <6 years of age who were prescribed elevated doses of azathioprine (3 mg/kg/day) due to suspected differences in pharmacokinetics in this age group. Two patients (6.7%) developed abnormal liver biochemistry that resolved without dose discontinuation. Both these patients had normal levels of thiopurine methyltransferase (TPMT), the enzyme implicated in toxicity when deficient [62]. Another study of 22 children with IBD by Kader et al. in 2000 also found that TPMT levels did not correlate with hepatotoxicity in the 2 children who developed hepatitis [63]. A dose monitoring strategy for thiopurine administration may include liver biochemistry at baseline, and then weekly for the first 4 weeks of therapy, twice monthly for the following second and third months, and then monthly [64].

Other IBD Therapies and the Liver

Other IBD treatments have reported rare cases of hepatic disturbance. Within the 5-aminosalicylic acid class of medications, sulfasalazine has been associated with significant cases of fever, rash, jaundice, hepatomegaly that either progressed to acute liver failure, or resolved with corticosteroid administration [65, 66]. These cases were suspected to be idiosyncratic reactions to the sulfa moiety within this compound.

Hepatic steatosis can occur with glucocorticoid administration due to increased lipogenesis and decreased free fatty acid oxidation pathways [67]. Children with IBD who are treated with corticosteroids are at risk of this complication. However, despite frequent use of this medication, there are few, if any, biopsy-proven case reports of this complication in adults or children [68]. This likely indicates that the short courses of steroids used in IBD do not frequently cause significant liver disease.

Hepatotoxicity with anti-TNF use is rare. However, after 35 cases of hepatitis, cholestasis, and acute liver failure were reported to the FDA MedWatch program, in patients using anti-TNF agents, a black-box warning was issued to alert physicians to the possible associated hepatotoxicity [69]. Also concerning were the findings of increased hepatitis B reactivation in patients on these biologic agents. It is possible that endogenous TNF promotes viral clearance and its loss contributes to the increased viral replication [69]. Cyclosporine was studied in 111 patients with IBD in 2008 and 21 (19%) were found to develop mild elevations in liver biochemistry that did not cause any adverse effects. Only one patient was investigated further and was found to have biliary sludge on ERCP [70].

Finally, total enteral nutrition (TEN) is a therapy that has been used to both induce and maintain remission in Crohn disease. This treatment is preferred to the use of total parenteral nutrition (TPN) due to a more physiologic delivery of nutrition as well as a lower side effect profile thus avoiding the feared intestinal failure-associated liver disease. Two previous reports have studied the liver biochemistry profile in TEN for IBD: Dolz et al. in 1989 did not find any statistical differences between IBD patients on TEN vs. not on TEN (though this was not randomized). Meanwhile, Schtorje and Hoekstra in 2010 found a transient increase in liver biochemistry in the first 6 weeks of treatment, that subsequently normalized spontaneously without progression to liver disease, over a mean follow-up period of 2.1 years [71, 72].

Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is a rare malignancy that has been associated with immunocompromised patients. In this disease, activated T cells appear to infiltrate the sinusoids of the liver, spleen, and bone marrow. Though rare, this lymphoma is aggressive, extraordinarily difficult to treat, and almost uniformly fatal. In general, the median age at diagnosis is 32 years (range 10–80 years), with a 70% male predominance [73]. Retrospective analysis of 2 case series (up to 61 patients total) demonstrated that 98% of patients presented with splenomegaly, 77% with hepatomegaly, 70% with systemic "B" symptoms, and 29% with jaundice [73]. Investigations performed on these patients revealed bone marrow infiltration in 100%, liver enzyme abnormalities in 40%, thrombocytopenia in 89%, and anemia in 80%. In the IBD population, reports of HSTCL have been published in children and young adults who were treated with concomitant infliximab and 6-MP/AZA therapy [73]. A retrospective review of all cases of HSTCL in patients on anti-TNF agents that were reported to the US Food and Drug Administration between 2004 and 2009 was recently published [74]. A total of 25 cases were found, 18 of which were patients under 50 years of age. Of the 18, the mean age was 23.6 years (±7.1 years), 17/18 (94.4%) were male, all had IBD and all were co-treated with 6-MP/AZA. Unfortunately, 14/18 (77.7%) were confirmed to have died at the time of publication. This risk of malignancy has led to a change in

practice, as many doctors and families are now reluctant to use combinations of biologic agents with 6-MP/AZA. Clearly, in a patient where this regimen has been employed and the symptoms listed earlier develop, further investigation and an oncology consultation is warranted.

Other Liver Diseases and IBD

Cholelithiasis

There is an increased prevalence of gallstone disease in patients with IBD. Though rare in pediatrics, 2.3% of 1649 children with IBD in an American consortium developed gallstones compared to a population prevalence of approximately 0.88–0.99% in a British prospective cohort (<30 years of age) [75, 76]. Previous adult studies have described a 13–28% prevalence rate in CD and 4.6% in UC [77–79]. Significant associations with an increased rate of cholelithiasis include increased age, increased duration of disease, increased extent of disease, and prior intestinal surgery. The etiology of this problem is unclear and is hypothesized to be due to increased enterohepatic recirculation of bilirubin as elevated levels of bilirubin (increased three to tenfold) can be found in the bile of patients with ileal disease, or past resections, compared to patients with colitis [80]. In contrast, a study in Crohn disease found an increased prevalence of gallstones with colonic disease compared to disease limited to the ileum [78]. Akerlund et al., in 2000, assessed the bile biochemical composition in patients with UC status-post colectomy undergoing ileal pouch re-anastomosis. They found the bile composition in patients with IBD to be different from non-IBD patients undergoing cholecystectomy for cholelithiasis, but similar to healthy patients who had cholecystectomy for other reasons [81]. While the pathophysiology remains uncertain in IBD, once gallstones have been identified, cholecystectomy may be indicated as these patients have a higher propensity to develop further stones.

Liver Abscesses

Cases of liver abscesses in both children and adults with IBD have been reported. They can arise at presentation of IBD or while on immunosuppressant therapy. A 17-year-old adolescent with ileocecal CD, who presented with right upper quadrant abdominal pain, hepatomegaly, and chills, was found to have multiple liver abscesses. These lesions required antibiotic treatment over 6 weeks, but subsequently resolved [82]. In the adult literature, liver abscesses arise more commonly in Crohn disease than in ulcerative colitis [83, 84]. An elevated index of suspicion is required with the aforementioned symptoms as the diagnosis can usually be made relatively easily on ultrasonography.

Vascular Lesions

There is an increased propensity for developing vascular thrombotic lesions in the IBD population. Hepatic vein thrombosis (HVT: Budd–Chiari syndrome) has also been reported in IBD and requires a high index of suspicion as diagnosis on imaging can be challenging. HVT causes an impaired vascular outflow from the liver with subsequent hepatomegaly, ascites, and portal hypertension [85]. One case report describes 12-year-old girl who presented to hospital 6 months after her diagnosis with IBD. She had uncontrolled IBD with bloody diarrhea and anemia. She developed abnormal liver biochemistry and an abdominal ultrasound demonstrated hepatomegaly. A Doppler examination was performed and the hepatic vein had a decreased diameter with old organized thrombi in the lumen [85]. Diuretics and treatment for her underlying IBD were administered and she subsequently improved (without anticoagulant therapy). In 1986, 2 cases of HVT in adults with IBD were described, and both patients presented with ascites and hepatomegaly. One patient was diagnosed on necropsy, while the other had evidence of sinusoidal dilatations on liver biopsy that was consistent with HVT. He received treatment with diuretics as well as anticoagulation therapy and he improved with time [86]. HVT is uncommon; however, it occurs more frequently in patients with IBD and requires particular consideration. Initially, investigations with Doppler ultrasonography can be helpful in identifying HVT. If there is uncertainty, computed tomography, magnetic resonance imaging, liver biopsy, or percutaneous venography can be used for diagnostic confirmation. The therapeutic goal is to prevent progression of disease with thrombolytic therapy, anticoagulant therapy, angioplasty or vascular stents, although caution should be exerted in patients with active bleeding [85]. Symptomatic treatment of HVT includes management of ascites with diuretics and paracentesis.

Nonalcoholic Fatty Liver Disease

There are no current reports in the literature of nonalcoholic fatty liver disease (NAFLD) in pediatric IBD; however, with evidence of increased obesity in developed countries, this may change in the near future [87]. In a multicenter study assessing BMI of children at time of diagnosis with IBD, 10% of 456 children with CD and 20–30% of 156 children with UC were found to be overweight or at risk of being overweight [88].

A Clinical Approach to Children with IBD and Liver Abnormalities

Patients with IBD who develop abnormal liver biochemistry or physical stigmata of liver disease, may be manifesting signs or symptoms of a range of potential diagnoses, as described in this chapter. Based on the available (limited) literature we suggest the following algorithm to approach hepatic involvement in pediatric IBD (Fig. 11.4). All children with IBD should have routine liver biochemistry with liver enzymes, albumin, and bilirubin at 6–12-month intervals when the child is well. This schedule may be increased when the child is unwell or if they are being treated with hepatotoxic medications. If abnormalities in liver enzymes are detected and are low grade, the tests may be repeated in 1–2 weeks, to ensure they are not increasing acutely, and subsequently followed for the first few months. With higher elevations, or if other stigmata of liver disease appear, including hepatomegaly, splenomegaly, or jaundice, further investigations should be considered including autoimmune antibody, viral hepatitis and celiac testing, ceruloplasmin and alpha-1-antitrypsin level assessment, abdominal ultrasound, MRCP, and/or liver biopsy. The cut-off points between low- and

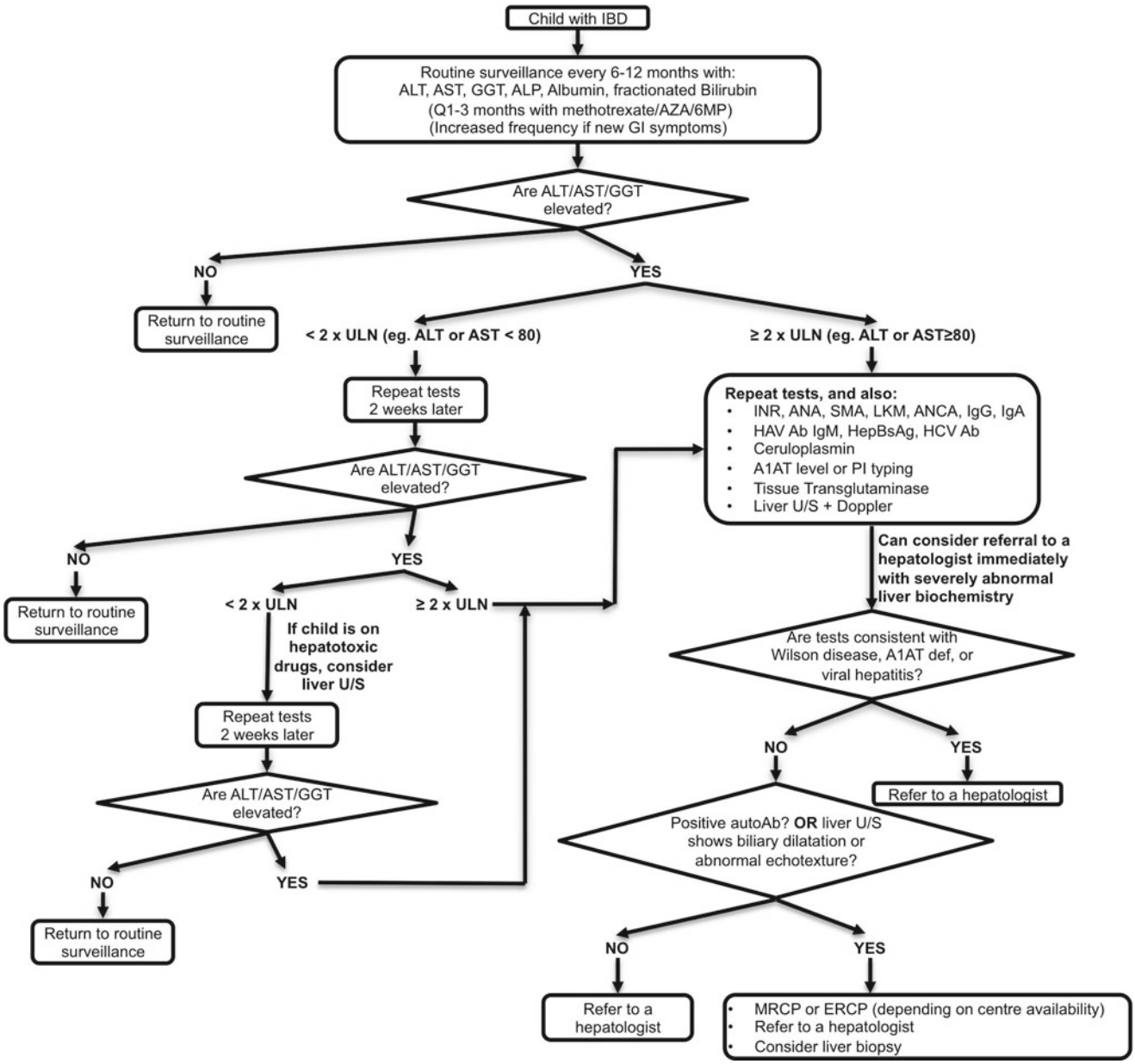

Fig. 11.4 Diagnostic algorithm for abnormal liver biochemistry in a child with IBD (without previous evidence of liver disease)

high-grade liver biochemistry disturbance is often a point of contention between hepatologists. With limited evidence in children with IBD, we suggest that 2–3 times above the upper limit of normal may be considered a significant elevation that requires further investigation. Consultation with a hepatologist may also be appropriate at this stage of evaluation. Subsequent evaluation may also include an MRCP and/or liver biopsy. Further studies are required to devise an evidence-based diagnostic algorithm for the approach to abnormal liver biochemistry in children with IBD.

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