Hepatic Issues and Complications Associated With Inflammatory Bowel Disease: A Clinical Report From the NASPGHAN Inflammatory Bowel Disease and Hepatology Committees

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ABSTRACT

Hepatobiliary disorders are common in patients with inflammatory bowel disease (IBD), and persistent abnormal liver function tests are found in approximately 20% to 30% of individuals with IBD. In most cases, the cause of these elevations will fall into 1 of 3 main categories. They can be as a result of extraintestinal manifestations of the disease process, related to medication toxicity, or the result of an underlying primary hepatic disorder unrelated to IBD. This latter possibility is beyond the scope of this review article, but does need to be considered in anyone with elevated liver function tests. This review is provided as a clinical summary of some of the major hepatic issues that may occur in patients with IBD.

Key Words: autoimmune hepatitis, Crohn disease, hepatitis, inflammatory bowel disease, primary sclerosing cholangitis, ulcerative colitis

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Hepatobiliary disorders are common in patients with inflammatory bowel disease (IBD), and persistent abnormal liver enzyme tests are found in approximately 20% to 30% of individuals with IBD (1–4). In most cases, the cause of these elevations will fall into 1 of 3 main categories. They can be a result of extraintestinal manifestations of the disease process, related to medication toxicity, or the result of an underlying primary hepatic disorder unrelated to IBD (Table 1). This latter possibility is beyond the scope of this clinical report, but does need to be considered in anyone with elevated liver enzyme levels. This report is provided as a clinical summary of some of the major hepatic issues that may manifest in patients with IBD.

Extraintestinal Associations of Inflammatory Bowel Disease

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, progressive, cholestatic liver disease. It is characterized by inflammation and fibrosis of the entire biliary tree, with multifocal bile duct strictures. PSC is rare in the general pediatric population, with an incidence and prevalence of 0.2 and 1.5 cases per 100,000 children, respectively (5). The majority of PSC cases appear concurrently with IBD, particularly ulcerative colitis (UC) (6,7). The proportion of patients with IBD with PSC varies and is most often reported to be 4% or less (6,8,9). Study designs vary greatly and may underestimate the true prevalence, however. Rates of PSC in IBD are 10% to 25% in series that are population based, that have longer follow-up (10), or where groups of patients are screened with liver biopsy and/or cholangiography regardless of symptoms (11,12).

Intestinal inflammation in a patient with PSC may represent a unique phenotype of IBD, termed PSC-IBD (7). PSC-IBD is characterized by more frequent pancolitis with rectal sparing, and a higher incidence of backwash ileitis compared with UC (7). Patients with Crohn disease (CD) and PSC are more likely to have Crohn colitis (7,13–15). The IBD activity of PSC-IBD may be less severe (15,16), with a lower rate of colectomy (17). Patients with PSC-IBD are, however, at much greater risk of colorectal carcinoma (18), and have a worsened overall survival compared with patients with traditional UC (7). In addition, pouchitis is more common in PSC-IBD after colectomy with ileal pouch-anal anastomosis surgery (19,20).

Diagnosis

The diagnosis of PSC is based on a cholestatic serum biochemical profile with characteristic changes on liver histology

TABLE 1. Hepatobiliary issues to consider in patients with inflammatory bowel disease

Extraintestinal manifestations:
    Immune-related:
        Primary sclerosing cholangitis
        Autoimmune hepatitis
        Autoimmune sclerosing cholangitis
    Thrombotic disorders:
        Portal vein thrombosis
        Venous thromboembolism
        Hepatic vein thrombosis
Medication Toxicity:
    Glucocorticoids
    Sulfasalazine
    Thiopurines
    Methotrexate
    Anti-TNFs
Underlying disorder:
    Cholelithiasis
    Viral Hepatitis
    Transplant issues
    IgG4 cholangiopathy
    Granulomatous hepatitis
    Primary biliary cirrhosis
    Hepatic amyloidosis
    Nonalcoholic fatty liver disease/steatohepatitis

TNF = tumor necrosis factor.

(fibro-obliterative cholangitis, periductal fibrosis), and/or cholangiography (multifocal bile duct strictures and segmental dilations) typically initially imaged by magnetic resonance cholangiopancreatography (MRCP), and confirmed by endoscopic retrograde cholangiopancreatography (ERCP) if needed (21). Liver involvement of PSC progresses independent of the bowel involvement in IBD (7,22). In fact, patients who undergo total colectomy for IBD continue to have PSC activity. Immunosuppressive therapy for IBD does not appear to affect the progression of PSC. Clinicians must consider PSC even in patients with IBD who are in complete remission of their IBD, and anyone initially presenting with PSC should undergo endoscopic testing for IBD (23). Many patients with PSC are diagnosed within 1 year of an IBD diagnosis (5). A recent analysis of abnormal liver enzymes in pediatric patients with IBD found that a γ-glutamyl transpeptidase (GGT) of >252 U/L was highly sensitive (99%) and had good specificity (71%) for PSC/autoimmune sclerosing cholangitis (ASC), whereas an elevated alanine aminotranotransferase (ALT) had a low specificity for it (4). In a large, prospective pediatric series, patients with IBD with elevated ALT and GGT within 3 months of diagnosis were 660 times more likely to develop IBD-related liver disease compared with those with normal ALT and GGT (24). The authors recommended screening all newly diagnosed patients with IBD with ALT and GGT (24). If the elevated ALT and GGT tests resolve rapidly after diagnosis and treatment of their IBD, then they would not require further evaluation with MRCP or ERCP and can be periodically monitored by laboratory testing. It must, however, be realized that cholangiopathy may develop at any time, and as many as a third of patients with PSC may not show symptoms or biochemical changes for 2 or more years after their IBD diagnosis (5).

Outcomes

Cholangitis, cirrhosis, end-stage liver disease, and/or cholangiocarcinoma develop in up to 37% of pediatric patients within 5 years of PSC diagnosis (3). The 5-year survival with the native liver is approximately 80% (5,25,26). PSC is one of the most important sources of morbidity and mortality for pediatric patients with IBD. In a population-based study of more than 600 pediatric patients with IBD followed for a median of approximately 6 years, 8 deaths or liver transplants were related to PSC, 2 deaths were from hematologic malignancy, and only 1 death was secondary to complications of intestinal disease (colorectal cancer [CRC]) (5).

Treatment

Treatment of PSC is mainly supportive and palliative. Bile acids and antimicrobials have received the most attention and clinical use, and are discussed below. Several medicines have been shown to improve liver biochemistry with prolonged therapy, but no drug has been proven to alter the natural history of the disease. Liver transplantation (LT) remains the only option for progressive PSC.

Pediatric data on ursodeoxycholic acid (ursodiol) are limited. Small series have shown improvement in liver biochemistries, but data are lacking on histology, cholangiography, and survival outcomes (25–27). Currently a prospective trial of ursodiol treatment for PSC in children is underway and is recruiting subjects (*ClinicalTrials.gov* NCT01088607). Ursodiol has been extensively studied in adult PSC, and doses of 17 to 23 mg$\cdot$kg$^{-1}\cdot$day^{-1} will generally lead to improvement in liver biochemistries, but patient survival has not improved (25–27). Conversely, concerns over adverse effects from high-dose ursodiol have been raised. A randomized trial of ursodiol (28–30 mg$\cdot$kg$^{-1}\cdot$day^{-1}) for adults with PSC was terminated early due to clinical deterioration of patients in the treatment arm (28). Ursodiol use was associated with a 2-fold risk of death or transplant and a 4-fold risk of CRC (28). One expert group now specifically recommends against the use of ursodiol for PSC in adults in general, although it remains widely prescribed in moderate doses (21). Based on these adult data, high-dose ursodiol (28–30 mg$\cdot$kg$^{-1}\cdot$day^{-1}) should be avoided in children.

Limited anecdotal evidence supports the use of oral vancomycin as a potential treatment of pediatric PSC. A case series of 14 pediatric patients treated with oral vancomycin described complete normalization in ALT, GGT, and erythrocyte sedimentation rate in all noncirrhotic PSC patients (4). In contrast, during prospective trials, only 0% to 40% of adult patients with PSC achieved normal liver biochemistry endpoints after, and up to, 1 year of vancomycin therapy (5,6). Two prospective open-label trials of vancomycin therapy in pediatric PSC are currently enrolling patients (*Clinicaltrials.gov* identifiers: NCT02137668 and NCT01802073). Additional adult PSC studies have shown positive effects on liver biochemistry with minocycline (7) and metronidazole (8), although no effect was seen with rifaximin (9). Data demonstrating improvement in liver histology, cholangiography, or patient survival with any antibiotic therapy are lacking. At this time, antibiotic therapy for PSC in children is still considered experimental.

Despite at least a partially immune-mediated etiology of PSC, immunosuppressive and immunomodulatory medications have not proven to be beneficial. Infliximab (29), budesonide (30), azathioprine (AZA), calcineurin inhibitors, and mechanistic target of rapamycin inhibitors are ineffective (31). The lack of efficacy of these medications is supported by the general observation of progression of PSC in some patients despite concurrent immunosuppression for their IBD (32).

Patients with PSC with advanced disease will need access to centers that perform ERCP. Chronic cholangitis may require biliary stent placement, balloon stricture dilation, and/or sphincterotomy to relieve an obstruction (33). Dominant strictures require brush cytology for evaluation of cholangiocarcinoma (17,21,34). Balloon dilation of dominant strictures before end-stage liver disease may

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improve patient survival with the native liver (35). ERCP should be performed by interventional endoscopists with experience in PSC management. Perioperative antibiotics should be administered for any interventional procedure involving the biliary system in a patient with PSC, and often involves a fluoroquinolone such as ciprofloxacin. The use of rectal or intramuscular indomethacin, or other nonsteroidal anti-inflammatory drugs to reduce post-ERCP pancreatitis has not been specifically evaluated in the setting of PSC.

LT in PSC should be considered in the presence of end-stage liver disease with decompensated cirrhosis, hilar cholangiocarcinoma (with protocol chemotherapy and radiation), intractable pruritus, and chronic cholangitis refractory to biliary stenting and/or stricture dilation. Survival after LT for PSC is similar to that for other pediatric indications (36); however, the disease may recur in the graft in up to 20% of patients (37). Traditionally surgeons avoid duct to duct biliary anastomoses in these patients; however, more recent data suggest that outcomes with duct to duct are at least no worse than with duct to roux limb (38), or perhaps better (39). Because of higher risk of colorectal carcinoma in PSC, adult recommendations are for these patients to undergo surveillance colonoscopy every 1 to 2 years (40). Although similar recommendations do not exist for pediatric patients with PSC, most pediatric IBD clinicians will follow this surveillance protocol. Similarly from a hepatic standpoint, adult patients typically undergo annual MRCP imaging, CA 19–9, and AFP levels that are not routinely performed on children due to the low risk of cancer development in this population (21). Some pediatric IBD clinicians may choose to do this surveillance protocol as well.

Autoimmune Hepatitis and Inflammatory Bowel Disease

Autoimmune hepatitis (AIH) is the most common immune-mediated liver disease, and is characterized by elevated serum transaminase levels, interface hepatitis on liver biopsy, increased levels of immunoglobulin G and the presence of specific autoantibodies (41). Although AIH is relatively common in the general population, it is also associated with IBD, but seen less often than PSC. Thus, it remains an important and treatable hepatic complication of IBD.

Multiple studies have described the frequency of AIH in IBD as ranging from 0.6% to 1.6% (9,42,43). The diagnostic criteria for AIH were, however, not robust in these studies, and evaluation was not done for the overlap syndrome, ASC, that is discussed below. In a carefully constructed population-based study in Utah, the frequency of AIH in IBD was found to be only 0.3%, whereas ASC was 5 times more frequent (5). In general, AIH has a female preponderance but it is not clear if this association persists in patients with IBD.

Two broad types of AIH are recognized. In AIH type 1, antinuclear antibodies and/or smooth muscle antibodies (ANAs/SMAs) are positive, whereas in AIH type 2 antibodies to liver/kidney microsomal type 1 and/or antiliver cytosol type 1 are positive (44). In children, lower antibody titers are still considered significant for all cases of AIH (IBD and non-IBD alike), such that 1:20 for ANA or SMA, and 1:10 for anti–liver/kidney microsomal type 1 are considered to be of diagnostic importance (whereas in adults 1:40 is clinically relevant) (45). In addition, p-ANCA is frequently positive in AIH type 1, yet is typically negative in AIH type 2 (46). AIH type 1 accounts for two-thirds of the cases and presents often around puberty, whereas AIH type 2 tends to present at a younger age. Currently, insufficient data exist to indicate if one type is more prevalent in IBD than the other (5).

Autoimmune Hepatitis Clinical Presentation

Although the clinical presentation of AIH can include nonspecific symptoms such as fatigue, nausea, abdominal pain, and arthralgia, patients may present with more typical symptoms and signs of liver disease including jaundice, acute hepatitis, or even fulminant hepatic failure (45). In association with IBD, AIH is usually, however, diagnosed after the identification of elevated serum transaminases. A liver biopsy is typically necessary to confirm the diagnosis and to rule out other causes of liver biochemistry derangement, such as PSC or drug toxicity, and, in addition, to provide information regarding the extent of liver damage. Characteristic histologic findings in AIH include dense portal tract inflammation, lobular activity, interface hepatitis, and potentially fibrosis (47).

AIH is particularly aggressive in children, but responds well to immune suppression, which should be instituted promptly to avoid disease progression (45). Elevations of serum transaminases may fluctuate in AIH, and therefore it is important to evaluate the patient with IBD with abnormal liver biochemistry early by measuring autoantibodies and performing a liver biopsy, if warranted. Prednisone (up to $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ or 40–60 mg/day maximum dose) is used to induce remission and can be continued at a lower dose (0.1–$0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ or 5 mg/day) as long-term maintenance therapy (48). Budesonide is currently being investigated as a potential alternative to prednisone for maintenance therapy in both adults and children due to less possible adverse effects. AZA is usually added for maintenance treatment, as recommended in the American Association for the Study of Liver Diseases guidelines (45). Thiopurine methyltransferase activity can be measured before starting therapy to predict who may develop rare myelosuppression from AZA therapy. AZA is usually started at a dose of 1 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, which in the absence of signs of toxicity is increased up to an approximate maximum of $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ until biochemical control of the disease is achieved (48).

Although cirrhosis is reported in 40% to 80% of children with AIH at diagnosis, progression to end-stage liver disease is rare, and most children remain clinically stable. With appropriate treatment, 80% of patients achieve remission and long-term survival with their native liver (49). At present, data are insufficient to allow us to determine whether the disease course of AIH in association with IBD differs from the general disease course seen in non-IBD patients.

Autoimmune Sclerosing Cholangitis and Inflammatory Bowel Disease

ASC is an overlap syndrome between AIH and PSC, occurring predominantly in children and young adults (50–52). ASC is characterized by marked autoimmune features, namely positive autoantibodies (typically ANA and SMA), elevated serum immunoglobulin G levels, and interface hepatitis on liver biopsy and cholangiopathy, as evidenced by an abnormal cholangiogram and/or histologic bile ductal involvement. In the same population-based study mentioned above, ASC was identified in 1.5% of children with IBD, with an increased frequency in UC (5). ASC affects boys and girls equally.

Autoimmune Sclerosing Cholangitis Clinical Presentation

The clinical presentation of ASC is similar to AIH type 1, although it has a stronger association with IBD. In a large prospective single-center study of immune-mediated liver disease, IBD was more common in ASC (45%) than in AIH type 1 (20%) (50). The primary distinguishing factor between AIH and ASC is evidence of cholangiopathy. Because the GGT may be low-normal in

the early course of ASC, it is important that children with IBD and apparent AIH are routinely investigated for evidence of biliary disease with MRCP, and careful examination of the liver biopsy for any ductal involvement. In addition, atypical p-ANCA antibodies are far more common in children with ASC than AIH type 1; 74% positivity, versus 45% (50). It is essential to correctly identify ASC as the prognostic implications are different than for AIH. It should also be noted that AIH has been reported to evolve into ASC in association with IBD, suggesting that these conditions are actually on a disease spectrum.

Autoimmune Hepatitis/Autoimmune Sclerosing Cholangitis Treatment

ASC responds to the same immunosuppressive combination therapy used for AIH. Abnormal liver biochemistries generally improve within months of starting treatment. The prognosis is, however, worse in ASC compared to AIH, because the biliary disease progresses in approximately half of the patients with ASC. In the Utah study of immune mediated liver disease, 42% of children with ASC developed complications of liver disease as compared to only 18% of the children with AIH (5).

Ursodeoxycholic acid ($15-20$ mg$\cdot$kg$^{-1}\cdot$day^{-1}) is often used to help with the biliary disease component, but as with PSC, it is unknown if this has any effect in slowing the progression of the disease. Elevations of serum transaminases can often follow IBD exacerbations, and the progression of biliary disease may be associated with persistent intestinal inflammation (50).

Overall, approximately 10% of children with AIH and 20% with ASC require LT (41). In the Kings College prospective study, transplant-free survival was longer in AIH than in ASC, the estimated survival with native liver was 65% at 10 years for patients with ASC and 100% for children with AIH (50). Recurrence may occur years after LT, and therefore, steroid-based immunosuppression should be maintained at a higher dose than that used for patients transplanted for non-AIH (37). After transplantation, recurrent AIH has been described in ∼20% of cases and recurrent ASC in ∼70%. Currently, little data support the assertion that AIH/ASC recurrence after LT is more common in poorly controlled IBD.

Portal Venous Thrombosis and Hypercoagulability and Inflammatory Bowel Disease

IBD is associated with an increased risk of vascular complications, such as arterial and venous thromboembolism (VTE), which are considered extraintestinal manifestations of the disease. Arterial TE (ischemic stroke, cardiac ischemia, peripheral vascular disease, and mesenteric ischemia) and VTE (deep vein thrombosis and pulmonary embolism; cerebral venous sinus thrombosis; hepatic, portal, and mesenteric vein thrombosis) belong to the group of extraintestinal complications in patients with IBD that are associated with a high morbidity and mortality. Epidemiologic reports of TE and the specific subtypes of TE in children with IBD are limited. Kappelman et al (53) used a Danish cohort to study venous TEs in adults and children in the hospital and outpatient settings, and reported that 40 of 5424 (0.7%) children with IBD had a venous TE.

Portal Vein Thrombosis

Portal vein thrombosis (PVT) is a rare but potentially life-threatening complication, with an incidence in patients with IBD higher than that of the general population. Patients with IBD may have elevated platelet counts, fibrinogen, and factor V and VIII levels. There is also a concomitant decrease in antithrombin 3 levels.

PVT is more likely to occur in the postoperative setting and has been reported in patients with UC after restorative proctocoletomy. In a Mayo Clinic study, portal/mesenteric vein thrombosis was reported in 1.3% of IBD cases, with mortality of 50% (54). Recent abdominal surgery, younger age, and female sex are associated with a higher incidence of PVT (55). The factors involved in this pathogenesis are diverse. Acquired prothrombotic factors can be identified, such as inflammation, immobilization, extent of colon disease, surgery, central catheters, corticosteroids, and smoking (56,57). Inflammation is the most common risk factor.

Presentation and Diagnosis of Portal Vein Thrombosis

PVT may present in many ways from an acute abdomen to a more chronic and insidious presentation (58). Symptoms will vary based on the acuity and degree of vessel involvement. Acute PVT is rare, but should be considered in those presenting with acute abdominal or lumbar pain, nonspiking fevers, and moderate abdominal distension (due to an ileus). If the superior mesenteric vein is also occluded then they may have nonbloody diarrhea and intermittent abdominal pain that can progress to possible bowel infarction, ascites, and hematochezia. In contrast, chronic PVT more commonly presents as an incidental finding on imaging, although it can present as a gastric or esophageal variceal bleed associated with portal hypertension (58).

A range of imaging modalities may be used in the diagnosis of PVT. An accurate diagnosis is made in most cases using color Doppler ultrasound, contrast-enhanced computerized tomography (CT) scanning, or magnetic resonance angiography. The use of abdominal ultrasound, which is infrequently employed to assess the bowel and upper abdomen in the management of IBD, does allow detection of PVT in most patients. On the contrary, the accuracy of ultrasound coupled with color Doppler as a screening test for assessing PVT has been well known for a long time (59). CT scan is more sensitive than ultrasound (which can be operator dependent) for detecting a thrombus within the splenic and mesenteric veins (60). CT scan also provides a better assessment of bowel viability and the presence of a perforation (60). With chronic PVT, portal bilopathy, due to bile duct compression, can also sometimes be identified on imaging in a subset of patients and result in jaundice (61).

Treatment of Portal Vein Thrombosis

Anticoagulants, such as low-molecular-weight heparin and warfarin, are mainstays of primary therapy, even in the setting of gastrointestinal bleeding (57). The duration of systemic anticoagulation is not well established in the literature. It is important to clarify the goal of therapy for PVT. As a means to reduce PVT-associated morbidity and mortality, there are 2 broad intentions: to reverse or prevent the advancement of thrombosis within the portal venous system and to treat the complications of established PVT, most specifically gastrointestinal varices or portal biliopathy.

Venous Thromboembolism and Hepatic Vein Thrombosis

Cases of hepatic vein thrombosis (Budd-Chiari syndrome) in patients with IBD have been reported. This thromboembolic phenomenon can occur in patients with UC, but in the setting of an acute flare the risk is up to 8 times higher. The perioperative period is also a significant risk period for TE (62,63).

It is important to review any family history of thrombosis and bleeding with a new onset colitis patient. It is also important to counsel patients about smoking, inactivity, and long travel, because these are risk factors for developing clots. Patient hydration is an important factor to address on admission and also during a prolonged hospitalization. One should also address other mobility factors, and consider a physical therapy consultation along with a plan for ambulation. It is worthwhile to consider evaluation by a

coagulation specialist who can check levels of pro- and anticoagulants in those patients at risk.

Treatment of Venous Thromboembolism in Inflammatory Bowel Disease

A recent consensus statement by the Canadian Association of Gastroenterology (64) provides guidelines for treating pediatric patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor. These guidelines recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. For pediatric patients with IBD diagnosed with their first episode of VTE in the presence of active disease, it has been suggested that anticoagulant therapy continue until the IBD is in remission for 3 months, rather than stopping treatment at 3 months or continuing indefinite anticoagulant therapy.

In terms of thromboprophylaxis, for pediatric patients with IBD (younger than 18 years of age) without a previous VTE who are admitted for an IBD flare, anticoagulant thromboprophylaxis is not routinely recommended. Although hospitalized pediatric patients with IBD have an increased relative risk of VTE compared with children without IBD, the absolute risk of VTE is much lower than in adults with IBD (53). A more recent study of IBD patients at a tertiary referral center assessed risk factors and recommended thromboprophylaxis in those considered high risk (65). These included hospitalized patients with IBD with colonic involvement or undergoing major surgery, and one of the following: a personal history of VTE; a first-degree family member with VTE history, known thrombophilia, a persistent antiphospholipid antibody, oral contraceptive use, smoking, obesity, thalidomide, or having a central venous catheter (65). If thromboprophylaxis is planned, then low-molecular-weight heparin is recommended. The dosing of enoxaparin is weight based with patients >60 kg receiving either 30 mg subcutaneous twice daily, or 40 mg once daily, and patients <60 kg receiving 0.5 mg/kg subcutaneous twice daily, based on current dosing recommendations for pediatric patients (66).

Cholelithiasis in Inflammatory Bowel Disease

A relation between IBD and cholelithiasis has been described since the 1970s (67). For CD, a population-based study that included 131 patients with CD and 556 controls found a significant increase in the prevalence of cholelithiasis with a relative risk of 1.8 (95% confidence interval, 1.2–2.7) (68). Another referral center–based study identified that the prevalence of cholelithiasis among patients with CD was 11% compared with controls at 5.5% ($P < 0.05$) (69). Finally, a study by Parente et al (70), published in 2007 reported follow-up of patients with CD and matched controls for over 7 years and found the incidence of cholelithiasis to be 14 of 1000 patients/year in CD compared with 8 of 1000 patients/year for controls ($P < 0.05$).

Some of this increase may be related to an increased risk of cholelithiasis after ileal resection in CD; with resections >30 cm are associated with an odds ratio of 7 (95% confidence interval, 2.6–19.3] for the development of gallstones (70). Similarly, another study showed a prevalence of cholelithiasis of 48% in patients who underwent >3 intestinal resections compared with only 21% in those not having undergone a resection (68). The increased risk for cholelithiasis after ileal resection may be related to changes in bile composition. When patients who had resections were examined, cholesterol saturation was significantly lower, and bilirubin concentrations were 45% to 50% higher (71). These results suggest an increased risk of developing bilirubin-type gallstones

after ileal resection. Currently insufficient information, however, exists about gallstone composition in general for both CD and UC to confirm this association. In addition to undergoing surgery, patients with CD are more likely to have impaired gall bladder emptying (72). Other identified risk factors for cholelithiasis in CD include age, the duration of disease, number of clinical recurrences, number of hospitalizations, and total parental nutrition (70,73,74).

In contrast to CD, when examining cholelithiasis in UC the majority of the available data do not support any increased risk compared with controls. Although the prevalence of cholelithiasis in UC has been reported to range from 4.6% to 36.4% only 1 study demonstrated an increased prevalence compared with controls. In one of the more recent studies examining this question the incidence rate of cholelithiasis was 7.5 of 1000 patients/year for UC compared with 6 of 1000 patients/year for controls ($P = 0.38$) (70).

The histologic findings in cholecystectomy specimens from patients with IBD have been examined compared with age- and sex-matched non-IBD patients who underwent cholecystectomies for abdominal pain, vomiting, fever, or jaundice (75). Both chronic cholecystitis and acute serositis were significantly more common in UC and CD patients compared with non-IBD controls (75). The cholecystectomy findings also, however, revealed that the rate of cholelithiasis is similar between those with and without IBD (75). Therefore, even though stones are more common in CD, they are not more commonly found compared to those who undergo cholecystectomies in the general population.

Presentation and Diagnosis

Cholelithiasis in children with IBD will generally present in a similar fashion to the general population. They may initially present with biliary colic and have symptoms of intermittent cramping right upper quadrant pain associated with mild nausea. These symptoms will generally be exacerbated after meals high in fat content. They may find that a bland diet helps to limit their symptoms. Their examination may be nonspecific with perhaps subjective complaints of right upper quadrant tenderness to deep palpation. Laboratory tests (including biochemistry and hematology panels) are generally within normal limits. An ultrasound of the right upper quadrant showing gallstones along with a classic symptomatology generally confirms the diagnosis. If no stones are identified and symptoms persist and remain suspicious for biliary disease, a cholecystokinin/hepatobiliary iminodiacetic acid scan can be useful to evaluate gall bladder function and reproduction of symptoms. Gallbladder emptying of <15% along with reproduction of symptoms may confirm the gallbladder as the likely source of symptoms (76). Whether or not a cholecystectomy should be performed on these individuals with biliary dyskinesia remains controversial (77–79). Children with symptomatic cholelithiasis should, however, be referred to a pediatric surgeon for cholecystectomy.

In children with IBD, ensuring that the symptoms are not related to a flare is also important and depending on the presenting symptoms, these patients may warrant endoscopy or enterography. Also, in children who have had distal ileal resections and prolonged ileostomies, a preoperative screening ultrasound should be considered before ileostomy closure if any upper abdominal symptoms exist. No evidence, however, advocates for prophylactic or ''incidental'' cholecystectomy at the time of other surgical procedures in this population.

In conclusion, clinicians need to be aware of the increased incidence of cholelithiasis in patients with CD especially in those with severe disease affecting the terminal ileum. Care should be taken not to overlook cholelithiasis as a source of abdominal pain in these patients especially given the histologic evidence of chronic serositis in removed specimens.

Viral Hepatitis and Inflammatory Bowel Disease

Viral hepatitis infections can pose a significant burden on the management of IBD. Although hepatitis A virus (HAV) causes an acute hepatitis that is rarely associated with significant morbidity and mortality, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections can cause liver disease with progression to cirrhosis. Chronic liver disease may preclude the use of potentially hepatotoxic medications, such as methotrexate (MTX), to avoid further liver damage, and thus potentially limiting IBD treatment options. Furthermore, patients with chronic viral hepatitis in whom immunosuppressant medications are used are at increased risk of fulminant liver failure.

The prevalence of infections with HBV and HCV in the IBD population was high in early epidemiologic studies. In an Italian cohort from the late 1990s, 24.7% of patients had at least one positive test for HBV or HCV (80). This was likely due to transmission via blood transfusions and surgeries before the widespread availability and use of viral screening tests in blood donors. More recent reports on the prevalence of positive HBV and HCV markers in adults with IBD have demonstrated lower rates. Specifically, hepatitis B surface antigen (HBsAg) positivity was 0.3% to 0.7%, antibody to hepatitis B core (anti-HBc) positivity was 7.5%, and antibody to HCV (anti-HCV) positivity was 0.9% to 1.8% (81–84). Despite a lack of prevalence data in children with IBD, the latest studies in adults have identified similar HBV and HCV rates in patients with IBD as in the general population (81). Although lower compared to historical data, the rates of HBV and HCV infection in patients with IBD are not negligible and deserve special management consideration.

Hepatitis B

Significant risk of viral reactivation, with or without liver dysfunction, exists with the use of immunosuppressant therapies, including anti-tumor necrosis factor (TNF) biologics, in individuals with chronic HBV infection. Loras et al (85) reported liver dysfunction in 9 of 25 (36%) HBsAg-positive IBD patients who received various immunosuppressants (corticosteroids 84%, AZA 69%, anti-TNF agents 34%); 24% developed liver failure. The rate of hepatic dysfunction increased with the use of more or prolonged immunosuppressants. No hepatic complications were seen with the use of these medications when patients had only anti-HBc without HBsAg. In another study of 22 patients with IBD and anti-HBc who were HBsAg negative, no HBV-related complications were observed (82).

The efficacy of treatment of HBV infection concurrent with use of anti-TNF agents has been studied. Thirty-three patients with IBD and HBV markers (29 only anti-HBc positive, 4 HBsAg positive, none with circulating HBV DNA at baseline) received antiviral agents concurrently with anti-TNF treatment (86). Lamivudine was used initially, but treatment was changed to entecavir and tenofovir following reports of higher efficacy and less resistance. Seven percent of the anti-HBc-positive patients had circulating HBV DNA on follow-up, without elevated liver enzymes. HBV DNA remained negative in the 4 HBsAg-positive patients (86). The American Association for the Study of Liver Diseases recommends the use of prophylactic antivirals (such as lamivudine or tenofovir) in HBV-infected patients who will be treated with anti-TNF agents (87). Indeed, antivirals should be started in any HBV carrier starting immunosuppressive therapy irrespective of ALT or evidence of inflammation/fibrosis (87). HBV treatment should be continued until 6 months after discontinuation of the anti-TNF agents or until therapeutic endpoints are obtained in patients with elevated HBV DNA ($\geq$2000 IU/mL). Of note, the efficacy and safety of this approach has not been studied in pediatrics.

Hepatitis C

In patients with IBD and HCV infection, treatment with anti-TNF agents is well tolerated in the majority of cases. Elevated TNF-α levels have been demonstrated in patients with HCV infection, and may contribute to the pathophysiology of liver disease (88). Furthermore, antiviral treatment failure has been associated with higher levels of TNF-α, indicating a theoretical benefit to HCV treatment with TNF-α inhibitor use (89). In a study of 5 patients with concurrent IBD and HCV infection who were treated with anti-TNF agents most had either unchanged or better liver biochemistry results. One patient with worsening ALT values was coinfected with HIV (83). Another patient treated concurrently with 6-mercaptopurine experienced a transient elevation in liver biochemistry that improved with dose reduction. A systematic review of the safety profile of infliximab treatment in patients with chronic diseases identified 6 patients with IBD and HCV who did not have worsening liver biochemistries with treatment (90). In a recent study of treatment with anti-TNF agents, no patients with IBD and anti-HCV antibody were taking antiviral agents, and none developed worsening of liver disease, although only 1 patient had detectable HCV RNA (86).

Viral hepatitis C treatment in children is currently limited to pegylated interferon and ribavirin; the direct-acting antiviral agents are under investigation in pediatrics. To date, treatment of adults with HCV and IBD using direct-acting antiviral agents and immunomodulators or anti-TNF agents has not been reported. Treatment of HCV in children with IBD should be individualized, weighing the risks and benefits of available therapies with the potential for a higher sustained virologic response rate, and likely better side effect profile, with newer antiviral agents.

Outcomes and General Treatment Recommendations

No studies have examined the outcomes of treatment with anti-TNF agents in children with IBD and HBV or HCV infection. Consultation with a pediatric hepatologist and treatment of chronic HBV should be considered in children with IBD and HBV in whom anti-TNF agents are required. Treatment of IBD in children with HCV infection, on the contrary, is likely much safer and may be considered without treatment of the underlying infection, although data substantiating this strategy in children are lacking. In all cases, routine surveillance with measurement of liver enzymes, and viral levels, including HBV DNA or HCV RNA, should be performed at regular intervals while infected children are receiving anti-TNF agents.

Vaccination for Viral Hepatitis in Pediatric Inflammatory Bowel Disease

Immunization practices present a challenge in the management of children with IBD. Patients with immune-mediated inflammatory diseases, such as IBD, typically have lower response rates to vaccines and may not be completely protected against these infections (91). Furthermore, immunization boosters may require extended periods of time for vaccine schedule completion. Specifically, vaccination against HAV involves 2 doses with a minimum interval of 6 months, whereas protection against HBV requires 3 doses, at 0, 1, and 6 months. Unfortunately, the treatment of IBD with immunosuppressants often cannot be postponed, and these medications may increase the patient's risk of vaccine-preventable

infections (91). Despite this risk and recent recommendations for universal vaccination for hepatitis A and hepatitis B, substandard vaccination rates have been reported. In 106 French children with IBD, HBV and HAV vaccinations were provided to only 38% and 1.8% of children, respectively. These vaccines were reportedly either not proposed by the health care professionals, or refused by the patients and family members. In contrast, a Canadian study of 145 children with IBD demonstrated that only 6% had not received the HBV vaccine; the use of HAV vaccine was not assessed (92). This highlights the importance of the health care professional's role in ensuring that children with IBD undergo appropriate vaccination for viral hepatitis A and B.

HAV vaccination is effective in patients with IBD. Recent prospective studies in both pediatric and adult IBD populations demonstrated high seroconversion rates, 97% (N = 66) and 97.6% (N = 419), respectively, following a 2-dose vaccination schedule (93,94). Patients being treated with anti-TNF agents have been shown to develop anti-HAV antibodies with immunization, although the rate was significantly lower than that in patients with IBD not receiving this therapy (92.4% vs 99.1%, $P = 0.001$) (94). Vaccination for HAV before treatment with anti-TNF agents is preferable; however, seroconversion is still likely and should be attempted regardless of use of these agents.

Seroconversion rates with HBV vaccination are lower than those achieved with HAV vaccine. In 1 report, 70% of 47 children with IBD demonstrated seroprotection (hepatitis B surface antibody [HBsAb] $\geq$10 mIU/mL) following the 3-dose schedule, compared to 90% of 50 healthy controls (95). With an extra booster dose, the rates increased to 85% and 96%, respectively. In 100 children with IBD receiving infliximab, 87% had been previously vaccinated for hepatitis B (96). Of those, only 49 (56%) were immune at the time of testing; the time from initial vaccination was 13.3 ± 3.8 years for immune patients and 12.6 ± 4.3 years for the nonimmune patients. Older age, pancolitis, and lower serum albumin levels were associated with absence of immunity. Booster immunizations of this cohort induced a protective immune response, in 26 of 34 patients (76%).

One strategy evaluated to improve HBV immunity in adults with IBD is an accelerated course with double vaccine doses at 0, 1, and 2 months. Efficacy of this regimen was tested in 148 patients, 70% of whom were receiving immunosuppressive agents (23% anti-TNF only, 22% thiopurines only, 25% both) (97). Of the 80 patients who received the accelerated course, 75% developed adequate anti-HBs levels $\geq$10 mIU/mL, compared to 41% of 68 patients who had the routine vaccination schedule (97). In another large cohort, the rate of seroprotection was lower, only 43.5% (110/254), in adult patients with IBD on anti-TNF agents, even with the accelerated vaccination schedule (86). This vaccination strategy has not yet been evaluated in children with IBD; however, it has been tried in other pediatric chronic diseases with good seroprotection rates, indicating the need for further study in pediatric IBD (98). In the meantime, patients with IBD who have nonimmune HBsAb levels (<10 mIU/mL) should be revaccinated with the routine 3-dose regimen, even though these low levels do not necessarily imply a lack of immunity to the virus (99).

Viral hepatitis infections are infrequent in pediatric IBD, but have the potential to cause significant liver disease, especially with immunosuppression from anti-TNF agents. HAV and HBV are vaccine-preventable, so special attention to a child's immunization history is essential at the time of IBD diagnosis, to allow for catch-up. Also, laboratory investigations should include HBsAb to assess for immunity, and HBsAg, anti-HBc, and anti-HCV to assess for history of infection. Close monitoring is prudent in children with IBD and infection with a hepatitis virus.

Drug-induced Liver Disease in Inflammatory Bowel Disease

Approximately 30% of patients with IBD are reported to show abnormalities in liver biochemical tests during the course of the disease (3,100,101); and several reports suggest that most drugs used for treatment of IBD have side effects of hepatotoxicity (102–106). A cause-effect association between liver injury and some of these medications is sometimes difficult due to confounding factors such as concomitant disease; moreover, the mechanisms that underlie hepatotoxicity of some of these drugs remain unclear.

Glucocorticoids

Chronic exposure to glucocorticoids is associated with central adiposity, dyslipidemia, insulin resistance, glucose intolerance, and overt diabetes; and it is speculated that changes in hepatic lipid metabolism may induce hepatic steatosis (107).

Sulfasalazine

Sulfasalazine causes 2 main forms of liver injury: acute hepatocellular damage (108) and cholestatic injury (109–111). Acute hepatocellular damage from sulfasalazine may present with symptoms of fever, rash, lymphadenopathy, hepatomegaly, atypical lymphocytosis, and eosinophilia; and typically develops as part of a generalized hypersensitivity reaction to the sulfapyridine moiety. Acute granulomatous hepatitis (GH) from sulfasalazine presents with high fever, malaise, right upper quadrant pain, elevated ALT and bilirubin, normal alkaline phosphatase, and noncaseating granulomas on histology (112). Rarely, acute liver failure has also been reported with sulfasalazine (113,114). Newer, enteric coated, 5-aminosalicylic acid formulations, such as mesalamine, do not appear to have any increased risk for hepatotoxicity in children (115).

Thiopurines

The incidence of thiopurine-associated hepatotoxicity markedly varies among different series and the data are sometimes contradictory (116). Both AZA and 6-mercaptopurine undergo metabolic transformations to 6-thioguanine, which is the final effector metabolite. Thiopurine-induced hepatotoxicity can be dose-dependent and dose-independent. Although elevated liver enzymes have been associated with various metabolites of thiopurines such as the 6-methylmercaptopurine-ribonucleotides (117,118), these metabolites are not routinely quantified in clinical laboratories. Moreover, the association between 6-methylmercaptopurine-ribonucleotides levels and liver enzyme elevation has not been consistently reported in all studies (119–121).

Other signs of dose-dependent hepatotoxicity of thiopurines include sinusoidal dilatation, nodular regenerative hyperplasia (NRH), peliosis hepatis, and sinusoidal obstruction syndrome (SOS). The pathogenesis of NRH is thought to be a compensatory hypertrophic response to the effects of hepatocyte atrophy caused by obliteration of portal venules by platelet aggregates and thrombi (122), and has been directly linked to treatment with 6-thioguanine (123). Peliosis hepatis is thought to share etiopathogenesis with SOS, NRH, and sinusoidal dilatation (124). The mechanism of SOS by AZA is thought to be associated with marked depletion of glutathione in sinusoidal endothelial cells (125,126).

Liver injury from thiopurines can present with asymptomatic liver enzyme elevations, liver cell necrosis, cholestasis, and the development of vascular endothelial lesions (NRH, SOS, peliosis

hepatis, and sinusoidal dilatation). Most patients with NRH are asymptomatic with mild elevations in alkaline phosphatase and aminotransferases, and an indolent clinical course (127). Serious outcomes such as elevated hepatic venous pressure gradients with clinically significant portal hypertension and hepatocellular carcinoma have, however, been reported (128–131). In other cases, isolated thrombocytopenia is the only laboratory abnormality (132). Imaging with a multiphasic gadolinium contrast-enhanced magnetic resonance imaging may show multiple fine nodules that do not enhance (127,133). On biopsy, the hallmark of NRH is the presence of small hyperplastic nodules without extensive fibrosis, verified on silver reticulin stain, with compressed and atrophic internodular parenchyma (122,134). Peliosis hepatis results in cystic blood filled spaces in the liver, spleen, lymph nodes, and other organs. These lesions can lead to hepatic hematomas and rarely overt hepatic rupture with hemoperitoneum. SOS presents with Budd-Chiari–like symptoms of rapid onset ascites, jaundice, and liver failure.

Methotrexate

MTX has been linked to severe fibrosis and cirrhosis when used in frequent, high cumulative doses in rheumatoid and psoriatic arthritis (135), but less so when used in IBD (117). The cause of MTX-induced fibrosis is unknown. Valentino et al (136) systematically reviewed and meta-analyzed incidence of hepatotoxicity with MTX among children with IBD. Although abnormal liver biochemistry was observed in 1 in 10 children on MTX, importantly, none of the included studies reported results of liver biopsies or cases of biopsy-proven MTX hepatotoxicity. In addition, the patients reported were also receiving concurrent IBD therapies (with known adverse effects of liver enzyme abnormality) in 11 of the 12 studies included. Thus, the reported rates of hepatotoxicity may be inaccurate as it is unknown whether the abnormal liver biochemistry is secondary to MTX use or other causes of enzyme elevation (137).

Elevations in aminotransferases are seen after chronic MTX administration in IBD, with the majority being transient and resolving spontaneously without dose reduction (104). The extent of histological features of hepatotoxicity secondary to long-term MTX use in IBD has been infrequently described (117,138–140); however, the incidence of significant abnormal histological findings appears to be rather low (117,140). Indeed, these reports suggest abnormal liver chemistry tests may not identify patients with refractory IBD on MTX who have liver fibrosis. The converse (normal aminotransferase levels in the setting of abnormal liver histology) has been described (135).

TNF-α Antagonists

Hepatotoxicity has been reported with use of infliximab (141,142). Based on postmarketing surveillance, the Food and Drug Administration has issued warnings regarding the potential risk for serious liver injury with biologics. Hepatotoxicity is postulated to be idiosyncratic, mediated by an aberrant immune response induced by blocking TNF in a susceptible host (143). Indeed, drugs interfering with cytokines such as anti-TNF-α may release hepatic antigens with resultant presentation of these autoantigens by immune cells leading to continued autoaggressive immune reaction in genetically susceptible individuals (105).

The pattern of liver enzyme elevation after infliximab use is a hepatocellular or cholestatic pattern with autoimmune characteristics (141). Infliximab-related hepatitis has been reported to resemble AIH with associated antinuclear, antismooth muscle and anti-double stranded DNA antibodies and a female predominance (142). Patients with autoimmune features may experience longer latency times and higher peak alanine aminotransferase levels compared to those lacking autoimmune features (141). Liver cell necrosis with resultant fulminant liver failure necessitating LT has been reported after the use of infliximab (144).

Liver Transplantation and Inflammatory Bowel Disease

Because of the association of IBD and PSC, the frequency of LT in patients with IBD is increased compared to that of the general population. Most children with IBD after orthotopic LT were known to have IBD before transplant. In the Studies of Pediatric Liver Transplant database analysis, additional data were available for 61 of 79 children who underwent LT for PSC; 31 (46%) of those had UC and 2 (3.3%) had CD at the time of transplant (36). An additional 6 (10%) of those 61 children who underwent LT for PSC developed IBD (4 UC and 2 CD) in the follow-up period (mean 36.6 ± 32.7 months).

LT recipients with comorbidities at the time of transplant have increased morbidity and mortality and this is an important consideration for those with IBD. As for any transplant candidate, nutrition should be optimized (using supplemental tube feedings or parenteral nutrition if necessary) and immunizations should be completed (on an expedited schedule where indicated) before listing/transplantation. In addition to these routine considerations (though of great importance for patients with IBD), children with IBD have increased risk for complications of surgery and medical management (such as vascular thrombosis and infection).

Studies have presented conflicting data regarding whether pre-existing IBD disease activity may be improved or worsened after LT (145–147). Jorgensen et al (148) identified age <20 years, use of tacrolimus, and use of tacrolimus + mycophenolate mofetil as risk factors for more active IBD after LT, whereas the use of cyclosporine and AZA were potentially protective. Other studies have implicated symptomatic IBD at the time of LT, short interval between diagnosis of IBD and LT, PSC as indication for LT, and discontinuation of 5-aminosalicylic acid (or other existing therapy) at the time of transplant as additional risk factors (145,146). Of note, PSC/UC with more severe liver disease requiring LT is associated with milder clinical course of UC, less steroid requirement, and reduced incidence of dysplasia and colon carcinoma compared with patients with milder liver disease (17,22).

Thrombotic events at the time of LT are more common in adult patients with IBD/PSC compared with patients with PSC alone. This may be a particular risk for patients with active IBD at the time of LT (149).

In some patients, de novo IBD develops after transplant. The incidence after solid organ transplant is higher than that in the general population (206 vs 20 cases per 100,000 patients per year) (150). This incidence is higher after LT compared with other solid organ transplants, possibly due to the higher rate of PSC as an indication as approximately 14% to 30% of adult patients with PSC develop de novo IBD 10 years after LT (146). In a study of 14 adult patients with de novo IBD after liver or kidney transplant, 71% had been treated with tacrolimus, raising the possibility that tacrolimus may be an independent risk factor (151). Several small subsequent studies have also suggested this, although data have been conflicting and there are many potential confounders (146,147,152–154). Treatment with cyclosporine may not have similar effect on IBD disease progression (153). In addition, cytomegalovirus mismatch or infection may be a risk factor for the development of de novo IBD posttransplant (150,155).

In general, the medical management of IBD after LT can be similar to typical treatment. Treatment with oral 5-aminosalicylate

posttransplant may help prevent UC relapse and decrease risk of colectomy. (147,153) Immunosuppression/modulation is the mainstay of medical management for both IBD and LT; however, the medications used are generally quite different. Other than steroids (avoided for long-term therapy) and purine analogs (used as adjuvant therapy in both settings), IBD immunosuppressive management is mainly composed of biologics (anti-TNF), whereas LT therapy is founded upon calcineurin inhibitors, and mechanistic target of rapamycin, inhibitors. AZA may reduce the risk of relapse for pre-existing IBD and development of de novo IBD posttransplant (146,152). Of note, the typical AZA dose used posttransplant $(1-1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1})$ is lower than the typical IBD treatment dose $(2-2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1})$ (152). Corticosteroids have been associated with improved IBD disease activity post-LT, including possibly decreased risk of colectomy (147). The considerable risk of prolonged corticosteroid exposure and lack of efficacy for maintenance of remission for IBD, however, need to be considered. Ileal-release or MMX budesonide can be considered as a corticosteroid-sparing agent for post-LT patients with active IBD (156).

Anti-TNF therapy (infliximab) has been used in adult LT recipients for management of IBD with similar efficacy as compared to IBD in the general population (157,158). These should, however, be used with caution because of high risk of adverse events, such as serious infections, lupus and malignancy (146). To date, no data have been published regarding the use of infliximab for treatment of IBD for pediatric LT patients. The utility of mycophenolate mofetil (commonly utilized post-LT) in the treatment of IBD is unclear.

For LT patients with UC for whom medical management is not adequate, proctocolectomy with or without ileal-pouch anal anastomosis is an alternative. For patients with UC/PSC who have already undergone ileal pouch anal anastomosis before LT, graft survival, patient survival, and postoperative complications are similar to patients who are medically managed (159). LT does not seem to increase the risk of pouchitis in patients with UC/PSC, although the incidence is high in general for this patient population (146).

Patients with longer duration of IBD and extensive colonic involvement are known to have an increased risk of CRC. Routine CRC surveillance should continue for patients with IBD who have had LT, even in the setting of clinically quiescent disease.

Miscellaneous Rare Hepatic Disorders and Inflammatory Bowel Disease

IgG4 Cholangiopathy

IgG4 cholangiopathy is best known for its association with autoimmune pancreatitis, but it is also recognized as a probable causative etiology in a subset of cases of PSC. As discussed in the section on PSC, this hepatobiliary complication affects approximately 5% of subjects with UC (160). Elevated IgG4 have been reported in 9% to 36% of patients with PSC (161,162); however, there are now case reports of patients with UC and IgG4 cholangitis, including presentations in childhood (163). Although the clinical presentation of adults affected with IgG4 cholangitis is sometimes distinguished from that of PSC by being older and having obstructive jaundice, for most described patients the conditions are symptomatically and cholangiographically indistinguishable (164).

Diagnosis is based on a combination of diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct with thickening of the bile duct wall; serum IgG4 concentrations ≥135 mg/dL; coexistence of autoimmune pancreatitis, dacryoadenitis/sialadenitis, or retroperitoneal fibrosis; and marked periductular portal lymphocytic and plasmacytic infiltration in the liver with at least 10 IgG4-positive plasma cells/high powered field (165). Children often do not present with all of the diagnostic features, and may actually have normal IgG4 levels. A high level of suspicion and staining the liver or papillary tissue for increased IgG4 immunoblasts is necessary.

Although the clinical presentations of PSC and IgG4-cholangiopathy may be similar, the distinction is important as the latter entity is responsive to corticosteroid therapy and appears to be less progressive in nature (163,166). As opposed to the unresponsiveness of PSC, corticosteroids result in resolution of jaundice, improved liver laboratory values, and reduced serum IgG4 levels, and most importantly result in resolution of the strictures on cholangiogram in patients with IgG4 cholangiopathy (166,167). Given the experience with AIH, expectant AZA appears to be also effective for the long-term management of IgG4 cholangiopathy (166,168).

Granulomatous Hepatitis

GH, diagnosed histologically in the liver, is a rare complication seen in IBD thought to occur in <1% of patients (166,169). Observed more frequently in those with CD than UC, GH usually manifests itself as an increase in the cholestatic enzymes, most classically alkaline phosphatase. Although the most common cause of GH in the setting of IBD is medications, predominantly sulfasalazine, GH can be an extraintestinal manifestation of the IBD, or have infectious or malignant etiologies (164,166). When the cause is thought likely an extraintestinal manifestation of CD, corticosteroids and immunosuppressive medications have been used as effective treatment (164).

Primary Biliary Cirrhosis (Cholangitis)

Although the link between celiac disease and primary biliary cirrhosis/cholangitis (PBC) is well established (170), the link with IBD is less clear and is rare, if ever, in the pediatric population. A few reports of patients with coincident disease have been reported (171,172), and a population-based study of PBC in UC showed a higher than expected prevalence of PBC than would be expected by chance alone (173). When associated with IBD, the PBC occurs in males with UC most commonly, and the UC is typically mild and limited to left-sided involvement (164,166,170).

Although the pathogenesis for an IBD-PBC association is not fully understood, they are both autoimmune diseases, suggesting a common pathogenesis. The theory of microbial-mediated mimicry as a trigger for PBC (174) and the growing number of studies suggesting a link between the gut microbiota and IBD (175), support the possibility of a common pathogenic link between the 2 conditions.

Hepatic Amyloidosis

Hepatic amyloidosis complicating IBD is rare, with an overall prevalence of approximately 0.5%, occurring in approximately 0.9% of patients with CD and 0.07% of those with UC (166,176). Patients at highest risk are boys with long-standing severe small intestinal or colonic disease. Although the amyloid deposition most commonly involves the kidney, cases of hepatic localization are well described, occurring in both adults and children. In one series of 18 patients with IBD, 11 were found to have hepatic amyloidosis, and the amyloidosis was either present at the time of IBD diagnosis, or discovered within 5 years of IBD diagnosis (177). The clinical signs and symptoms of hepatic amyloidosis are usually scant, with hepatomegaly being the most common. Serum laboratory

evaluations are typically normal and most cases are diagnosed at the time of autopsy (178,179). Liver biopsy is necessary to make the diagnosis (166). Mortality is most tightly related to the renal involvement, with a 5-year survival rate reported of 89% but a 15-year survival rate of only 60% (177). Medical treatment has traditionally been with colchicine, but recent reports of treatment with budesonide and infliximab have suggested these as possible effective alternatives (170,180–182).

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

The inherent rise in obesity rates has made nonalcoholic fatty liver disease (NAFLD) a ubiquitous presence in the world of pediatric medicine today (183). Given the intermittent inflammatory state of children afflicted by IBD one would surmise that the rates of NAFLD should be increased in overweight children with IBD. Upon inspection of the relatively scant data available, the estimated 10% prevalence of NAFLD in the general population is, however, not too different from the 8.2% that seen in the IBD population (184). Smaller case series (185) have found similar results, highlighting for clinicians that NAFLD should be considered whenever elevated liver enzymes are seen in patients with IBD that have a high body mass index (BMI). Similarly, a subset of patients with NAFLD could develop nonalcoholic steatohepatitis (NASH) with the consequent risk of progressive liver injury. In general, boys of Hispanic ancestry with metabolic syndrome and a BMI >30 are at greatest risk for NASH.

Although diagnosis must be confirmed histologically, screening can be accomplished via analysis of serum aminotransferases, GGT, and triglyceride levels. The only proven treatment for NASH/NAFLD is weight loss to an ideal BMI (186,187). In the setting of IBD especially, consultation with a nutritionist familiar with the dietary needs of children with IBD, is recommended, so that the energy, protein, and nutrient needs for growth and healing are maintained while attainment of an ideal body weight is achieved.

OVERALL SUMMARY

Hepatobiliary issues are frequently diagnosed in pediatric patients with IBD, and abnormal liver enzyme levels should prompt further investigations for medication toxicity, diseases related to IBD such as PSC, and AIH or cholelithiasis/cholecystitis. Viral hepatitis, primarily regarding vaccinations and HBV reactivation, is a major concern in conjunction with biologic therapy, and recommendations for vaccinations should be followed before initiating therapy. Other causes for abnormal liver enzyme levels from common disorders, such as NAFLD, to rare entities such as thrombotic disorders, granulomatous disease, and post-liver transplant situations will need to be considered in the appropriate clinical setting. Close collaboration between IBD clinicians, pediatric hepatologists, and primary care providers should be encouraged for optimal outcome and shared decision making.

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