Liver Disease in Pediatric Inflammatory Bowel Disease

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Introduction

Diseases involving the hepatobiliary system are among the most common extraintestinal manifestations of inflammatory bowel disease (IBD). They can be classified into a few broad categories: (1) liver diseases that may share a common pathogenic mechanism with IBD, such as primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and PSC/AIH overlap, also known as autoimmune sclerosing cholangitis (ASC); (2) liver diseases that reflect the pathophysiology of IBD, such as cholelithiasis and portal vein thrombosis; and (3) liver diseases that result from the adverse effects of IBD therapy, such as drug-induced hepatitis [1]. In addition, an association has been noted between a number of other less common hepatobiliary diseases and IBD, including IgG4-associated cholangitis (IAC). Some of the conditions listed above are observed more frequently in Crohn disease (CD) or ulcerative colitis (UC), while others occur at similar rates in both types of IBD (Table 11.1). Liver enzyme abnormalities are common in IBD and, while often transient and inconsequential, deranged hepatic biochemistry may herald serious underlying liver disease, such as PSC. The challenge lies in determining which patients merit further work-up versus observation. No standardized algorithm exists to guide clinicians in this decision-making process, particularly in children, in whom there is a relative paucity of data. This chapter strives to facilitate this task by providing an overview of liver disease occurring in association with pediatric IBD.

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Abnormal Liver Chemistry

Abnormal liver chemistry is common in IBD. Liver enzyme abnormalities (any value exceeding the upper limit of normal (ULN)) have been reported in 15–40% of adults with IBD over 1–5 years of follow-up [2–4], with more marked elevations (>2× the ULN) occurring in 5% [2]. Abnormal liver biochemistry appears to be similarly frequent in pediatric IBD. Nemeth described "pathological liver function tests" in 52% of his 46-patient cohort in 1990 [5], and similar findings have since been reproduced by two large retrospective pediatric studies, in which at least one liver enzyme elevation was observed in 40–60% of children with IBD over 3 years [6, 7], even after excluding patients with PSC/ASC. No differences were observed between patients with CD and UC. Liver enzyme elevations >2× the ULN occur in a smaller proportion of children, roughly 15–30% [7, 8]. The pattern of biochemical injury is typically hepatocellular, but can be mixed or, less commonly, cholestatic [4, 6]. ALT is the most frequently abnormal test [7], with the caveat that ALT also tends to be measured more often than other tests, like GGT. The majority of these biochemical abnormalities are mild, transient, and benign in nature [4, 6–8,]. The degree of transaminase elevation appears to correlate with the likelihood of identifying underlying liver disease; in one study, 95% of children with peak ALT <2× ULN were found to have no specific liver disease [6], and conversely, in another, 93% of children with PSC or ASC had liver enzymes 2× the ULN or greater, sustained for 30–90 days [7]. In this latter study, GGT was found to be particularly useful for identifying PSC/ASC, with a value of 252 U/L, having a sensitivity of 99% and specificity of 77% for PSC or ASC [7].

Well-defined chronic liver disease (PSC/ASC and AIH) accounts for only 1.4–6% of elevated liver enzymes in pediatric IBD, whereas the majority of cases remain idiopathic [6, 7, 9]. The most common etiology, when one is identified, is drug toxicity [2, 6, 8]. In children, steroids,

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Table 11.1 Hepatobiliary diseases associated with pediatric IBD

Hepatobiliary disease	Ulcerative colitis	Crohn disease
Primary sclerosing cholangitis (PSC)	++	+
Autoimmune hepatitis (AIH)	++	++
Autoimmune sclerosing cholangitis (ASC)	++	+
IgG4-associated cholangitis (IAC)	++	+
Cholelithiasis	–	++
Portal vein thrombosis and hepatic abscess	+	++
Drug-induced hepatitis	++	++
Hepatitis B reactivation (infliximab)	++	++
Hepatosplenic T-cell lymphoma	+/–	+
Fatty liver	++	++
Hepatic amyloidosis	–	++
Granulomatous hepatitis	–	++
Primary biliary cholangitis (PBC)	++	–

antibiotics, methotrexate, adalimumab, as well as exclusive enteral nutrition, have been positively associated with liver enzyme abnormalities [7]. Conversely, liver enzyme abnormalities appear to be less frequent in children taking 5-ASA and sulfasalazine, although these agents may simply be surrogates for milder IBD [3, 7]. Other less common causes of deranged hepatic biochemistry in pediatric IBD include infection (particularly CMV and EBV), nonalcoholic fatty liver disease (NAFLD), cholelithiasis, and vascular abnormalities [6]. Active IBD has also been proposed as a cause of abnormal liver enzymes, but the evidence is conflicting; several studies lend support to this hypothesis [4, 8, 10], while others refute it. One such study in adults actually found a higher prevalence of liver enzyme abnormalities in patients in remission compared to those with active IBD [3]. In children, biochemical abnormalities do not appear to be associated with IBD duration or extent [5, 6, 9]. With regard to prognosis, death was found to be 4.8 times higher in adults with abnormal liver biochemistry, even after excluding those with any diagnosis of liver disease [3]. No equivalent pediatric data exist.

In summary, abnormal liver biochemistry is common in children with IBD. Most cases are mild and resolve spontaneously, and such cases tend to be associated with undefined etiologies. However, a small subset of patients with more severe, prolonged derangements has serious disease or medication adverse effects. Given this, it seems reasonable to adopt a period of watchful waiting in patients with mild elevations (<2× the ULN) unless there are overt signs of underlying liver disease. More marked or persistent (>1 month) abnormalities may warrant further investigation. We suggest obtaining a liver biochemical panel, including ALT and GGT, in all newly diagnosed IBD patients and repeating this at least every 6–12 months for surveillance.

Primary Sclerosing Cholangitis

Epidemiology and Pathogenesis

Primary sclerosing cholangitis (PSC) is a chronic, progressive, cholestatic liver disease characterized by inflammation and obliterative fibrosis of the intrahepatic and/or extrahepatic biliary tree, resulting in multifocal strictures and dilatation. It is a rare disease, with an incidence and prevalence of 0.1–0.2 and 1.5 per 100,000 children, respectively, which is substantially lower than in adults [11–13]. Pediatric PSC typically presents early in the second decade of life and has a modest male predominance, as in adults [12, 14–16]. The link between PSC and IBD has been known for greater than five decades [17]. As many as 60–80% of adults with PSC in North America and Northern Europe have IBD, primarily ulcerative colitis (UC) [18, 19]. The prevalence of IBD in children with PSC is also very high, >50% in most series and up to 97% in a recent population study [12, 14–16, 20]. Conversely, only a minority of children with colitis, <10% in most series, have or develop concurrent PSC [7, 12, 21, 22]. However, these reports may underestimate the true prevalence of PSC in IBD as neither adult nor pediatric IBD patients are systematically investigated with liver biopsy and cholangiography to screen for liver disease. Most patients are found to have PSC within a year of their IBD diagnosis [12], but the two can occur years apart, and PSC can manifest first, in which case a full colonoscopy is recommended to screen for IBD [23].

The pathogenesis of PSC remains incompletely understood. Genomewide association studies have identified a number of HLA and non-HLA risk loci [24, 25], some of which are shared with IBD, and a hallmark paper in 2004 reported an accumulation of gut-homing CCR9-positive T cells in explanted human livers of patients with PSC [26], findings that point to both a genetic and immunological basis

for PSC. In addition, there is growing evidence for the role of the "gut-liver" axis in the pathogenesis of PSC. Several animal models and human tissue-based translational studies support that enteric microbial molecules/dysbiosis can lead to PSC-like hepatobiliary inflammation [27].

Primary Sclerosing Cholangitis and IBD

The intestinal inflammation in individuals with PSC and colitis may represent a distinct IBD phenotype, termed PSC-IBD. This has been well characterized in adults as extensive colonic involvement, often worse on the right, and relatively frequent "backwash ileitis," rectal sparing, and pouchitis post colectomy [28]. Crohn disease (CD) is uncommon in the setting of PSC, but, when it does occur, it too tends to have an extensive colonic distribution; isolated small bowel, perianal, and fistulizing disease are uncommon [29]. Despite the extensive nature of the colonic inflammation, PSC-IBD tends to have a relatively mild clinical course with a paucity of overt clinical symptoms [30, 31]. There are significantly less data pertaining to the phenotype of pediatric PSC-IBD, but findings analogous to those in adults have been reported in two small studies [32, 33]. In addition, a recent study specifically aimed at investigating the phenotype of pediatric PSC-IBD compared 37 children with IBD and PSC or ASC to 137 non-PSC matched IBD controls. In keeping with the above, the authors found a higher proportion of pancolitis in the PSC-IBD group, although this was only marginally statistically significant. In contrast to some of the adult evidence, both groups were similar in terms of the proportion of patients with rectal sparing (defined histologically) and disease activity, as reflected by physician's global assessment, Mayo endoscopic scores, admission rates, and colonic surgery rates [34].

The interplay between IBD and PSC remains to be elucidated. Adults with severe PSC requiring liver transplant (LT) have been found to have milder UC than patients with less severe liver disease, suggesting that PSC may have a "protective" effect on colonic disease [35]. Furthermore, while it has long been maintained that PSC and IBD progress independently, as supported by older studies indicating that the natural history of PSC is unaffected by colectomy [36], more recent findings suggest that colectomy may reduce the risk of PSC recurrence post LT [37]. The interaction between PSC and IBD, including the effect of ongoing colonic inflammation on PSC progression, if any, requires further clarification.

Diagnosis

The diagnosis of PSC in a child is based on a compatible clinical presentation and biochemistry, with characteristic changes on cholangiography and/or liver biopsy, after excluding secondary causes of sclerosing cholangitis. The most common presenting symptoms and signs are hepatomegaly and abdominal pain, followed by diarrhea, splenomegaly, fatigue, pruritus, weight loss, impaired growth, and jaundice [15]. The presenting features may also, uncommonly, be those of advanced liver disease, such as gastrointestinal bleeding and cholangitis, or those of associated colitis, especially bloody diarrhea. About 20% of children with PSC are asymptomatic at presentation and come to medical attention solely due to deranged liver biochemistry. Transaminases are often modestly elevated, with a predominantly cholestatic pattern [15]. GGT is more reliable in children as ALP elevations may reflect bone growth. The odds of PSC are 660-fold greater in children with ALT and GGT elevations >50 U/L within 3 months of their IBD diagnosis compared to children whose values remain <50 U/L [9]. INR, albumin, and conjugated bilirubin, which reflect synthetic function, are generally normal at presentation. Elevated conjugated bilirubin may signal a stricture, cholangitis, or a mass, and warrants further work-up. Serum immunoglobulin G (IgG) levels may be elevated, and a variety of autoantibodies may be present, the most common of which is antineutrophil cytoplasmic antibody (ANCA), usually with an atypical perinuclear ("p") pattern, which is found in up to 80% of patients. None of these are specific to PSC, however [12, 23]. Serum IgG4 should be measured at least once in children with PSC. An elevated IgG4 may denote IgG4-associated cholangitis (IAC), which has important implications, given its favorable response to corticosteroids [38]. Ultrasound is a reasonable initial imaging modality; it may reveal bile duct wall thickening, focal bile duct dilatations, and/or gallbladder changes, including wall thickening, enlargement, cholecystitis, and mass lesions. It is also useful for ruling out alternate etiologies. However, none of these findings are diagnostic, and ultrasound may be normal in the setting of PSC [23]. Cholangiography, preferably by magnetic resonance cholangiopancreatography (MRCP), which has supplanted endoscopic retrograde cholangiopancreatography (ERCP) as the first-line diagnostic imaging modality due its less invasive nature and lower cost, is a vital component of the PSC diagnostic work-up [39]. Characteristic cholangiographic findings include multifocal, short strictures alternating with normal or dilated segments, producing a "beaded" appearance (Fig. 11.1) [23]. The gallbladder, cystic duct, and pancreatic duct may also be abnormal [40]. Contrary to adult guidelines, a liver biopsy is almost always performed in a child with suspected PSC. Histopathological assessment is necessary to distinguish PSC from autoimmune sclerosing cholangitis (ASC), which occurs frequently in children and mandates

different treatment. A liver biopsy is also useful to diagnose small-duct PSC, a label applied to cases with compatible histological changes but without cholangiographic abnormalities, and to stage the degree of fibrosis. Periductular concentric fibrosis, or "onion-skinning" (Fig. 11.2), is pathognomonic for PSC, but not always observed. Other, nonspecific findings may include ductular proliferation or periductular inflammation, with variable types of portal inflammation and fibrosis. The diagnostic work-up for suspected PSC in children is illustrated in Fig. 11.3.

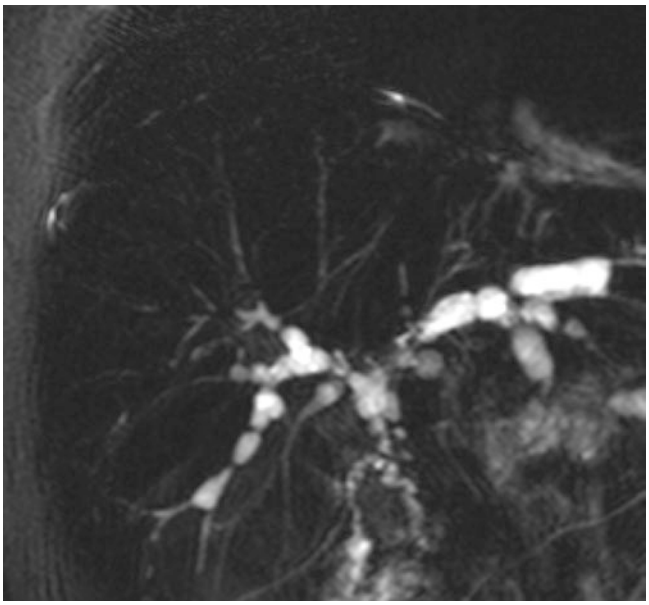

Fig. 11.1 Cholangiographic appearance of PSC with typical "beading"

Outcomes

PSC is one of the most important sources of morbidity and mortality in IBD, but few studies have examined its natural history in children. Based on limited data, the probability of developing complicated liver disease, defined as clinical portal hypertension, obstructive cholangitis, cholangiocarcinoma, liver transplant, or death, over 5 years in children with PSC, is 37% [12]. About 20% of children with PSC ultimately require a liver transplant (LT), a figure that has remained fairly constant over the past 20 years. The median time from diagnosis to LT is 7–12 years [14–16, 41]. Survival is significantly shorter in children with PSC compared to age-matched and gender-matched American children. Lower platelet count, splenomegaly, and older age are associated with shorter survival [14]. Adults with UC and PSC have an almost five times greater risk of colorectal neoplasia compared to adults with UC alone [42]. Surveillance colonoscopies every 1–2 years from the time of diagnosis are recommended in adults [23]. No equivalent pediatric guidelines exist, but it seems reasonable for similar screening practices to be applied to older children and teenagers. There is a markedly increased risk of cholangiocarcinoma in adults with PSC [43], but this malignancy is exceedingly rare in children. Nevertheless, a handful of cases has been reported in older teenagers [12]. While adult guidelines suggest consideration be given to screening for cholangiocarcinoma with regular cross-sectional imaging and CA 19-9, this is not routinely recommended in children [23, 39]. However, based on clinical experience and expert opinion, the authors suggest an ultrasound yearly, an MRI every 2 years, and CA 19-9 levels yearly in children with PSC to screen for cholangiocarcinoma.

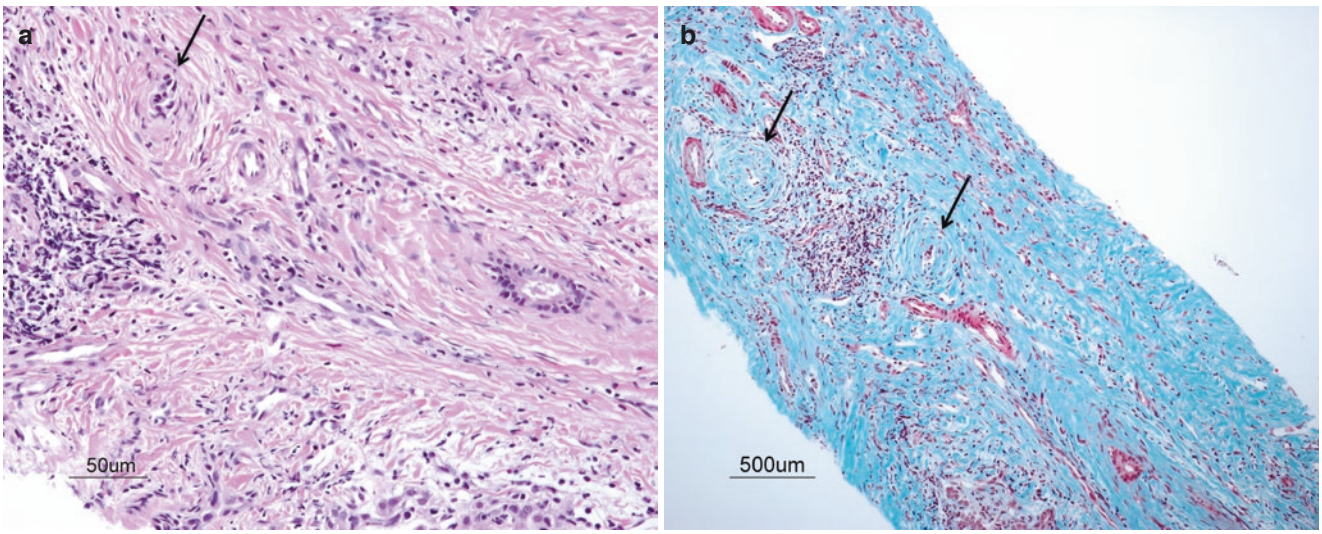

Fig. 11.2 Liver biopsy showing typical histological changes of PSC, including periductular concentric fibrosis denoted by the arrows with (**a**) H&E and (**b**) trichrome staining

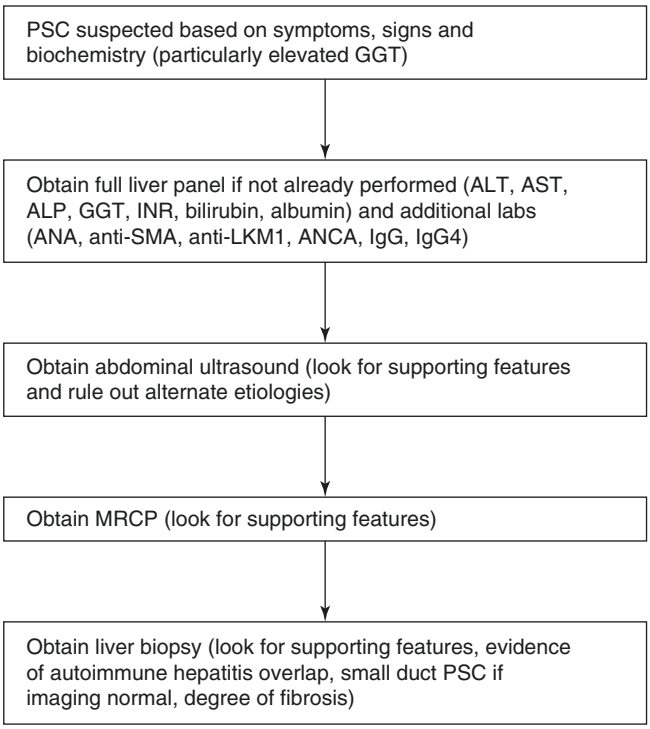

Fig. 11.3 Diagnostic work-up for suspected pediatric PSC. *ANA* antinuclear antibody, *ANCA* antineutrophil cytoplasmic antibody, *LKM1* liver kidney microsomal type 1, *MRCP* magnetic resonance cholangiopancreatography, *PSC* primary sclerosing cholangitis, *SMA* smooth muscle antibody

Small-duct PSC may have a more favorable prognosis than classic PSC. It has been associated with a longer transplant-free survival in adults, and there have been no reports of cholangiocarcinoma occurring with small-duct PSC. However, small-duct PSC can progress to classic PSC with cholangiographic abnormalities over time, and it can recur post transplant [44]. It is unclear whether small-duct PSC represents an early stage of classic PSC or a distinct entity.

Treatment

Data pertaining to the medical management of PSC in children are scarce, and current practices largely derive from adult studies. No medical therapy currently exists to reverse or halt the progression of PSC liver disease. As such, treatment is mainly supportive. Although numerous aspects of PSC invoke an autoimmune basis for the disease, thus far, no single immunosuppressive or immune-modulating agent has been found to be efficacious [45].

Ursodeoxycholic acid (UDCA) is widely used in adults and children with cholestatic liver disease, including PSC. Although biochemical improvement has been demonstrated in children, a beneficial effect on the natural history of PSC, as reflected by a decrease in mortality and/or LT rates, has never been shown [14, 15, 46]. Similarly, adult studies have documented improvements in biochemistry, but not in hard outcomes [47]. Furthermore, the use of high-dose UDCA >28 mg/kg has been associated with a twofold increased risk of death/transplant and a fourfold increased risk of colorectal cancer in adults [48]. There is no consensus regarding the use of UDCA in adults with PSC, with one expert group advising against its use entirely [23] and another merely recommending against the use of high doses [39]. In light of this, it appears prudent to avoid high-dose UDCA in children with PSC, but continued use of low-to-moderate doses, not exceeding 20 mg/kg/day, is reasonable.

Limited anecdotal evidence supports the use of oral vancomycin for treating pediatric PSC [49–51]. Oral vancomycin's therapeutic effect may occur through immunomodulation, by increasing transforming growth factor-β (TGF-β) and peripheral levels of regulatory T cells [52]. Data from prospective pediatric trials are pending. Metronidazole and minocycline, but not rifaximin, have also been associated with improved liver biochemistry in adults with PSC [53–55]. At the current time, the use of oral antibiotics for pediatric PSC remains experimental, as a benefit beyond biochemical has yet to be demonstrated.

Dominant strictures are less common in children than adults, but should, when identified in association with symptoms or signs such as cholangitis, jaundice, pruritus, right upper quadrant pain, or worsening biochemistry, be managed with ERCP and balloon dilatation, often with sphincterotomy, with or without stent placement [23]. This may prolong symptom-free intervals prior to LT [56]. Although cholangiocarcinoma is rare in pediatrics, brush cytology in the setting of a dominant stricture remains important. ERCP should be performed by a physician who is adequately trained in and experienced with the procedure, which often requires collaboration with an adult gastroenterologist.

Liver transplant remains the only definitive treatment for PSC and should be considered for children with decompensated cirrhosis, recurrent or chronic cholangitis refractory to ERCP, hilar cholangiocarcinoma, and intractable pruritus [23, 57]. PSC accounts for 2.6% of pediatric transplants [58]. The mean age at transplant is 12.6 years. Patient and graft survival after LT for PSC is comparable to that for non-PSC pediatric indications, with 1-year and 5-year patient and graft survival rates of 99% and 97%, and 93% and 76%, respectively. However, a diagnosis of IBD prior to LT is associated with an increased risk of death post LT. Intrahepatic biliary strictures and cholangitis are more common in the first 6 months post LT in children with PSC compared to other liver diseases [59]. Furthermore, PSC recurs in about 10% of children post LT [14, 59, 60]. A diagnosis of IBD and younger age have been linked with an increased risk of PSC

recurrence [59, 60]. As mentioned above, colectomy prior to or during LT may decrease the risk of PSC recurrence [37].

Other Autoimmune Liver Diseases

Autoimmune Hepatitis

Epidemiology and Pathogenesis

Autoimmune hepatitis (AIH) is an idiopathic, progressive, inflammatory liver disease characterized by elevated transaminases, interface hepatitis on biopsy, hypergammaglobulinemia, and autoantibody positivity. It is the most common pediatric autoimmune liver disease, with an incidence and prevalence of 0.23–0.4 and 3 per 100,000 children, respectively [12, 61]. The prevalence of IBD in children with AIH, which approaches 20% [61–63], exceeds that in the general pediatric population, but the magnitude of the association between AIH and IBD is less than that between PSC and IBD. Only 0.3–0.6% of children with IBD develop AIH and, unlike in PSC, this proportion does not differ substantially between children with UC and CD [12]. Two main types of AIH are recognized: AIH type 1 (AIH-1), which accounts for the majority (60–87%) of cases, is characterized by positive antinuclear (ANA) and/or anti-smooth muscle (SMA) autoantibodies, whereas AIH-2 is distinguished by positive antiliver kidney microsomal type 1 (LKM-1) and/or antiliver cytosol type 1 (LC-1) autoantibodies. Of note, lower antibody titers are considered significant in children, namely, 1:20 for ANA and SMA, and 1:10 for LKM1 and LC-1, compared to a threshold of 1:40 in adults [64]. Both types of AIH have a female predominance [61], although it is not clear whether this is also true of cases associated with IBD [61, 62, 65]. The pathogenesis of AIH is unknown, but is likely multifactorial, involving genetic susceptibility and immune dysregulation, modified by environmental factors. An aberrant immune response targeting liver autoantigens has been implicated [66].

Diagnosis

Pediatric AIH can present in a highly variable manner, ranging from nonspecific insidious symptoms to fulminant liver failure. The most common presenting symptoms are fatigue, jaundice, and abdominal pain, which occur in about half of patients. Hepatomegaly and splenomegaly are the most frequently observed abnormalities on physical exam [61]. In the context of IBD, however, AIH typically comes to light as a result of elevated transaminases, which can fluctuate over time. The pattern of injury is predominantly hepatocellular, with AST and ALT values typically in the several hundred range. Conjugated bilirubin is generally normal, but GGT can be modestly elevated. Serum IgG is elevated in 80% of cases, but a normal result does not rule out AIH. Although none of the autoantibodies listed above are entirely specific to AIH, the presence of high-titer autoantibodies, in combination with compatible clinical features and histological findings, strongly supports a diagnosis of AIH. A liver biopsy is typically performed to confirm a diagnosis of AIH and to establish the severity of liver damage. Characteristic findings include interface hepatitis, lymphoplasmacytic infiltrates, and rosetting of hepatocytes. Biliary changes, such as ductular proliferation, can be seen, as well as fibrosis. Cirrhosis is observed in 20–80% of children at presentation and is more common in AIH-1 [61, 67, 68]. Of note, the distinction between AIH and drug-induced liver injury, which is particularly relevant in children with IBD, can be very challenging. In addition to the AIH work-up presented above, it is recommended that all children with presumed AIH undergo cholangiography to investigate for ASC or PSC.

Outcomes and Treatment

Although a significant fraction of children with AIH present with cirrhosis and AIH has an aggressive natural history in children, when treatment is instituted promptly, outcomes are usually favorable. Conventional treatment is with prednisone 2 mg/kg/day (maximum 60 mg/day) to induce remission, decreased over 4–8 weeks, and then continued at a lower dose (0.1–0.2 mg/kg/day, or 2.5–5 mg/day) as maintenance, often with azathioprine. Azathioprine is generally started at a dose of 0.5–1 mg/kg/day and increased to a maximum of 2–2.5 mg/kg/day until remission is achieved [69, 70]. Thiopurine methyltransferase (TMPT) activity may be verified prior to initiating azathioprine to identify patients at heightened risk of myleosuppression, but this is not routinely recommended [66]. This treatment regimen is associated with biochemical remission (normalization of liver enzymes and IgG) rates >80% in children with AIH, although this can take several months, and relapses requiring temporary increases in immunosuppression are common [61, 65]. The optimal duration of treatment is not known. In patients who have had sustained biochemical remission for 2–3 years, a liver biopsy may be performed and, if resolution of histological inflammation has occurred, treatment withdrawal may be attempted [70].

Children with AIH have an approximately 15% probability of developing complicated liver disease, as defined above, over 5 years [12]. Transplant rates for AIH are variable, but range from 5 to 10% in recent studies [12, 61]. AIH can recur post transplant with recurrence rates varying between 12 and 46% [71]. It is therefore recommended that steroid-based immunosuppression be maintained at a higher dose than that used for non-AIH transplants [72]. At the current time, it is unclear whether the disease course of AIH occurring in association with IBD differs from that in children without IBD.

Autoimmune Sclerosing Cholangitis

Epidemiology and Pathogenesis

Autoimmune sclerosing cholangitis (ASC) is an overlap condition between AIH and PSC, characterized by the combination of autoimmune features, namely, positive autoantibodies (especially ANA and SMA), hypergammaglobulinemia and interface hepatitis on liver biopsy, and cholangiopathy, as demonstrated by an abnormal cholangiogram or histological evidence of ductal involvement [63]. However, there are no clear diagnostic criteria for ASC. The International Autoimmune Hepatitis Group (IAIHG) suggests that conditions with overlapping features between autoimmune liver diseases not be considered separate diagnostic entities [73]. Rather, ASC may exist along a continuum of pathological changes between AIH and PSC. This concept of a spectrum of autoimmune liver disease is supported by the observation of a child progressing from AIH to ASC after 8 years in a prospective study [62]. Given the lack of established diagnostic criteria, the epidemiology of ASC is difficult to ascertain. However, a recent population study reported an incidence and prevalence of 0.1 and 0.6 per 100,000 children, respectively [12]. ASC appears to occur predominantly in children and young adults: a quarter to a third of children with sclerosing cholangitis have autoimmune overlap features [14–16], compared to only 1.4–17% of adults [23]. Conversely, almost half of 55 children with features of autoimmune liver disease were found to have cholangiographic abnormalities compatible with ASC in a prospective study in the United Kingdom [62]. Similar to PSC, ASC is typically diagnosed in the first half of the second decade of life, but, unlike PSC, it tends to affect both sexes fairly equally [12, 15, 62]. A definite association exists between ASC and IBD, the magnitude of which appears to be intermediate between that of PSC and AIH. Up to 75% of children with ASC have IBD. Conversely, 1.5–1.7% of children with IBD, mostly UC, have ASC [7, 12]. Given this, all children with ASC should undergo an evaluation for IBD, even if asymptomatic.

Diagnosis

The clinical presentation of ASC in children is similar to that described above. Biochemistry can provide some guidance in distinguishing ASC from AIH and PSC. Compared to AIH, ASC is typically associated with a higher ALP to AST ratio (around 4), and p-ANCA positivity is more common (74% compared to 36% of cases). Anti-LKM1, on the other hand, is more specific to AIH [63]. Clues of a possible diagnosis of ASC rather than PSC include higher transaminases, elevated serum IgG, and high-titer ANA and SMA autoantibodies. However, none of these biochemical parameters is sufficiently specific to make a diagnosis of ASC. The ability to firmly diagnose ASC and to differentiate it from AIH and PSC requires both cholangiography and liver biopsy. This is particularly relevant in children with IBD given the known association between ASC and IBD.

Outcomes and Treatment

An accurate diagnosis of ASC is essential as it has important prognostic and therapeutic implications. ASC may respond to the immunosuppressive regimen outlined above for AIH and, as such, may have a more favorable prognosis than PSC. A trial of corticosteroids with or without azathioprine is generally warranted [74]. However, the biliary disease in ASC progresses in 50% of children despite treatment [62]. UDCA is often used at doses of 15–20 mg/kg/day to address the biliary component of the disease, but, as with PSC, there is no evidence that biochemical improvement translates into a positive effect on natural history [75]. Twenty-five percent of children with ASC develop complicated liver disease, as defined above, within 5 years of diagnosis, a rate that is intermediate between that for PSC and AIH [12]. Given the lack of well-defined diagnostic criteria, it is difficult to comment on precise LT and mortality outcomes in children with ASC and studies to date have yielded conflicting results. An older series reported a 65% 10-year survival with native liver, distinctly worse than the 100% survival in children with AIH [62], whereas a more recent study found a 90% 5-year survival with native liver, comparable to the rate observed in children with AIH. Overall, it is believed that transplant rates in ASC are similar to those in PSC, around 20% [63]. As with PSC and AIH, ASC can recur post LT, a phenomenon that has been observed in up to 70% of cases [71]. Uncontrolled intestinal inflammation in patients with IBD is thought to be a risk factor for ASC recurrence, but direct evidence to this effect is lacking [63].

IgG4-Associated Cholangitis

IgG4-associated cholangitis (IAC) is a rare inflammatory disorder of the biliary tree, characterized by elevated serum IgG4 levels and infiltration of IgG4+ plasma cells in the bile duct walls, causing thickening and stenoses. IAC is often associated with type 1 autoimmune pancreatitis (AIP), the pancreatic manifestation of IgG4-related disease (IgG4-RD), a systemic multiorgan disorder only defined during the last decade [76]. The typical IAC/IgG4-RD patient profile is that of an elderly man with obstructive jaundice, weight loss, and abdominal discomfort. However, IAC occurring in association with UC has been reported, including in children [77]. The clinical and cholangiographic presentation of IAC is often indistinguishable from that of PSC. Furthermore, 9–36% of patients with PSC have elevated serum IgG4 levels (although usually lower

than in IAC) [78, 79], and IgG4+ plasma cells have been documented on liver biopsy in PSC patients [80], further blurring the relationship between the two. However, PSC and IAC appear to be distinct entities, as evidenced by their very different response to corticosteroids; in contrast to PSC, IAC typically shows excellent response to immunosuppressive treatment, including resolution of strictures. However, relapse is common after tapering immunosuppression; long-term low-dose therapy with corticosteroids/azathioprine is often needed, analogous to the management of autoimmune hepatitis [81]. Diagnostic criteria have been proposed for IAC; these combine biochemical, radiographic, and histopathological characteristics with multiorgan involvement of IgG4-RD and responsiveness to immunosuppressive treatment [82].

Figure 11.4 graphically depicts the relationship between autoimmune liver diseases and IBD.

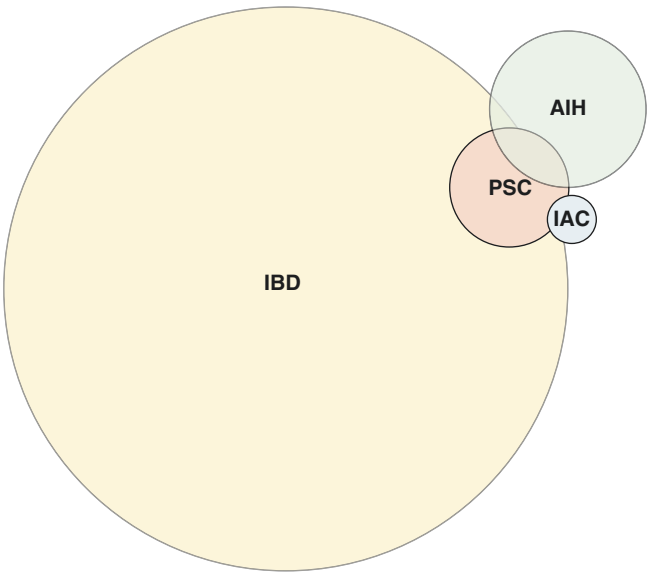

Fig. 11.4 The relationship between autoimmune liver disease and IBD. *AIH* autoimmune hepatitis, *IAC* IgG4-associated cholangitis, *IBD* inflammatory bowel disease, *PSC* primary sclerosing cholangitis

Drug Hepatotoxicity (Table 11.2)

Methotrexate

A recent systematic review and meta-analysis examining 32 randomized controlled trials, including a total of 13,177 adults primarily with rheumatological indications for treatment, demonstrated an increased risk of liver enzyme abnormalities in patients treated with methotrexate compared to a comparator agent, but no difference in the risk of liver failure, cirrhosis, or death [83]. The results of two adult IBD studies, in which fairly large numbers of liver biopsies were performed, also found very low rates of hepatic fibrosis in patients receiving methotrexate [84, 85], indicating that hepatic fibrosis is not as commonly observed in methotrexate users as suggested by older studies.

Pediatric IBD studies have found varying rates of biochemical liver abnormalities in children treated with methotrexate, ranging from 10% in a recent systematic review to 39% in a multicenter retrospective comparison of oral and subcutaneous methotrexate. Most resolved spontaneously or with dosage adjustment; medication discontinuation was required in only a minority (<5%) [86–88]. These studies are limited, however, by their retrospective nature, the inability to correlate biochemistry with histopathology, and the inability to definitively ascribe the biochemical abnormalities to methotrexate given the absence of documented normal laboratories prior to medication initiation in most cases. Conflicting data exist regarding whether higher methotrexate doses and parenteral versus oral administration are associated with a greater risk of hepatotoxicity [84, 87, 89]. The risk of hepatotoxicity may be higher in the immediate period after starting methotrexate [90]. Importantly, abnormal liver biochemistry does not reliably identify methotrexate-associated fibrosis.

Based on the available evidence, when initiating methotrexate in children with IBD, the authors recommend obtaining liver biochemistry at baseline, weekly for the first month and

Table 11.2 Differential diagnosis of clinical syndromes associated with IBD drugs causing liver injury

Syndrome	Drug
Acute hypersensitivity reaction	Sulfasalazine, mesalamine, thiopurines
Acute granulomatous hepatitis	Sulfasalazine, mesalamine
Autoimmune hepatitis-like	Anti-TNF
Noncirrhotic portal hypertension	Thiopurines
Fibrosis/cirrhosis	Methotrexate
Cholestatic jaundice	Sulfasalazine, mesalamine, thiopurines, anti-TNF
Sinusoidal obstruction syndrome	Thiopurines
Hepatic rupture	Thiopurines (peliosis)
Hepatic mass on imaging	Thiopurines (peliosis), anti-TNF/thiopurines (HSTCL)
Hepatitis B reactivation	Anti-TNF

HSTCL hepatosplenic T-cell lymphoma

every 2–3 months thereafter. In cases of persistent moderate enzyme elevations (up to 2–3× ULN), the dose of methotrexate can be adjusted, preferably in consultation with a pediatric hepatologist, whereas, when faced with more marked elevations (>5× ULN), methotrexate should be entirely held, at least temporarily. A liver biopsy should be performed in cases in which liver enzymes remain abnormal despite medication cessation, or when methotrexate discontinuation would be deleterious to IBD management. The use of methotrexate in patients with underlying liver disease, such as PSC, should generally be avoided, if possible.

Thiopurines

Azathioprine (AZA) is a prodrug for 6-mercaptopurine (6-MP), which is, in turn, converted to 6-thioguanine (6-TG), the final effector metabolite. The enzyme thiopurine methyltransferase (TPMT) catalyzes the formation of 6-methylmer captopurine (6-MMP) and 6-methylmercaptopurine ribonucleotides (6-MMPR) [91]. A systematic review, including 34 mostly adult IBD studies, found a mean overall prevalence of AZA/6-MP-induced "liver disorder" of 3.4% and a mean annual rate of abnormal liver tests (up to 2× ULN) per patient-year of 1.4%, suggesting that thiopurine-associated hepatotoxicity is relatively uncommon. However, most studies did not provide definitions for "liver disorder" and were retrospective in design [92]. Two large pediatric studies examining the use of thiopurines in IBD also found fairly low rates of hepatotoxicity, namely, 4.6% and <3%, respectively [93, 94].

Thiopurine-induced hepatotoxicity can be grouped into three syndromes: (1) hypersensitivity reactions; (2) idiosyncratic cholestatic reactions; and (3) presumed endothelial cell injury. Hypersensitivity reactions usually have their onset within 2–3 weeks. Non-allergic cholestatic injuries are characterized by increased serum bilirubin and ALP, with or without moderate aminotransferase elevations, and typically occur within 2–5 months of therapy initiation. Variable parenchymal cell necrosis is typically seen on liver biopsy. Jaundice regression is not universal upon medication cessation [92]. Nodular regenerative hyperplasia (NRH), peliosis hepatis, sinusoidal dilatation, and sinusoidal obstruction syndrome (SOS, or veno-occlusive disease) fall into the latter category and are felt to be dose-dependent. The inciting injury in this group of vascular pathology is at the level of the endothelial cells lining the sinusoids and terminal hepatic venules and tends to occur between 3 months and 3 years of treatment [95]. More specifically, NRH is thought to result from areas of hepatocyte hypoperfusion and atrophy alternating with adaptive hepatocyte hyperplasia. IBD patients treated with AZA have a cumulative incidence of NRH of approximately 0.6 and 1.3% at 5 and 10 years, respectively [96]. Patients with NRH may be asymptomatic with normal or only mild elevations in liver function tests or isolated thrombocytopenia, or may present with clinically evident portal hypertension (PHT). NRH can be detected on liver biopsy, which demonstrates diffuse transformation of normal hepatic parenchyma into small, regenerative nodules with little or no fibrosis [97], and on MRI, which shows multiple fine, nonenhancing nodules [98]. The course is usually indolent, but, rarely, NRH may progress to end-stage liver disease requiring LT [99]. NRH has also been postulated to be a preneoplastic condition, which may predispose some individuals to developing hepatocellular carcinoma [100]. Thiopurine cessation in patients with NRH is generally followed by biochemical normalization, but patients with PHT have a variable course, with resolution of PHT in some, but persistence in others. Peliosis hepatis results in multiple cystic blood-filled spaces in the liver, spleen, lymph nodes, and other organs, which can lead to hepatic hematomas and, rarely, hepatic rupture [101]. SOS typically presents with a Budd-Chiari like picture, with the triad of rapid-onset ascites, painful hepatomegaly, and jaundice.

A reasonable monitoring strategy when initiating thiopurine therapy might include liver biochemistry at baseline, weekly for the first month, biweekly for the second and third months, and monthly thereafter. 6-MMP levels >5700 pmol/8 × 10^8 red blood cells have been linked with liver toxicity in children [102], but this finding has not been consistent across all studies [103]. If available, metabolite levels may be used to complement liver enzyme monitoring, and TPMT genotype or activity may be determined prior to initiating therapy, but this remains controversial. Mild liver enzyme abnormalities in children on thiopurine therapy may be observed with repeat blood work, but the authors suggest that the dose of thiopurine be reduced by about 50% in patients with more marked derangements. If this does not result in biochemical normalization after several weeks to months, therapy should be withdrawn entirely. Immediate thiopurine discontinuation should be the approach in any patient with clinically overt jaundice. Liver biopsy should be considered if liver tests fail to normalize after medication withdrawal or if there is any suggestion of PHT, even in patients with normal laboratory parameters.

Antitumor Necrosis Factor α (Anti-TNFα)

Based on postmarketing surveillance, the Food and Drug Administration (FDA) has issued warnings about the potential risk of serious liver injury with the use of anti-TNFα antibodies [104]. TNFα plays an important role in many aspects of immune response regulation. The association between anti-TNFα use and the development of autoantibodies is well

known, although the pathological role of these antibodies remains unclear [105]. Anti-TNFα related hepatotoxicity does not appear to be dose-dependent, but instead is thought to occur in genetically susceptible individuals who generate an idiosyncratic immune response after inhibition of the TNFα pathway. The release and presentation of hepatic autoantigens by immune cells may be involved [106].

Infliximab (IFX) and adalimumab (ADA) have been implicated in drug-induced liver injury (DILI) in both rheumatology and IBD populations. The median latency period is 13–18 weeks, but is hugely variable; DILI may have its onset after a single infusion/injection, but 20% occur more than 6 months into therapy [107, 108]. DILI seems to occur more frequently with IFX than ADA; the rate of DILI has been found to be 1/120 IFX-treated patients compared to 1/270 ADA-treated patients [109]. This is in keeping with the findings of a large retrospective review of adult IBD patients, in which IFX accounted for a disproportionate fraction of the 2.7% of patients who developed significant liver enzyme elevations felt to be secondary to anti-TNFα therapy [108]. The most common presentation is an autoimmune phenotype with primarily hepatocellular injury, high rates of autoantibody (especially ANA) positivity, and histological findings compatible with autoimmune hepatitis. However, mixed nonautoimmune and predominantly cholestatic patterns also occur. Cases with autoimmune features may have a longer latency and higher peak ALT [107]. Autoantibody positivity prior to anti-TNFα initiation does not appear to predict the risk of DILI [109]. Cases of DILI with AIH features should be managed with anti-TNFα discontinuation, in which case the prognosis is favorable. Some patients benefit from treatment with corticosteroids [107]. Anti-TNFα associated DILI does not seem to be a class effect, and switching to a different anti-TNFα, with close observation, appears safe. Milder cases of hepatotoxicity without overt autoimmune features often resolve spontaneously without anti-TNFα discontinuation [108]. No data currently exist regarding anti-TNFα associated liver injury in pediatric IBD.

Another concern with anti-TNFα agents is the risk of viral reactivation, in patients with chronic hepatitis B (HBV) infection, particularly those who are HBsAg-positive. Approximately one-third of HBsAg-positive IBD patients were observed to develop liver dysfunction while receiving immunosuppressive therapy, including anti-TNFα [110]. Treatment with anti-TNFα in IBD patients with hepatitis C (HCV) appears to be less of a concern and is generally well tolerated, with most patients displaying either unchanged or even improved biochemistry while receiving anti-TNF therapy [111]. Notably, no pediatric data exist regarding the outcomes of children with IBD and HBV or HCV receiving anti-TNFα. Strong consideration should be given to treating chronic HBV infection in children who are to commence anti-TNF therapy, whereas this may not be necessary in children with HCV. Regardless, routine surveillance with liver enzymes and viral loads should be performed regularly in such children.

A child's immunization history should be carefully reviewed at the time of IBD diagnosis, and laboratory investigations, including HBsAb, HBsAg, anti-HBc, and anti-HCV, should be obtained. Although it is preferable to vaccinate for hepatitis A (HAV) prior to anti-TNFα initiation, seroconversion is still likely once on therapy and should be attempted regardless [112]. Patients with IBD who have nonimmune HBsAb levels (<10 mIU/mL) should be revaccinated with the routine three-dose regimen.

Sulfasalazine and Mesalamine

Sulfasalazine causes two main forms of hepatic injury. First, acute hepatocellular damage may develop as part of a generalized hypersensitivity reaction. This reaction, sometimes referred to as DRESS (drug rash with eosinophilia and systemic symptoms), is characterized by fever, rash, hepatomegaly, lymphadenopathy, atypical lymphocytosis, and eosinophilia, and is thought to be due to the sulfapyridine moiety [113]. The injury typically manifests within 2 months of starting therapy, with a shorter latency upon re-exposure [114]. This reaction is uncommon with data from the UK suggesting an incidence of 0.4% [115]. Prompt sulfasalazine discontinuation is critical, and corticosteroids may be helpful. However, progression to acute liver failure and death has been reported [115, 116]. Second, acute granulomatous hepatitis, characterized by fever, malaise, right upper quadrant pain, variable transaminases, and ALP and noncaseating granulomas on biopsy, may also occur [117]. In addition, cholestatic injury has been described with sulfasalazine use [118]. Mesalamine-induced hepatotoxicity is rare. A UK audit reported an incidence of 3.2 cases per million prescriptions, which was not statistically different from the six cases per million for sulfasalazine [119]. Cholestatic injury, with or without granulomatous hepatitis, resolving upon mesalamine discontinuation has been reported [120–122]. An apparent cross-reactive hypersensitivity reaction with mesalamine after a reaction to sulfasalazine [123] and a case of chronic hepatitis with autoimmune features have also been described [124].

Glucocorticoids

It is postulated that glucocorticoid-related alterations in hepatic lipid metabolism may lead to hepatic steatosis. Steroid use has been identified as an independent risk factor for nonalcoholic fatty liver disease (NAFLD) identified by abdominal imaging in IBD patients [125].

Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive, and almost uniformly fatal extranodal lymphoma. The usual presentation includes fever, fatigue, abnormal liver tests, hepatosplenomegaly, and pancytopenia. Between 1996 and 2011, 36 cases of HSTCL were reported in IBD patients, the majority of whom were young (<35 years) male patients with Crohn disease. Sixteen had received thiopurine monotherapy, and 20 had received a combination of anti-TNF and thiopurine (all had been exposed to IFX) [126]. The absolute risk of HSTCL in all patients receiving thiopurines has been estimated to be 1:45,000 compared to 1:7404 in men <35 years old, whereas the absolute risk for all patients receiving concomitant thiopurine and anti-TNF has been estimated to be slightly less than 1:22,000 compared to approximately 1:3534 in men <35 years [127]. In keeping with this, in a case-control study, anti-TNF combined with thiopurine therapy was associated with a higher risk of HSTCL compared to infliximab alone. At the current time, the role of anti-TNF agents, if any, in the development of HSTCL is uncertain, but the risk appears to be greater with combination therapy [128]. A high degree of suspicion must be maintained for this diagnosis, especially in young males.

Other Liver Diseases and IBD

Cholelithiasis

CD patients have an increased risk of gallstone disease, particularly in the setting of ileal disease and postileal resection. The incidence and prevalence of cholelithiasis in CD patients is 14.35 per 1000 person-years and 11–34%, respectively, compared to 7.75 per 1000 person-years and 5.5–15%, respectively, in controls [129, 130]. Overall, the odds of gallstones are 2.1-fold higher in CD patients compared to the general population. In contrast, definite evidence of an association between UC and cholelithiasis is lacking [129]. Although gallstones are relatively unusual in pediatric populations, 2.3% of children with IBD in an American consortium developed cholelithiasis [22], which significantly exceeds the population prevalence of 0.88–0.99% in individuals <30 years [131]. Bile in patients with CD postileal resection contains higher concentrations of bilirubin, suggesting an increased risk of developing pigment stones. Findings regarding the cholesterol component have been contradictory, with some studies reporting higher, and others lower, cholesterol saturation. The bile composition in patients with UC has not been consistently shown to differ from controls. Previous intestinal resection is the strongest risk factor for gallstone disease in patients with CD, with an ileal resection >30 cm increasing the odds of cholelithiasis sevenfold. Other risk factors include disease location and duration, age, number of clinical recurrences and hospitalizations, total parenteral nutrition, prolonged hospitalization, and female sex. Impaired gallbladder emptying may also be a contributing factor [129]. Symptomatic cholelithiasis should prompt a referral to a pediatric surgeon. Children may also present with cholecystitis, which should be managed with broad-spectrum antibiotics and a general surgery consultation to guide eventual cholecystectomy.

Liver Abscess

Liver abscess is a rare complication of IBD. The precise incidence and prevalence are unknown, but it is more common in CD and in males and tends to occur in the setting of active disease. There is a tendency to develop multiple abscesses, which almost invariably involve the right lobe. The presentation is similar to that in non-IBD patients, but the diagnosis can be challenging and is often overlooked. Investigations, when suspected, should include an ultrasound and blood cultures, which are positive in 50% of cases. Compared to hepatic abscesses in the general population, which are usually polymicrobial, a single pathogen, often *Streptococcus milleri*, is frequently isolated in patients with IBD. Treatment is with prolonged parenteral antibiotics (commonly 4–8 weeks) with or without drainage, preferably percutaneously. An intra-abdominal source should be ruled out. Risk factors for liver abscess in IBD include intra-abdominal abscesses, fistulizing disease, intestinal perforation, abdominal surgery, and malnutrition [129, 132].

Portal Vein Thrombosis and Budd-Chiari Syndrome

Adult and pediatric patients with CD and UC are at increased risk of thromboembolism (TE). In a Danish cohort study using administrative data, the odds of thrombotic events were 1.5–1.8 times higher in IBD patients ≤20 years compared to controls [133]. The relative risk of TE was found to be slightly higher than this in hospitalized children with IBD, namely, 2.36, with an incidence of 118 per 10,000 [134]. Although the incidence of TE is lower in pediatric than adult IBD patients, the relative risk is higher in young patients with IBD [133]. To date, the mechanism behind this prothrombotic state is not fully understood, but it is likely multifactorial and related to the inflammatory state. The potential etiologies for increased thrombosis in IBD include thrombocytosis/platelet activation, hyperhomocysteinemia, increased fibrinogen, impaired fibrinolysis, increased procoagulation factors, decreased anticoagulation factors, and procoagulation mutations. The extent of IBD has also been

shown to correlate with the risk of TE, but TE can occur in patients with UC even after proctocolectomy [134].

Portal vein thrombosis (PVT) appears to occur at higher rates in the IBD population, particularly postoperatively. Most studies suggest it is a rare complication, with a prevalence of 0.1–1% in IBD [135]. The incidence specifically in pediatric IBD patients has been reported to be 9 per 10,000 hospitalizations, with sixfold increased odds compared to non-IBD controls [134]. Overall, the precise epidemiology of the condition is difficult to ascertain as most patients are asymptomatic. The diagnosis may be made at the chronic stage, at which time cavernomatous transformation of the portal vein may be evident on imaging. A variety of imaging modalities can be used to make the diagnosis, including ultrasound with Doppler, contrast-enhanced CT, and MR angiography. Treatment is generally with anticoagulation, although the duration is not well established. While older studies suggested high mortality rates with this complication, more recent publications indicate a more benign natural history [135].

Budd-Chiari syndrome is a rare complication of UC, mostly in adults, but has been reported in a small number of children as well, with an incidence of 2.1 per 10,000 hospitalized pediatric IBD patients [134, 136–138]. It typically presents with hepatomegaly, right upper quadrant pain, and rapid-onset ascites with abnormal liver tests, but 25% can be asymptomatic. Diagnosis is supported by imaging and/or liver biopsy. Therapy may include thrombolysis, anticoagulation, angioplasty, or vascular stents. More definitive treatment, such as porto-/mesocaval shunts, or even liver transplant, may be required in medically refractory cases. Symptomatic treatment of ascites is with diuretics and paracentesis. While outcomes have often been poor in adults, the pediatric cases reported to date have had a favorable evolution with resolution, with anticoagulation or even spontaneously.

Nonalcoholic Fatty Liver Disease

The prevalence of nonalcoholic fatty liver disease (NAFLD) in IBD has varied widely across different studies, ranging from 13 to 100% [1], depending on the diagnostic modality employed and the indication for screening/testing. According to a systematic review, the mean prevalence of fatty liver disease in adults is 23% in UC and 1.5–39.5% in CD, in comparison to 20% in the general population [129]. The prevalence of NAFLD in pediatric IBD patients has never been specifically examined. Overall, it would appear that fatty liver is common in the IBD population, but definitive evidence that the prevalence of NALFD in IBD exceeds that in the general population is lacking. Patients with metabolic risk factors, such as obesity and hypertension, are at increased risk, but these risk factors are not universally present in IBD patients with NAFLD. Coupled with the asymptomatic nature of NAFLD, a high degree of suspicion must to be maintained, particularly in the setting of raised liver enzymes. Diagnostic confirmation requires histopathological assessment, but screening can be performed with transaminases, GGT, and triglycerides. Management includes attaining adequate IBD control and working toward a healthy BMI in patients who are overweight, in conjunction with a pediatric dietitian.

Granulomatous Hepatitis

Granulomatous hepatitis is estimated to occur in <1% of IBD patients, primarily those with CD. It tends to present with a cholestatic picture, especially elevated ALP. The diagnosis is confirmed by visualizing granulomas on liver biopsy. The most common cause in the setting of IBD is medications, especially sulfasalazine, but granulomatous hepatitis can also be an extraintestinal manifestation of IBD, and can be associated with malignancy or infections. Corticosteroids and immunosuppressive agents have been used as treatment [1].

Hepatic Amyloidosis

Amyloidosis is a rare but serious complication of IBD, especially CD. It has a prevalence of 0.5% in IBD, more specifically 0.9–3% in CD, and 0–0.07% in UC [139–141]. The pathogenesis remains unclear. Patients are usually male with extensive, long-standing disease, although amyloidosis may be present at the time of, or even prior to, the diagnosis of IBD. Fistulae and/or abscesses, as well as other extraintestinal manifestations, are common. Amyloidosis is predominantly a disease of the kidneys, but hepatic involvement has been described in a small subset of patients, including in children [141]. Signs and symptoms of hepatic amyloidosis are few, and liver tests are generally normal. The diagnosis is established by biopsy, and, often, only comes to light at the time of autopsy. Mortality is intricately tied to the renal disease, but hepatic involvement is associated with a reduced likelihood of survival [142].

Primary Biliary Cholangitis (Previously Termed Primary Biliary Cirrhosis)

Primary biliary cholangitis (PBC) is characterized by chronic inflammatory destruction of the intrahepatic bile ducts and infiltration by lymphocytes and plasma cells into the portal

tract. To date, there have been approximately 20 reports of PBC occurring in association with UC, none of which have involved children [143, 144]. PBC associated with UC has less of a female predominance, and affects younger patients than PBC in the general population. In addition, the colitis tends to be mild, often limited to the rectum. The typical features of PBC include pruritus, cholestasis, and increased IgM, but these can be seen in other hepatobiliary disorders associated with UC, such as PSC. Serum antimitochondrial antibody (AMA), which is almost always positive in PBC, but generally negative in PSC, is very helpful for distinguishing the two. Liver biopsy can also provide additional useful information; it typically shows granulomatous inflammation of the periportal area in PBC.

A Clinical Approach to Children with IBD and Liver Abnormalities

Children with IBD who develop abnormal liver biochemistry or physical stigmata of liver disease may have a wide range of potential underlying diagnoses, as reviewed in this chapter. Based on the available but limited evidence presented, the authors suggest the following approach to liver disease in pediatric IBD (Fig. 11.5). All children with IBD should have routine liver biochemistry with ALT, AST, GGT, ALP, fractionated bilirubin, and albumin measured every 6–12 months when the child is well. The frequency of blood work can be increased if the child is unwell or receiving medications with known potential hepatotoxicity, as

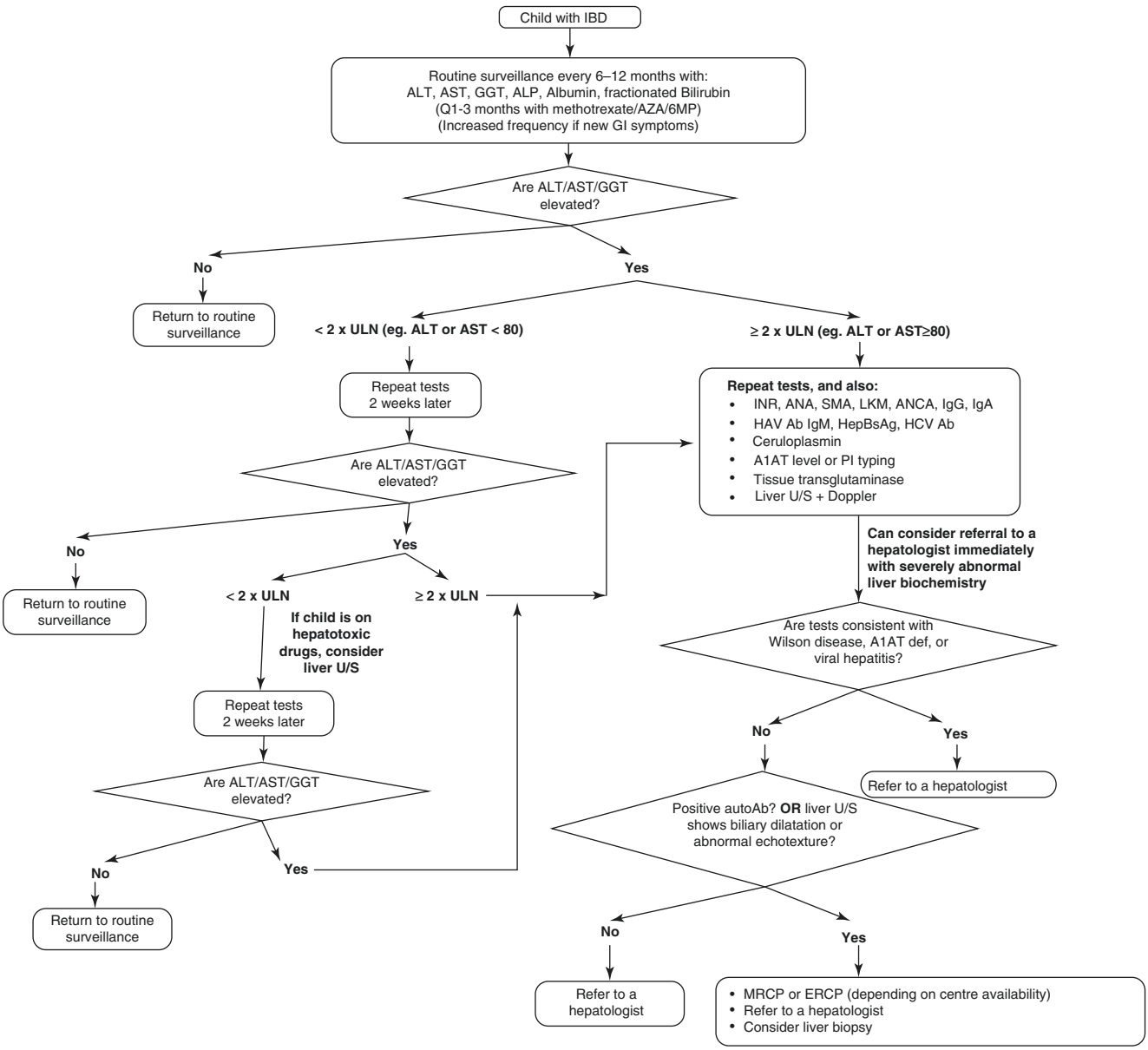

Fig. 11.5 Suggested approach to liver disease in pediatric IBD

detailed above. If low-grade abnormalities are detected, liver tests should be repeated in 1–2 weeks to ensure they are not rising acutely and subsequently followed for the first few months. With more marked elevations, or clinically overt evidence of liver disease, such as hepatosplenomegaly or jaundice, further investigations should be considered, including autoantibodies (ANA, SMA, LKM1, ANCA), serum IgG, viral hepatitis serologies, celiac serology, ceruloplasmin, and alpha-1 antitrypsin level, along with abdominal ultrasound. Depending on the clinical context, MRCP and/or liver biopsy may also be indicated. If medications are felt to be a potential contributor, a trial of reducing the dose or holding the medication entirely (if this is not felt to be detrimental to the child's IBD care) should be performed. The distinction between "low" and "high-grade" elevations is controversial. The authors propose that elevations >2–3× ULN are significant and require further investigation. Additional studies in pediatric IBD populations are required to construct truly evidence-based algorithms to guide the work-up and management of abnormal liver biochemistry and liver disease in children with IBD.

References

1. Navaneethan U, Shen B. Hepatopancreatobiliary manifestations and complications associated with inflammatory bowel disease. Inflamm Bowel Dis. 2010;16:1598–619. doi:10.1002/ibd.21219.
2. Gisbert JP, Luna M, Gonzalez-Lama Y, Pousa ID, Velasco M, Moreno-Otero R, Mate J. Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. Inflamm Bowel Dis. 2007;13:1106–14. doi:10.1002/ibd.20160.
3. Mendes FD, Levy C, Enders FB, Loftus Jr EV, Angulo P, Lindor KD. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. Am J Gastroenterol. 2007;102:344–50. doi:10.1111/j.1572-0241.2006.00947.x.
4. Yamamoto-Furusho JK, Sanchez-Osorio M, Uribe M. Prevalence and factors associated with the presence of abnormal function liver tests in patients with ulcerative colitis. Ann Hepatol. 2010;9:397–401.
5. Nemeth A, Ejderhamn J, Glaumann H, Strandvik B. Liver damage in juvenile inflammatory bowel disease. Liver. 1990;10:239–48.
6. Pusateri AJ, Kim SC, Dotson JL, Balint JP, Potter CJ, Boyle BM, Crandall WV. Incidence, pattern, and etiology of elevated liver enzymes in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2015;60:592–7. doi:10.1097/MPG.0000000000000672.
7. Valentino PL, Feldman BM, Walters TD, Griffiths AM, Ling SC, Pullenayegum EM, Kamath BM. Abnormal liver biochemistry is common in pediatric inflammatory bowel disease: prevalence and associations. Inflamm Bowel Dis. 2015; doi:10.1097/MIB.0000000000000558.
8. Hyams J, Markowitz J, Treem W, Davis P, Grancher K, Daum F. Characterization of hepatic abnormalities in children with inflammatory bowel disease. Inflamm Bowel Dis. 1995;1:27–33.
9. Goyal A, Hyams JS, Lerer T, et al. Liver enzyme elevations within 3 months of diagnosis of inflammatory bowel disease and likelihood of liver disease. J Pediatr Gastroenterol Nutr. 2014;59:321–3. doi:10.1097/mpg.0000000000000409.
10. Riegler G, D'Inca R, Sturniolo GC, et al. Hepatobiliary alterations in patients with inflammatory bowel disease: a multicenter study. Caprilli & Gruppo Italiano Studio Colon-Retto. Scand J Gastroenterol. 1998;33:93–8.
11. Card TR, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. J Hepatol. 2008;48:939–44. doi:10.1016/j.jhep.2008.02.017.
12. Deneau M, Jensen MK, Holmen J, Williams MS, Book LS, Guthery SL. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. Hepatology. 2013;58:1392–400. doi:10.1002/hep.26454.
13. Kaplan GG, Laupland KB, Butzner D, Urbanski SJ, Lee SS. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. Am J Gastroenterol. 2007;102:1042–9. doi:10.1111/j.1572-0241.2007.01103.x.
14. Feldstein AE, Perrault J, El-Youssif M, Lindor KD, Freese DK, Angulo P. Primary sclerosing cholangitis in children: a long-term follow-up study. Hepatology. 2003;38:210–7. doi:10.1053/jhep.2003.50289.
15. Miloh T, Arnon R, Shneider B, Suchy F, Kerkar N. A retrospective single-center review of primary sclerosing cholangitis in children. Clin Gastroenterol Hepatol. 2009;7:239–45. doi:10.1016/j.cgh.2008.10.019.
16. Wilschanski M, Chait P, Wade JA, et al. Primary sclerosing cholangitis in 32 children: clinical, laboratory, and radiographic features, with survival analysis. Hepatology. 1995;22:1415–22.
17. Warren KW, Athanassiades S, Monge JI. Primary sclerosing cholangitis. A study of forty-two cases. Am J Surg. 1966;111:23–38.
18. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol. 2012;56:1181–8. doi:10.1016/j.jhep.2011.10.025.
19. Schrumpf E, Boberg KM. Epidemiology of primary sclerosing cholangitis. Best Pract Res Clin Gastroenterol. 2001;15:553–62. doi:10.1053/bega.2001.0204.
20. Batres LA, Russo P, Mathews M, Piccoli DA, Chuang E, Ruchelli E. Primary sclerosing cholangitis in children: a histologic follow-up study. Pediatr Dev Pathol. 2005;8:568–76. doi:10.1007/s10024-005-0020-0.
21. Dotson JL, Hyams JS, Markowitz J, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr. 2010;51:140–5. doi:10.1097/MPG.0b013e3181ca4db4.
22. Jose FA, Garnett EA, Vittinghoff E, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15:63–8. doi:10.1002/ibd.20604.
23. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51:660–78. doi:10.1002/hep.23294.
24. Mells GF, Kaser A, Karlsen TH. Novel insights into autoimmune liver diseases provided by genome-wide association studies. J Autoimmun. 2013;46:41–54. doi:10.1016/j.jaut.2013.07.004.
25. Williamson KD, Chapman RW. Primary sclerosing cholangitis: a clinical update. Br Med Bull. 2015;114:53–64. doi:10.1093/bmb/ldv019.
26. Eksteen B, Grant AJ, Miles A, et al. Hepatic endothelial CCL25 mediates the recruitment of CCR9+ gut-homing lymphocytes to the liver in primary sclerosing cholangitis. J Exp Med. 2004;200:1511–7. doi:10.1084/jem.20041035.
27. Tabibian JH, O'Hara SP, Lindor KD. Primary sclerosing cholangitis and the microbiota: current knowledge and perspectives on

etiopathogenesis and emerging therapies. Scand J Gastroenterol. 2014;49:901–8. doi:10.3109/00365521.2014.913189.
28. Loftus Jr EV, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut. 2005;54:91–6. doi:10.1136/gut.2004.046615.
29. Halliday JS, Djordjevic J, Lust M, Culver EL, Braden B, Travis SP, Chapman RW. A unique clinical phenotype of primary sclerosing cholangitis associated with Crohn disease. J Crohn Colitis. 2012;6:174–81. doi: http://dx.doi.org/10.1016/j.crohns.2011.07.015.
30. Lundqvist K, Broome U. Differences in colonic disease activity in patients with ulcerative colitis with and without primary sclerosing cholangitis: a case control study. Dis Colon Rectum. 1997;40:451–6.
31. Schaeffer DF, Win LL, Hafezi-Bakhtiari S, Cino M, Hirschfield GM, El-Zimaity H. The phenotypic expression of inflammatory bowel disease in patients with primary sclerosing cholangitis differs in the distribution of colitis. Dig Dis Sci. 2013;58:2608–14. doi:10.1007/s10620-013-2697-7.
32. Faubion Jr WA, Loftus EV, Sandborn WJ, Freese DK, Perrault J. Pediatric "PSC-IBD": a descriptive report of associated inflammatory bowel disease among pediatric patients with psc. J Pediatr Gastroenterol Nutr. 2001;33:296–300.
33. Ordonez F, Lacaille F, Canioni D, et al. Pediatric ulcerative colitis associated with autoimmune diseases: a distinct form of inflammatory bowel disease? Inflamm Bowel Dis. 2012;18:1809–17. doi:10.1002/ibd.22864.
34. Lascurain L, Jensen MK, Guthery SL, Holmen J, Deneau M. Inflammatory bowel disease phenotype in pediatric primary sclerosing cholangitis. Inflamm Bowel Dis. 2016;22:146–50. doi:10.1097/MIB.0000000000000586.
35. Marelli L, Xirouchakis E, Kalambokis G, Cholongitas E, Hamilton MI, Burroughs AK. Does the severity of primary sclerosing cholangitis influence the clinical course of associated ulcerative colitis? Gut. 2011;60:1224–8. doi:10.1136/gut.2010.235408.
36. Cangemi JR, Wiesner RH, Beaver SJ, et al. Effect of proctocolectomy for chronic ulcerative colitis on the natural history of primary sclerosing cholangitis. Gastroenterology. 1989;96:790–4.
37. Cholongitas E, Shusang V, Papatheodoridis GV, et al. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. Liver Transpl. 2008;14:138–43. doi:10.1002/lt.21260.
38. Bjornsson E, Chari S, Silveira M, Gossard A, Takahashi N, Smyrk T, Lindor K. Primary sclerosing cholangitis associated with elevated immunoglobulin G4: clinical characteristics and response to therapy. Am J Ther. 2011;18:198–205. doi:10.1097/MJT.0b013e3181c9dac6.
39. Lindor KD, Kowdley KV, Harrison ME. ACG Clinical Guideline: primary sclerosing cholangitis. Am J Gastroenterol. 2015;110:646–59. quiz 660 doi:10.1038/ajg.2015.112.
40. MacCarty RL, LaRusso NF, Wiesner RH, Ludwig J. Primary sclerosing cholangitis: findings on cholangiography and pancreatography. Radiology. 1983;149:39–44. doi:10.1148/radiology.149.1.6412283.
41. Deneau M, Adler DG, Schwartz JJ, et al. Cholangiocarcinoma in a 17-year-old boy with primary sclerosing cholangitis and inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2011;52:617–20. doi:10.1097/MPG.0b013e3181f9a5d2.
42. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. Gastrointest Endosc. 2002;56:48–54.
43. Ponsioen CY, Vrouenraets SM, Prawirodirdjo W, et al. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. Gut. 2002;51:562–6.
44. Bjornsson E, Olsson R, Bergquist A, et al. The natural history of small-duct primary sclerosing cholangitis. Gastroenterology. 2008;134:975–80. doi:10.1053/j.gastro.2008.01.042.
45. Tabibian JH, Lindor KD. Primary sclerosing cholangitis: a review and update on therapeutic developments. Expert Rev Gastroenterol Hepatol. 2013;7:103–14. doi:10.1586/egh.12.80.
46. Gilger MA, Gann ME, Opekun AR, Gleason Jr WA. Efficacy of ursodeoxycholic acid in the treatment of primary sclerosing cholangitis in children. J Pediatr Gastroenterol Nutr. 2000;31:136–41.
47. Triantos CK, Koukias NM, Nikolopoulou VN, Burroughs AK. Meta-analysis: ursodeoxycholic acid for primary sclerosing cholangitis. Aliment Pharmacol Ther. 2011;34:901–10. doi:10.1111/j.1365-2036.2011.04822.x.
48. Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology. 2009;50:808–14. doi:10.1002/hep.23082.
49. Cox KL, Cox KM. Oral vancomycin: treatment of primary sclerosing cholangitis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1998;27:580–3.
50. Davies YK, Cox KM, Abdullah BA, Safta A, Terry AB, Cox KL. Long-term treatment of primary sclerosing cholangitis in children with oral vancomycin: an immunomodulating antibiotic. J Pediatr Gastroenterol Nutr. 2008;47:61–7. doi:10.1097/MPG.0b013e31816fee95.
51. Tabibian JH, Weeding E, Jorgensen RA, Petz JL, Keach JC, Talwalkar JA, Lindor KD. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. Aliment Pharmacol Ther. 2013;37:604–12. doi:10.1111/apt.12232.
52. Abarbanel DN, Seki SM, Davies Y, et al. Immunomodulatory effect of vancomycin on Treg in pediatric inflammatory bowel disease and primary sclerosing cholangitis. J Clin Immunol. 2013;33:397–406. doi:10.1007/s10875-012-9801-1.
53. Farkkila M, Karvonen AL, Nurmi H, Nuutinen H, Taavitsainen M, Pikkarainen P, Karkkainen P. Metronidazole and ursodeoxycholic acid for primary sclerosing cholangitis: a randomized placebo-controlled trial. Hepatology. 2004;40:1379–86. doi:10.1002/hep.20457.
54. Silveira MG, Torok NJ, Gossard AA, Keach JC, Jorgensen RA, Petz JL, Lindor KD. Minocycline in the treatment of patients with primary sclerosing cholangitis: results of a pilot study. Am J Gastroenterol. 2009;104:83–8. doi:10.1038/ajg.2008.14.
55. Tabibian JH, Gossard A, El-Youssef M, et al. Prospective clinical trial of rifaximin therapy for patients with primary sclerosing cholangitis. Am J Ther. 2014;doi:10.1097/mjt.0000000000000102.
56. Johnson GK, Saeian K, Geenen JE. Primary sclerosing cholangitis treated by endoscopic biliary dilation: review and long-term follow-up evaluation. Curr Gastroenterol Rep. 2006;8:147–55.
57. Venkat VL, Ranganathan S, Sindhi R. The challenges of liver transplantation in children with primary sclerosing cholangitis. Expert Rev Gastroenterol Hepatol. 2015;9:289–94. doi:10.1586/17474124.2015.1002085.
58. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, Mazariegos GV. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2014;59:112–31. doi:10.1097/mpg.0000000000000431.
59. Miloh T, Anand R, Yin W, Vos M, Kerkar N, Alonso E, Studies of Pediatric Liver Transplantation Research Group. Pediatric liver transplantation for primary sclerosing cholangitis. Liver Transpl. 2011;17:925–33. doi:10.1002/lt.22320.
60. Venkat VL, Ranganathan S, Mazariegos GV, Sun Q, Sindhi R. Recurrence of primary sclerosing cholangitis in pediatric liver

transplant recipients. Liver Transpl. 2014;20:679–86. doi:10.1002/lt.23868.
61. Jimenez-Rivera C, Ling SC, Ahmed N, et al. Incidence and characteristics of autoimmune hepatitis. Pediatrics. 2015; doi:10.1542/peds.2015-0578.
62. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, Mieli-Vergani G. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology. 2001;33:544–53. doi:10.1053/jhep.2001.22131.
63. Mieli-Vergani G, Vergani D. Paediatric autoimmune liver disease. Arch Dis Child. 2013;98:1012–7. doi:10.1136/archdischild-2013-303848.
64. Mieli-Vergani G, Vergani D. Autoimmune hepatitis in children: what is different from adult AIH? Semin Liver Dis. 2009;29:297–306. doi:10.1055/s-0029-1233529.
65. Gregorio GV, Portmann B, Reid F, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology. 1997;25:541–7. doi:10.1002/hep.510250308.
66. Manns MP, Lohse AW, Vergani D. Autoimmune hepatitis–update 2015. J Hepatol. 2015;62:S100–11. doi:10.1016/j.jhep.2015.03.005.
67. Mieli-Vergani G, Vergani D. Autoimmune hepatitis. Nat Rev Gastroenterol Hepatol. 2011;8:320–9. doi:10.1038/nrgastro.2011.69.
68. Radhakrishnan KR, Alkhouri N, Worley S, et al. Autoimmune hepatitis in children–impact of cirrhosis at presentation on natural history and long-term outcome. Dig Liver Dis. 2010;42:724–8. doi:10.1016/j.dld.2010.01.002.
69. Floreani A, Liberal R, Vergani D, Mieli-Vergani G. Autoimmune hepatitis: contrasts and comparisons in children and adults – a comprehensive review. J Autoimmun. 2013;46:7–16. doi:10.1016/j.jaut.2013.08.004.
70. Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 2010;139:1198–206. doi:10.1053/j.gastro.2010.06.046.
71. Liberal R, Longhi MS, Grant CR, Mieli-Vergani G, Vergani D. Autoimmune hepatitis after liver transplantation. Clin Gastroenterol Hepatol. 2012;10:346–53. doi:10.1016/j.cgh.2011.10.028.
72. Liberal R, Zen Y, Mieli-Vergani G, Vergani D. Liver transplantation and autoimmune liver diseases. Liver Transpl. 2013;19:1065–77. doi:10.1002/lt.23704.
73. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol. 2011;54:374–85. doi:10.1016/j.jhep.2010.09.002.
74. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51:2193–213. doi:10.1002/hep.23584.
75. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51:237–67. doi:10.1016/j.jhep.2009.04.009.
76. Beuers U, Hubers LM, Doorenspleet M, et al. IgG4-associated cholangitis – a mimic of PSC. Dig Dis. 2015;33(Suppl 2):176–80. doi:10.1159/000440830.
77. Dastis SN, Latinne D, Sempoux C, Geubel AP. Ulcerative colitis associated with IgG4 cholangitis: similar features in two HLA identical siblings. J Hepatol. 2009;51:601–5. doi:10.1016/j.jhep.2009.05.032.
78. Hirano K, Kawabe T, Yamamoto N, et al. Serum IgG4 concentrations in pancreatic and biliary diseases. Clin Chim Acta. 2006;367:181–4. doi:10.1016/j.cca.2005.11.031.
79. Mendes FD, Jorgensen R, Keach J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006;101:2070–5. doi:10.1111/j.1572-0241.2006.00772.x.
80. Zhang L, Lewis JT, Abraham SC, et al. IgG4+ plasma cell infiltrates in liver explants with primary sclerosing cholangitis. Am J Surg Pathol. 2010;34:88–94. doi:10.1097/PAS.0b013e3181c6c09a.
81. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134:706–15. doi:10.1053/j.gastro.2007.12.009.
82. Ohara H, Okazaki K, Tsubouchi H, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci. 2012;19:536–42. doi:10.1007/s00534-012-0521-y.
83. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Risk of liver injury among methotrexate users: a meta-analysis of randomised controlled trials. Semin Arthritis Rheum. 2015;45:156–62. doi:10.1016/j.semarthrit.2015.05.003.
84. Fournier MR, Klein J, Minuk GY, Bernstein CN. Changes in liver biochemistry during methotrexate use for inflammatory bowel disease. Am J Gastroenterol. 2010;105:1620–6. doi:10.1038/ajg.2010.21.
85. Te HS, Schiano TD, Kuan SF, Hanauer SB, Conjeevaram HS, Baker AL. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol. 2000;95:3150–6. doi:10.1111/j.1572-0241.2000.03287.x.
86. Sunseri W, Hyams JS, Lerer T, et al. Retrospective cohort study of methotrexate use in the treatment of pediatric Crohn disease. Inflamm Bowel Dis. 2014;20:1341–5. doi:10.1097/mib.0000000000000102.
87. Turner D, Doveh E, Cohen A, et al. Efficacy of oral methotrexate in paediatric Crohn disease: a multicentre propensity score study. Gut. 2015;64(12):1898–904. doi:10.1136/gutjnl-2014-307964. Epub 2014 Nov 21.
88. Valentino PL, Church PC, Shah PS, Beyene J, Griffiths AM, Feldman BM, Kamath BM. Hepatotoxicity caused by methotrexate therapy in children with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2014;20:47–59. doi:10.1097/01.MIB.0000436953.88522.3e.
89. Khan N, Abbas AM, Whang N, Balart LA, Bazzano LA, Kelly TN. Incidence of liver toxicity in inflammatory bowel disease patients treated with methotrexate: a meta-analysis of clinical trials. Inflamm Bowel Dis. 2012;18:359–67. doi:10.1002/ibd.21820.
90. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol. 2009;60:824–37. doi:10.1016/j.jaad.2008.11.906.
91. Bousvaros A. Use of immunomodulators and biologic therapies in children with inflammatory bowel disease. Expert Rev Clin Immunol. 2010;6:659–66. doi:10.1586/eci.10.46.
92. Gisbert JP, Gonzalez-Lama Y, Mate J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. Am J Gastroenterol. 2007;102:1518–27. doi:10.1111/j.1572-0241.2007.01187.x.
93. Lee MN, Kang B, Choi SY, et al. Relationship between azathioprine dosage, 6-thioguanine nucleotide levels, and therapeutic response in pediatric patients with IBD treated with azathioprine. Inflamm Bowel Dis. 2015;21:1054–62. doi:10.1097/MIB.0000000000000347.
94. Riello L, Talbotec C, Garnier-Lengline H, et al. Tolerance and efficacy of azathioprine in pediatric Crohn disease. Inflamm Bowel Dis. 2011;17:2138–43. doi:10.1002/ibd.21612.
95. Haboubi NY, Ali HH, Whitwell HL, Ackrill P. Role of endothelial cell injury in the spectrum of azathioprine-induced liver disease after renal transplant: light microscopy and ultrastructural observations. Am J Gastroenterol. 1988;83:256–61.
96. Dubinsky MC, Vasiliauskas EA, Singh H, et al. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. Gastroenterology. 2003;125:298–303. doi:10.1016/s0016-5085(03)00938-7.

97. Calabrese E, Hanauer SB. Assessment of non-cirrhotic portal hypertension associated with thiopurine therapy in inflammatory bowel disease. J Crohns Colitis. 2011;5:48–53. doi:10.1016/j.crohns.2010.08.007.
98. Seiderer J, Zech CJ, Reinisch W, et al. A multicenter assessment of liver toxicity by MRI and biopsy in IBD patients on 6-thioguanine. J Hepatol. 2005;43:303–9. doi:10.1016/j.jhep.2005.02.051.
99. Musumba CO. Review article: the association between nodular regenerative hyperplasia, inflammatory bowel disease and thiopurine therapy. Aliment Pharmacol Ther. 2013;38:1025–37. doi:10.1111/apt.12490.
100. Russmann S, Zimmermann A, Krähenbühl S, Kern B, Reichen J. Veno-occlusive disease, nodular regenerative hyperplasia and hepatocellular carcinoma after azathioprine treatment in a patient with ulcerative colitis. Eur J Gastroenterol Hepatol. 2001;13:287–90.
101. Khokhar OS, Lewis JH. Hepatotoxicity of agents used in the management of inflammatory bowel disease. Dig Dis. 2010;28:508–18. doi:10.1159/000320410.
102. Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Theoret Y, Seidman EG. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology. 2000;118:705–13.
103. Konidari A, Anagnostopoulos A, Bonnett LJ, Pirmohamed M, El-Matary W. Thiopurine monitoring in children with inflammatory bowel disease: a systematic review. Br J Clin Pharmacol. 2014;78:467–76. doi:10.1111/bcp.12365.
104. Connor V. Anti-TNF therapies: a comprehensive analysis of adverse effects associated with immunosuppression. Rheumatol Int. 2011;31:327–37. doi:10.1007/s00296-009-1292-x.
105. Vaz JL, Fernandes V, Nogueira F, Arnobio A, Levy RA. Infliximab-induced autoantibodies: a multicenter study. Clin Rheumatol. 2015; doi:10.1007/s10067-015-3140-6.
106. Weiler-Normann C, Schramm C, Quaas A, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. J Hepatol. 2013;58:529–34. doi:10.1016/j.jhep.2012.11.010.
107. Ghabril M, Bonkovsky HL, Kum C, et al. Liver injury from tumor necrosis factor-alpha antagonists: analysis of thirty-four cases. Clin Gastroenterol Hepatol. 2013;11:558–564.e553. doi:10.1016/j.cgh.2012.12.025.
108. Shelton E, Chaudrey K, Sauk J, et al. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41:972–9. doi:10.1111/apt.13159.
109. Bjornsson ES, Gunnarsson BI, Grondal G, et al. Risk of drug-induced liver injury from tumor necrosis factor antagonists. Clin Gastroenterol Hepatol. 2015;13:602–8. doi:10.1016/j.cgh.2014.07.062.
110. Loras C, Gisbert JP, Minguez M, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. Gut. 2010;59:1340–6. doi:10.1136/gut.2010.208413.
111. Lin MV, Blonski W, Buchner AM, Reddy KR, Lichtenstein GR. The influence of anti-TNF therapy on the course of chronic hepatitis C virus infection in patients with inflammatory bowel disease. Dig Dis Sci. 2013;58:1149–56.
112. Park SH, Yang SK, Park SK, et al. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2014;20:69–74. doi:10.1097/01.MIB.0000437736.91712.a1.
113. Boyer DL, Li BU, Fyda JN, Friedman RA. Sulfasalazine-induced hepatotoxicity in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1989;8:528–32.
114. Bashir RM, Lewis JH. Hepatotoxicity of drugs used in the treatment of gastrointestinal disorders. Gastroenterol Clin North Am. 1995;24:937–67.
115. Jobanputra P, Amarasena R, Maggs F, et al. Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: a case series from a local surveillance of serious adverse events. BMC Musculoskelet Disord. 2008;9:48. doi:10.1186/1471-2474-9-48.
116. Ribe J, Benkov KJ, Thung SN, Shen SC, LeLeiko NS. Fatal massive hepatic necrosis: a probable hypersensitivity reaction to sulfasalazine. Am J Gastroenterol. 1986;81:205–8.
117. Namias A, Bhalotra R, Donowitz M. Reversible sulfasalazine-induced granulomatous hepatitis. J Clin Gastroenterol. 1981;3:193–8.
118. Quallich LG, Greenson J, Haftel HM, Fontana RJ. Is it Crohn disease? A severe systemic granulomatous reaction to sulfasalazine in patient with rheumatoid arthritis. BMC Gastroenterol. 2001;1:8.
119. Ransford RA, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut. 2002;51:536–9.
120. Braun M, Fraser GM, Kunin M, Salamon F, Tur-Kaspa R. Mesalamine-induced granulomatous hepatitis. Am J Gastroenterol. 1999;94:1973–4. doi:10.1111/j.1572-0241.1999.01245.x.
121. Stelzer T, Kohler S, Marques Maggio E, Heuss LT. An unusual cause of febrile hepatitis. BMJ Case Rep. 2015; 2015. doi:10.1136/bcr-2014-205857.
122. Stoschus B, Meybehm M, Spengler U, Scheurlen C, Sauerbruch T. Cholestasis associated with mesalazine therapy in a patient with Crohn disease. J Hepatol. 1997;26:425–8.
123. Hautekeete ML, Bourgeois N, Potvin P, et al. Hypersensitivity with hepatotoxicity to mesalazine after hypersensitivity to sulfasalazine. Gastroenterology. 1992;103:1925–7.
124. Deltenre P, Berson A, Marcellin P, Degott C, Biour M, Pessayre D. Mesalazine (5-aminosalicylic acid) induced chronic hepatitis. Gut. 1999;44:886–8.
125. Sourianarayanane A, Garg G, Smith TH, Butt MI, McCullough AJ, Shen B. Risk factors of non-alcoholic fatty liver disease in patients with inflammatory bowel disease. J Crohns Colitis. 2013;7:e279–85. doi:10.1016/j.crohns.2012.10.015.
126. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9:36–41 e31. doi:10.1016/j.cgh.2010.09.016.
127. Mason M, Siegel CA. Do inflammatory bowel disease therapies cause cancer? Inflamm Bowel Dis. 2013;19:1306–21. doi:10.1097/MIB.0b013e3182807618.
128. Deepak P, Sifuentes H, Sherid M, Stobaugh D, Sadozai Y, Ehrenpreis ED. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha) inhibitors: results of the REFURBISH study. Am J Gastroenterol. 2013;108:99–105. doi:10.1038/ajg.2012.334.
129. Gizard E, Ford AC, Bronowicki JP, Peyrin-Biroulet L. Systematic review: the epidemiology of the hepatobiliary manifestations in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2014;40:3–15. doi:10.1111/apt.12794.
130. Parente F, Pastore L, Bargiggia S, et al. Incidence and risk factors for gallstones in patients with inflammatory bowel disease: a large case-control study. Hepatology. 2007;45:1267–74. doi:10.1002/hep.21537.
131. Ehlin AG, Montgomery SM, Ekbom A, Pounder RE, Wakefield AJ. Prevalence of gastrointestinal diseases in two British national birth cohorts. Gut. 2003;52:1117–21.
132. Margalit M, Elinav H, Ilan Y, Shalit M. Liver abscess in inflammatory bowel disease: report of two cases and review of the literature. J Gastroenterol Hepatol. 2004;19:1338–42. doi:10.1111/j.1440-1746.2004.03368.x.
133. Kappelman MD, Horvath-Puho E, Sandler RS, et al. Thromboembolic risk among Danish children and adults with inflammatory bowel diseases: a population-based nationwide study. Gut. 2011;60:937–43. doi:10.1136/gut.2010.228585.
134. Nylund CM, Goudie A, Garza JM, Crouch G, Denson LA. Venous thrombotic events in hospitalized children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2013;56:485–91. doi:10.1097/MPG.0b013e3182801e43.

135. Maconi G, Bolzacchini E, Dell'Era A, Russo U, Ardizzone S, de Franchis R. Portal vein thrombosis in inflammatory bowel diseases: a single-center case series. J Crohns Colitis. 2012;6:362–7. doi:10.1016/j.crohns.2011.10.003.
136. Kraut J, Berman JH, Gunasekaran TS, Allen R, McFadden J, Messersmith R, Pellettiere E. Hepatic vein thrombosis (Budd-Chiari syndrome) in an adolescent with ulcerative colitis. J Pediatr Gastroenterol Nutr. 1997;25:417–20.
137. Rahhal RM, Pashankar DS, Bishop WP. Ulcerative colitis complicated by ischemic colitis and Budd Chiari syndrome. J Pediatr Gastroenterol Nutr. 2005;40:94–7.
138. Socha P, Ryzko J, Janczyk W, Dzik E, Iwanczak B, Krzesiek E. Hepatic vein thrombosis as a complication of ulcerative colitis in a 12-year-old patient. Dig Dis Sci. 2007;52:1293–8. doi:10.1007/s10620-006-9503-8.
139. Greenstein AJ, Sachar DB, Panday AK, et al. Amyloidosis and inflammatory bowel disease. A 50-year experience with 25 patients. Medicine (Baltimore). 1992;71:261–70.
140. Serra I, Oller B, Manosa M, Naves JE, Zabana Y, Cabre E, Domenech E. Systemic amyloidosis in inflammatory bowel disease: retrospective study on its prevalence, clinical presentation, and outcome. J Crohns Colitis. 2010;4:269–74. doi:10.1016/j.crohns.2009.11.009.
141. Wester AL, Vatn MH, Fausa O. Secondary amyloidosis in inflammatory bowel disease: a study of 18 patients admitted to Rikshospitalet University Hospital, Oslo, from 1962 to 1998. Inflamm Bowel Dis. 2001;7:295–300.
142. Sattianayagam PT, Gillmore JD, Pinney JH, et al. Inflammatory bowel disease and systemic AA amyloidosis. Dig Dis Sci. 2013;58:1689–97. doi:10.1007/s10620-012-2549-x.
143. Tada F, Abe M, Nunoi H, et al. Ulcerative colitis complicated with primary biliary cirrhosis. Intern Med. 2011;50:2323–7. doi:10.2169/internalmedicine.50.5919.
144. Xiao WB, Liu YL. Primary biliary cirrhosis and ulcerative colitis: a case report and review of literature. World J Gastroenterol. 2003;9:878–80.